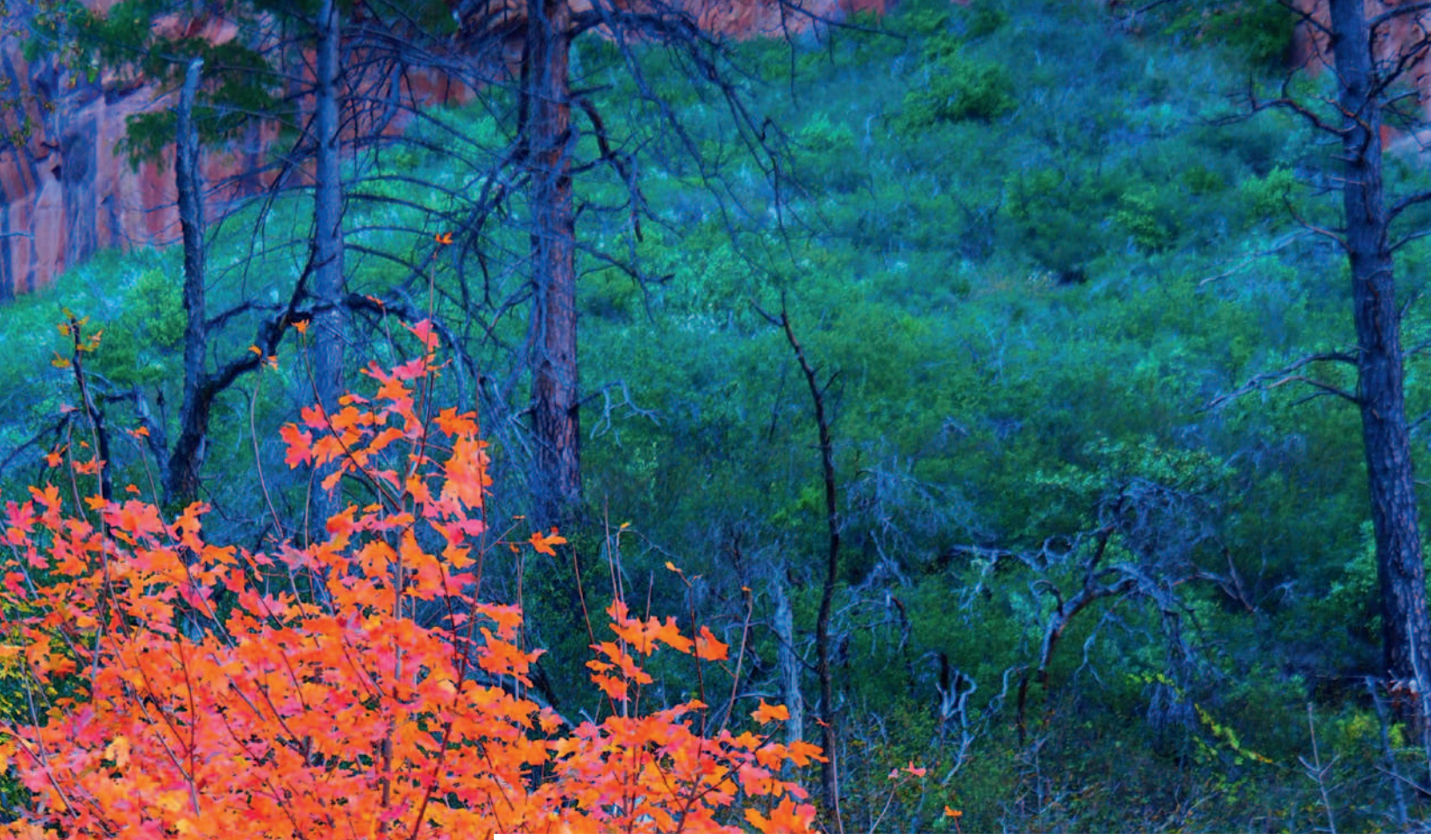


PART 2

# Cold and Heat

CHAPTER 6

# Thermoregulation

NISHA CHARKOUDIAN AND LARRY I. CRAWSHAW

A warm body has long been recognized as one of the primary conditions of human life. Although humans have physiologic, intellectual, and cultural capabilities that equip them to maintain viable body temperatures under many climatic conditions, thermal extremes, heavy exercise, and injury can rapidly lead to dangerous internal temperatures. For a physician who is operating in primitive circumstances, maintaining or restoring a patient's body temperature can require quick action and ingenuity, both of which are aided by an understanding of the physiology of temperature regulation.

Because the thermal environment can be extremely complicated and the thermoregulatory system of humans is complex, making decisions about body temperature maintenance in the field can be difficult. This chapter is designed to aid in the decision process by providing a basic understanding of the relationships among the ambient thermal environment, thermal characteristics of the body, and physiologic systems that govern human thermoregulation. First, some overall concepts of temperature regulation are reviewed, as well as a way to conceptualize the system. Second, the range of normal body temperatures is covered, along with the consequences of higher and lower body temperatures. Third, methods and potential pitfalls of monitoring body temperature are outlined, after which the physical factors that affect heat flow are discussed. Fourth, the neuronal systems involved in processing thermal information (i.e., sensation, integration, and output) are reviewed, followed by a detailed description of the effector organ responses involved in the maintenance of thermal homeostasis. Last, modifications of thermoregulatory responses, induced alterations of the regulated temperature, and changes in the responsiveness as well as in the capabilities of the thermoregulatory system are noted. In this chapter, when values are given for "a person," they refer to a 70-kg (154-lb) man.

## CONCEPTUALIZING THE THERMOREGULATORY SYSTEM

Humans are homeotherms and as such are capable of maintaining a relatively constant body temperature across a wide range of ambient temperatures. Such constancy is attained through the use of behavioral processes that involve maintaining or searching for a preferable environment and physiologic (autonomic) processes such as dilation of the skin blood vessels, sweating in the heat, and shivering in the cold. Figure 6-1 provides an overview of this process.[38] Information about body temperature is integrated by central nervous system (CNS) structures, which elicit efferent neurogenic responses to correct any changes. Increases in body temperature elicit efferent neurogenic cutaneous vasodilation and sweating to increase heat dissipation. Conversely, decreases in body temperature elicit cutaneous vasoconstriction (decreased heat dissipation) and shivering (increased heat generation).

Figure 6-2 emphasizes how these responses are controlled—via negative feedback systems with a primary feed-forward input from skin sensors that monitor ambient temperature.[106] The feed-forward input from the skin allows for the elicitation of thermoregulatory responses without an "error signal" from the primary regulated variable, core body temperature.[148] Thus, core temperature can remain relatively constant under widely varying environmental conditions. This is particularly helpful in cold environments, where decreases in skin temperature can elicit substantial vasoconstriction and shivering before dangerous core hypothermia develops. In addition, without this feed-forward input, when large thermal stresses are encountered, greater deviations in core temperature would be necessary to elicit sufficient restorative responses.

Figure 6-3 illustrates some of the concepts that relate to the thermoregulatory system and are discussed in this chapter. Under normal conditions, body temperature is relatively constant over a range of ambient temperatures, as depicted by trace "a." The breadth of this range of ambient temperature is called the *range of normothermia*. The midpoint of this range can be conveniently called the *regulated temperature,* which is shown by the dot in trace "a." Toward the upper and lower ends of trace "a," the core temperature inflects up and down. These inflections represent ambient temperature extremes at which the regulation begins to fail. Altered core temperatures can also accrue when there are alterations in the regulated temperature. Such alterations could be caused by the presence of bacterial toxins (e.g., fever) or starvation, which would cause increases (trace "b") or decreases (trace "c") in the regulated temperature. In addition, under various conditions, the effector responses can become compromised, which leads to decreases in the ability to defend against low temperatures (dashed line at "d"). This could indicate a problem with metabolic stores, or high temperatures (dashed line at "e"), which may indicate dehydration. Various combinations of regulatory changes and altered effector responsiveness occur in conjunction with many threatening situations.

## BASICS OF CORE TEMPERATURE

Typical measurements of core temperature provide a good estimate of the temperature of critical internal organs and are quite stable across individuals. In a study that involved 700 observations of 148 healthy individuals,[131] 90% of the early-morning oral core temperature measurements were between 36.0°C (96.9°F) and 37.1°C (98.9°F). Core temperature is vigorously defended by the thermoregulatory system. At low environmental temperatures, regional heterothermy that results from peripheral vasoconstriction forms an important aspect of this defense. The lowered skin temperature decreases the thermal gradient from the skin to the environment and thus decreases heat loss. At cooler temperatures, there can be a large amount of peripheral tissue that is well below core temperature, which leads to a major decrease in the overall heat content of the body. A nude human resting at 35°C (95°F) or 20°C (68°F) exhibits similar temperatures at various locations within the core. However, because of decreased temperatures in the outer shell, a nude person resting at 20°C will have a total heat content that is about 200 kilocalories (kcal) lower than when resting at 35°C.[197] If the peripheral vessels were suddenly dilated, an immediate drop in core temperature of about 3.5°C (6.3°F) would result. Because of local and systemic influences of temperature on skin blood flow, this type of extensive vasodilation can happen in a wilderness medicine setting if a hypothermic individual is rapidly rewarmed using surface rewarming methods. In a hypothermic individual, the discrepancy between core and shell temperatures could be considerably greater and could result in a dangerous postdilation drop in core temperature. Such an extensive vasodilation would also result in a large drop in peripheral vascular resistance, which would put the individual at risk for dangerous hypotension. Therefore, such methods should be used with caution while carefully monitoring a patient's vital signs. A method for

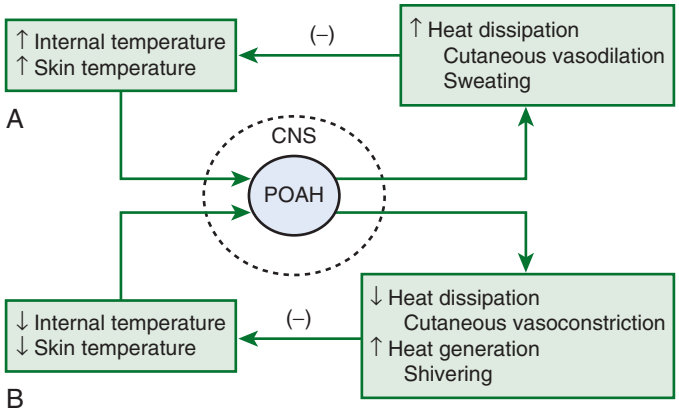



**FIGURE 6-1** Schematic overview of the integrative control of thermoregulation in humans. As shown at *A*, an increase in internal and/or skin temperature is relayed by neural signals to the central nervous system (CNS) nuclei involved in thermoregulation (primarily the preoptic area/anterior hypothalamus, POAH). This then elicits efferent neurogenic cutaneous vasodilation and sweating, which increases heat dissipation, minimizing further increases in body temperature. As shown at *B*, a decrease in internal and/or skin temperature is sensed by the CNS and results in increased cutaneous vasoconstriction (decreased heat dissipation) and shivering (increased heat generation). *(From Charkoudian N: Skin blood flow in adult human thermoregulation: How it works, when it does not, and why,* Mayo Clin Proc *78:603-612, 2003.)*

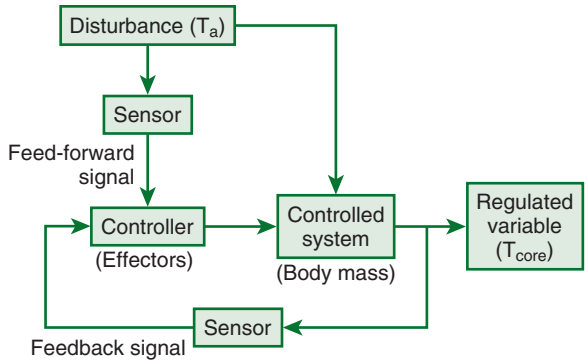



**FIGURE 6-2** Negative feedback system with feed-forward input from the main disturbance (ambient temperature), which decreases variation of the main regulated variable (core temperature). *(From Kanosue K, Crawshaw LI, Nagashima K, et al: Concepts to utilize in describing thermoregulation and neurophysiological evidence for how the system works,* Eur J Appl Physiol *109:5, 2010.)*

estimation of the potential drop in core temperature after peripheral vessel dilation is given in Estimating Mean Body Temperature, later.

A different type of heterothermy that occurs during hyperthermia in some species is known as "selective brain cooling." The idea is that, during severe heat stress, brain temperature can be maintained lower than the rest of body core temperature, thus protecting the brain from potential neuronal damage from excessively high temperatures. This phenomenon clearly exists in mammals with a carotid rete, where countercurrent heat exchange can cool the blood, which will then perfuse the brain.[138] Although humans do not possess a carotid rete, alternative mechanisms have been proposed as a basis for selective brain cooling. Existence of this phenomenon in humans has been vigorously debated for decades.[19,29,30,157,232] Recent, direct measurements of jugular venous temperature and calculations of thermal gradients in the areas perfusing the brain suggest that selective brain cooling is not a physiologically relevant phenomenon in humans during exercise or hyperthermic exposure,[158] although it may occur under certain, specialized "man-made" conditions, such as during surgery.[14]

Although an abnormal core temperature is often a signal that "something is wrong," it is not a very specific signal. A variety of conditions can lead to core hyperthermia or hypothermia. Under some circumstances, the central neural mechanisms that regulate body temperature may be defending an altered core temperature for reasons described later in this chapter. Alternatively, the thermal load posed by the environment or by heavy exercise may be too great for the capacity of the thermoregulatory effectors to dissipate heat. This is generally referred to as "uncompensable heat stress," whereas heat exposure in which body temperature can be regulated is referred to as "compensable." Finally, CNS control of body temperature could be deranged as a result of substance abuse, extreme temperatures, side effects of prescription drugs, or other factors. When interpreting a particular core temperature, it is important to evaluate all these alternatives. Accidents in the wilderness often involve many aspects of thermal balance being compromised, and an altered body temperature is likely.

## CONSEQUENCES OF ALTERED CORE TEMPERATURE

When tissue temperatures change, there are immediate and important effects on metabolism as well as on other physiologic mechanisms. This effect is characterized by an exponential equation, and for ease of comparison between different sensitivities to temperature change, the term $Q_{10}$ is typically used. $Q_{10}$ describes the factor by which a rate increases with a 10°C (18°F) increase in temperature. For example, with a 10°C (18°F) increase in tissue temperature, the metabolism of typical human tissue increases by a factor ($Q_{10}$) of about 2.7. The metabolic rate of the entire organism—apart from thermoregulatory responses—responds similarly. For temperature differences other than 10°C (18°F), these effects can be calculated with the following equation[197]:

$$R_2 = R_1 \times Q_{10}^{([T_2 - T_1]/10)}$$

where $R_2$ and $R_1$ are the two rates of physiologic response; $T_2$ and $T_1$ are the two temperatures; and $Q_{10}$ is the increase in rate caused by a 10°C (18°F) increase in temperature. Thus, if fever or strenuous exercise were to increase body temperature by 2°C (3.6°F), basal metabolic rate would be increased by 22%.

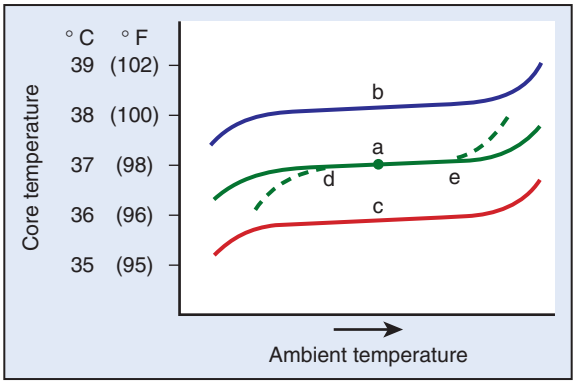



**FIGURE 6-3** Stylized diagram representing body temperature at different ambient temperatures. The relatively flat portion of the three traces *a*, *b*, and *c* represents the range of normothermia. Trace *a* represents regulation under normal conditions; traces *b* and c represent increased and decreased levels of regulation, respectively. Inflections at the trace extremes depict the ambient temperatures at which the effector responses are unable to compensate for the increased ambient thermal stress. The dashed traces *d* and *e* correspond with situations in which the effectors for cold defense and heat loss are compromised. *(Modified from Kanosue K, Crawshaw LI, Nagashima K, et al: Concepts to utilize in describing thermoregulation and neurophysiological evidence for how the system works,* Eur J Appl Physiol *109:5, 2010.)*

Within the normal range of body temperatures, higher temperatures favor speed at the expense of tissue resources, whereas lower temperatures conserve resources. Although both high and low temperature extremes pose a threat to humans, increased temperatures greatly accelerate the development of serious complications in many wilderness medical situations and therefore pose a much more immediate danger. A deviation of about 2°C (3.6°F) above or below normal core temperature is well tolerated by the various regulatory systems of the body, but a discrepancy of 3°C (5.4°F) begins to disrupt these systems, including those involved in temperature regulation. At this level of deviation, if there is no intervention, physiologic problems compound very rapidly.

Core hypothermia can also be dangerous to human survival and recovery from injury. Core temperatures of 34° to 36°C (93.2° to 96.9°F) disrupt many important physiologic functions, which, taken together, may significantly affect patient outcome. Such mild hypothermia impairs recovery from surgical procedures as a result of factors that include impaired peripheral blood flow and oxygen availability, increased possibility of cardiovascular complications, decreased antibody and cellular immune defenses, impaired coagulation, and increased metabolic expenditure for heat production.[59,70,118,123] In most situations, it is important to maintain the patient at normothermic levels.

Traumatic brain injury can be present in wilderness accidents, and it may be accompanied by unregulated hyperthermia. Heightened temperatures can exacerbate cerebral inflammation and lead to increased neuronal damage.[224] There is current interest in invoking mild hypothermia to minimize damage to the CNS after neurologic injury.[162] However, when this approach is used, care must be taken to deal with the side effects mentioned previously.[171]

# MONITORING TEMPERATURE OF THE CORE AND OTHER SITES

The overall status of the thermoregulatory system is determined by measuring the core temperature. This can be done at a number of sites with several types of instruments (i.e., thermometers). In the following paragraphs, the relative merits of locations and different types of thermometers are discussed.

## MONITORING THE CORE TEMPERATURE

A history of clinical thermometry is available,[130] as are good overviews of the assessment of core temperature.[12,36,245] Sites for measuring body temperature, in order of increasing invasiveness, include the forehead, axilla, oral cavity, tympanum, rectum, esophagus, bladder, and pulmonary artery. There is no clear-cut choice regarding the best site to monitor; particular situations demand different techniques. Thermometers that have been employed clinically include mercury-in-glass thermometers (which are now obsolete), electronic thermometers, tympanic radiation thermometers, and liquid-crystal thermometers. Whatever instrument is used should have an accuracy of ±0.1°C (0.2°F). The handheld electronic thermometer is a good choice for field emergencies.

## TYPES OF THERMOMETERS

The handheld electronic thermometer has replaced the mercury-in-glass thermometer, and it has been widely used for many years. Electronic thermometers can use thermistors or thermocouples as sensors, have the requisite degree of accuracy, and are flexible in application. Although an equilibration time of 1 minute is specified for the typical probe, this is largely because of the need for a stiff casing for ease of insertion; smaller probes are available that can equilibrate in seconds. The digital display of these instruments reduces errors, and the probes can be left in place for continuous monitoring. A quality instrument with a wide range of interchangeable probes is important. Even then, these devices are subject to the usual problems inherent with electronic instruments and rarely have a range low enough to monitor skin temperature in cold environments. A second electronic thermometer with a wide temperature range is important for measuring skin temperature, as a backup for the standard clinical thermometer, and for measuring the temperature of other objects such as liquids. Alternate probes and spare batteries for both instruments are essential.

Tympanic infrared (IR) radiometers are often used in hospital settings. However, even in this relatively predictable environment, some controversy exists regarding their ability to assess core temperature accurately.[160,179] These instruments monitor the electromagnetic radiation that emanates from the ear canal; various manufacturers make use of different and complicated electronic circuitry to produce a temperature display. An advantage is that the reading takes only a few seconds,[36] but questions remain regarding the overall accuracy of the measurement displayed. In a laboratory situation in which the auditory canal is plugged with a sponge and the probe measures only radiation that emanates from the tympanum, IR tympanic thermometry provides an excellent estimate of the core temperature.[203] In clinical settings, the results are less consistent. In one study, IR tympanic thermometry produced core temperatures that were much more variable than rectal temperatures. Even after correcting for the higher rectal values (0.5°C [0.9°F]), tympanic measurements still inaccurately displayed one-third of the temperatures that were more than 37.7°C (99°F). An extended training program did not significantly alter the accuracy of the readings.[170]

In one instance, a child who arrived at an emergency department (ED) presented with tachycardia and skin vasoconstriction. Separate tympanic IR thermometers gave core temperatures of 36.4° and 37.6°C (97.5° and 99.7°F); the rectal temperature was determined to be 42.2°C (108°F)[182]. Alternatively, in a hospital setting with a trained operator and immobile patients, two brands of IR tympanic thermometers produced readings that were closer to pulmonary artery readings than those obtained from the axilla or the rectum.[178]

The potential benefits of a continuous and easily applied core temperature monitor have led to repeated attempts to validate liquid-crystal thermometers, which are typically placed on the head or neck surface. Unfortunately, the temperature readings produced by this method are not reliable.[12,130] Because these measurements are compromised by the thermoregulatory vascular changes associated with heat conservation and heat dissipation and by changes in ambient temperature,[95] they are particularly unsuited for field emergency measurements.

## MEASUREMENT SITES

Although the deep internal temperatures of normothermic humans are reasonably similar, no specific anatomic site represents the "official" core temperature. The temperature at each location is a consequence of a combination of the local metabolic rate, local perfusion rate, proximity to the outer shell, and proximity to other locations that have differing rates of metabolism and perfusion. Nevertheless, because of the generally high overall rates of tissue perfusion in mammals, deep core temperatures rarely differ by more than 0.5°C (0.9°F). The temperature of the pulmonary artery is a good reference temperature for the overall status of the thermal core. At steady state, accepted sites for assessing core temperature differ with regard to varying amounts from this temperature. When carefully measured in a surgical or laboratory setting by trained personnel, esophageal and tympanic temperatures are essentially the same as the temperature of the pulmonary artery,[178,193] whereas rectal temperature averages about 0.4°C (0.7°F) lower, and axillary and oral temperatures are about 0.2°C (0.4°F) and 0.4°C (0.7°F) lower, respectively.[12,178]

Although esophageal temperature is somewhat difficult to obtain, this is the site that is most likely to reflect accurately the temperature of the pulmonary artery. Measurement at this location accurately follows changes in core temperature and is reasonably noninvasive. For placement, the probe is lubricated, and a small amount of local anesthetic is applied. It is then passed via a nasal passage into the distal portion of the esophagus to the level of the heart. The probe can be moved up and down

slightly to obtain the highest temperature. Although this procedure is routinely used in physiology experiments, it is somewhat unpleasant for conscious patients, particularly those with a strong gag reflex, and clearly inappropriate if airway problems are present. Esophageal temperature is affected by swallowing for about 30 seconds.

Tympanic temperature as an estimation of core temperature has long been controversial. Because the tympanic membrane is highly vascular and supplied by branches of the external and internal carotid arteries, it should be an ideal site. Nevertheless, many studies have indicated that tympanic temperature is affected by ambient temperature and local facial cooling.[193,223]

In steady-state conditions, rectal temperature is a good index of core temperature.[248] However, when the heat content of the body or of the internal thermal compartments is in flux, rectal temperature changes more slowly than temperatures measured in other commonly used sites.[178] There is a thermal gradient along the rectum, so all measurements should be made at a standard depth; 4 cm (1.6 inches) is recommended,[12] although in a careful study of different depths, sites less deep than 10 cm (4 inches) showed some systematic differences.[121] The higher temperatures recorded in this region may be caused by a combination of low perfusion rates, digestive reactions, and bacterial activity, but there is not clear evidence of this.[130] For assessing core temperature during outdoor exercise in the heat, the National Athletic Trainers' Association recommends using only rectal temperature.[33] A subsequent study and review of the literature also concluded that "rectal temperature is the only suitable and valid index for the monitoring of body temperature in a field setting."[73]

Oral (sublingual) temperature is an excellent index of core temperature, provided that the mouth is kept closed. The sublingual pocket is well perfused by blood flow and responds quite rapidly to alterations in core temperature. Mastication, smoking, fluid intake, and mouth breathing can affect sublingual temperature; these should be avoided during the period that immediately precedes the measurement.[12,130] The use of an electronic thermometer with a rapidly responding sensor makes this measurement considerably more accurate and rapid than when it is performed with a mercury-in-glass thermometer.

Although axillary temperature can reflect core temperature, it has a number of negative characteristics and should be used only as a last resort. Axillary temperature is affected by local blood flow as well as by thermal and nonthermal sweating.[12] Changes in core temperature are slow to affect the axillary temperature, and there is high interpatient variability.[178] However, this measurement has proved to be particularly useful for assessing core temperature in infants.[12,130]

## ESTIMATING MEAN BODY TEMPERATURE

Mean body temperature (MBT) provides a mass-weighted average of body tissue temperature and thus can be related to the heat content of the entire body. For a severely hypothermic patient, MBT provides a way to gauge the potential fall in core temperature (afterdrop) after vessel dilation caused by rapid surface warming. Traditionally, estimates of MBT have been made with the use of a formula that combines mean skin temperature and core temperature. Recently, the validity of such estimates was evaluated for patients undergoing various procedures, including cardiac surgery during extracorporeal circulation; these studies included core temperatures as low as 18.5°C (65.3°F).[122] "Peripheral compartment temperatures were estimated using fourth-order regression and integration over volume from 18 intramuscular needle thermocouples, 9 skin temperatures, and 'deep' hand and foot temperatures."[122] The authors concluded that the estimation of MBT from Burton's original formula[27] "is generally accurate and precise."[122] That formula is as follows:

$$\text{MBT} = 0.64\ (\text{Core temperature}) + 0.36\ (\text{Mean skin temperature})$$

Ramanathan[174] found that a reasonably accurate estimate of mean skin temperature could be provided by the temperature of the medial thigh, and that a very accurate estimate of mean skin temperature could be made by measuring and weighting the temperature of four skin sites as follows:

$$0.3\ \text{Chest} + 0.3\ \text{Arm} + 0.2\ \text{Thigh} + 0.2\ \text{Leg}$$

# PHYSICAL FACTORS THAT GOVERN HEAT EXCHANGE: THE HEAT BALANCE EQUATION

The physical laws that govern heat transfer determine the net energy flux into or out of the body.[49,85,142,151,197] The heat balance equation is a convenient method for partitioning and quantifying the flow of energy between the environment and the body. A high rate of metabolic heat production is critical for maintaining a constant body temperature in mammals. This is represented by total heat production ($H_{tot}$) on the left side of the following equation. For a person whose body is at thermal equilibrium, the equation is balanced and given as follows:

$$H_{tot} = \pm H_d \pm H_c \pm H_r \pm H_e$$

where $H_{tot}$ is the total metabolic heat production; $H_d$ is the conductive heat exchange; $H_c$ is the convective heat exchange; $H_r$ is the radiative heat exchange; and $H_e$ is the evaporative heat exchange. $H_{tot}$ is always positive. The various modes of heat exchange from the right side of the equation can be positive or negative, depending on the situation. Positive values refer to net heat loss from the body. If the equation does not balance, the body either loses or gains heat. When the sum of the net heat exchange through the various channels exceeds $H_{tot}$, heat content of the body will decrease, and MBT will fall. Alternatively, if $H_{tot}$ is greater than the net heat exchange, heat content of the body will increase, and MBT will rise.

## CONDUCTIVE HEAT EXCHANGE

Heat transfer between objects that are in direct contact is called *conduction* ($H_d$). The direction of heat flow is always from the higher to the lower temperature. Because conduction involves a direct interaction (i.e., contact) between molecules, this type of heat transfer is minimal except under certain circumstances, such as when sitting on a cold rock with little insulation. Under such conditions, the heat lost to the rock would be similar to that lost from the remainder of the body surface by radiation and convection. Adequate insulation should be placed under patients who are in contact with hot or cold substrates. The equation that governs heat exchange by conduction follows:

$$H_d = \frac{kA(T_{sk} - T_a)}{L}$$

where k is thermal conductivity; A is the area of contact; $T_{sk}$ is the skin temperature; $T_a$ is the ambient temperature; and L is the distance between the two surfaces.[143]

The thermal conductivity of several substances is given in Table 6-1. Note that water has 25 times the conductivity of air

**TABLE 6-1 Thermal Characteristics of Select Substances**

| Substance | Conductivity (cal • $s^{-1}$ • $cm^{-1}$ • $°C^{-1}$) | Specific Heat (cal • $g^{-1}$ • $°C^{-1}$) | Volumetric Heat Capacity (cal • $L^{-1}$ • $°C^{-1}$) |
|---|---|---|---|
| Air | 0.000057 | 0.24 | 0.29 |
| Water | 0.0014 | 1.0 | 1000 |
| Granite | 0.007 | 0.2 | 540 |
| Muscle tissue | 0.0011 | 0.8 | 850 |
| Fat tissue | 0.00051 | 0.5 | 460 |

Data from Schmidt-Nielsen K: *Animal physiology: Adaptation and environment*, ed 4, Cambridge, 1990, Cambridge University Press; Cossins AR, Bowler K: *Temperature biology of animals*, New York, 1987, Chapman & Hall; and Hodgman CD, editor: *Handbook of chemistry and physics: A ready-reference book of chemical and physical data*, ed 43, Cleveland, 1962, Chemical Rubber.

but only one-fifth that of granite. Muscle tissue has about twice the conductivity of fat tissue. The conduction of heat through a tissue is called *thermal diffusivity*. This expression is obtained by dividing the thermal conductivity by the product of the density and the specific heat. The specific heat of various substances is also given in Table 6-1. Water has particularly high specific heat, as does muscle tissue, which consists mostly of water. However, specific heats can be misleading, so volumetric heat capacities are also listed in Table 6-1. Although the specific heat of water is four times that of air, it takes about 3500 times as much heat to raise the temperature of a given volume of water by 1°C (1.8°F) as it does to accomplish the same feat with a similar volume of air. For a person in the water, the consequence of these properties is that skin temperature is almost always within 1°C of water temperature, and heat transfer to or from the environment is greatly facilitated. In cool water during rest, skin blood flow is minimized as a result of peripheral vasoconstriction. Heat loss is importantly determined by the subcutaneous fat layer; an average-size fat person with 36% body fat by weight begins shivering at a water temperature of about 27°C (81°F), whereas a lean person with less than 10% body fat starts shivering at about 33°C (91°F).[153]

## CONVECTIVE HEAT EXCHANGE

Convection ($H_c$) can be seen as the facilitation of conduction caused by the movement of molecules in a gas or liquid. This movement decreases the functional value of L, which is the denominator in the conduction equation. Convection can be either forced or natural (free). Forced convection results from gas or liquid movement caused by the application of an external force, such as the movement of a fan or the pumping of a heart. Natural convection results from density changes that are produced by heating or cooling molecules adjacent to the body. These density changes cause the molecules to move with respect to the body surface. For humans, natural convection predominates at air speeds of less than 0.2 m/sec (0.7 ft/sec), whereas forced convection is more important at greater air speeds.[142]

The relationships that define heat exchange as a result of convection can be complicated. They depend on surface temperature profiles, surface shape, flow dynamics, density, conductivity, and specific heat. Any factor that impedes the movement of the boundary layer (i.e., the molecules immediately adjacent to the body) greatly impairs convective heat transfer.

Brengelmann and Brown[20] have noted that, under relatively neutral conditions ($T_a$ = 29°C [84.2°F], wind velocity = 0.9 m/sec [3 ft/sec]), about 40% of heat loss from a nude human is mediated by convection. Increases in air or fluid velocity greatly increase convective heat transfer. Fanning a minimally clothed patient will greatly augment heat loss in a cool environment.

## RADIATIVE HEAT EXCHANGE

All objects at temperatures of more than absolute zero emit electromagnetic radiation. This energy transfer occurs through space and does not require an intervening medium. In any given situation, the object is both transmitting and receiving IR thermal radiation. In some cases, the object also receives solar radiation. The net heat transfer depends on the absolute temperatures, nature of the surfaces involved, and solar input. Surfaces that are effective absorbers of radiation are also effective emitters of radiation. The idealized "black body" illustrates this property; such bodies absorb all and reflect none of the incident radiation. Conversely, poor absorbers (e.g., a polished silver surface) are also poor emitters. Heat transfer that results from IR (first-term) radiation and solar (second-term) radiation is given by the following equation:

$$H_r = \sigma e_{sk} e_a (T_{sk}^4 - T_a^4) + a(1 + r)s$$

where $H_r$ is the radiative heat exchange; $\sigma$ is the Stefan-Boltzmann proportionality constant; $e_{sk}$ is the emissivity of the skin; $e_a$ is the emissivity of the environment; $T_{sk}$ is the skin temperature (given in kelvins [K]); $T_a$ is the ambient temperature (given in K); a is the absorptance; r is the reflectance; and s is the solar radiation.

For temperatures in the physiologic range and where ($T_{sk} - T_a$) is less than 20°C (68.0°F), several authors have noted that IR radiation heat exchange is about proportional to $T_{sk} - T_a$.[18,197] Also, the spectrum of emitted radiation depends on the temperature of the object. At physiologic temperatures, the predominant wavelengths of emitted radiation are longer (IR), whereas at higher temperatures (e.g., the sun's surface), the predominant wavelengths are shorter (visible radiation) and can be detected by the human eye. This difference leads to some important consequences. The middle IR radiation that is emitted by mammals is maximal, regardless of skin pigmentation or the color of clothing. However, solar radiation peaks in the visible portion of the spectrum and is differentially absorbed. In other words, dark clothes absorb more heat from solar radiation than do light clothes, but both types emit similar amounts of radiation energy.

Incident radiation can vary drastically under different environmental conditions and may severely tax the body's ability to respond. Heat input from solar radiation on a cloudless day may exceed by several times the heat produced by basal metabolism; on a cloudless night, there can be a significant net loss of radiation to the sky. Under the relatively thermoneutral conditions noted earlier,[20] radiant heat loss accounts for about 45% of the total heat loss.

## EVAPORATIVE HEAT EXCHANGE

When water changes state, a large amount of energy is either absorbed or given off. Evaporation of 1 gram (0.035 oz) of water at 35°C (95.0°F), which is the usual skin temperature of a person who is sweating,[197] requires the input of 0.58 kcal of thermal energy. In the field the preferred cooling measure is to splash water on the patient, coupled with air fanning.[81] Heat absorbed by the evaporation of 100 cc of water will lower body temperature by about 1°C (1.8°F). In a neutral thermal environment, active thermoregulatory sweating does not occur, and evaporation accounts for only 15% of the total heat loss. Of this, slightly more than one-half is the result of evaporation from the respiratory tract, with the remainder coming from water that passively diffuses through the skin and evaporates.[20]

Although it is unusual, the evaporation term ($H_e$) of the heat balance equation can become negative, which means that heat is being introduced into the body. This occurs during airway rewarming, when water-saturated oxygen is introduced into the respiratory system at about 43°C (109.4°F). Because the patient's body is considerably colder than 43°C, water condenses in the airways. For every gram (g) of liquid water that is formed, the body heat content increases by 0.58 kcal; the formation of 100 g of liquid will increase body temperature by about 1°C.

# THERMOREGULATORY NETWORK

A regulatory system requires sensing the controlled variable, comparing it with an ideal value, and producing an appropriate output signal. The following sections outline the role of the nervous system in maintenance of a stable body temperature.

## PERIPHERAL THERMAL SENSORS

The entire outer surface of the body (i.e., the skin) is well supplied with sensitive thermoreceptive structures. Because one destination of the output of these thermoreceptors is the sensory cortex, many properties of the receptors can be gleaned from direct experience. Afferent thermal information produces both hot and cold sensations, and the cutaneous thermoreceptors demonstrate substantial dynamic sensitivity.[9,88] Therefore, a change in ambient temperature can be perceived as "cool" or "warm" simply because of a change from a previous steady level of temperature (e.g., moving from a warm room to a cooler room), even if the absolute temperature is not objectively "cool."[9] In addition to cortical input that arrives via the medial lemniscus and the ventrobasal thalamus, the brain receives a large amount of thermal information from pathways that synapse in the reticular area.[24] Although cortical thermal input is part of the sensory information used to reconstruct the external thermal

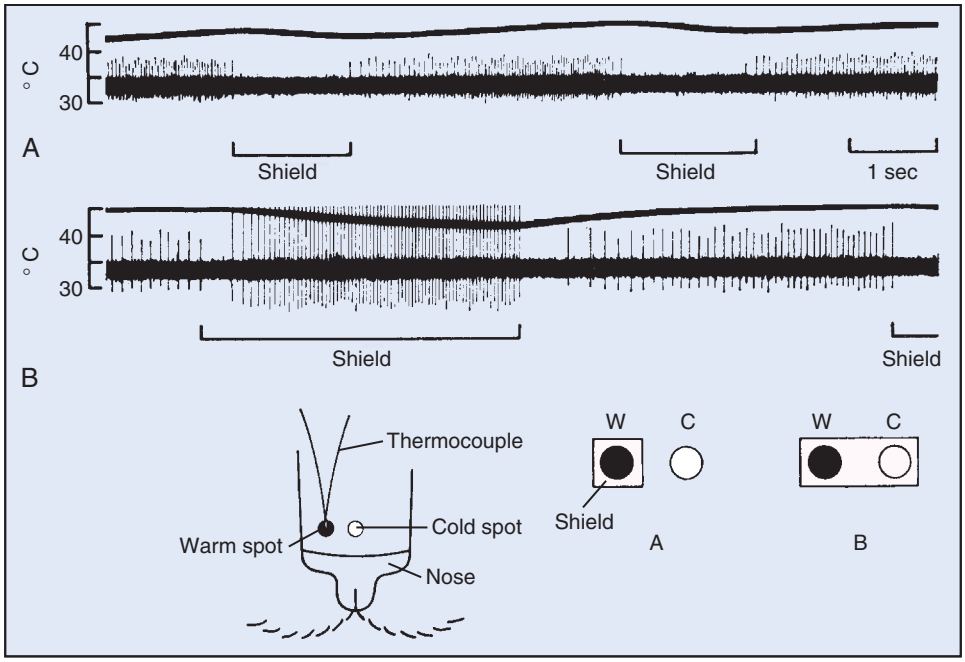



**FIGURE 6-4** Impulses from a recording that includes a single warm fiber and a single cold fiber. **A,** In this recording, a shield was periodically placed in front of and then moved away from the skin site that was innervated by the warm fiber. The discharge stops immediately when the skin is shielded from the radiation source. **B,** In this recording, the shield was simultaneously placed in front of the skin site innervated by both the warm fiber and the cold fiber. This caused excitation of the cold fiber and inhibition of the warm fiber. *(From Hensel H, Kenshalo DR: Warm receptors in the nasal region of cats,* J Physiol [Lond] *204:99, 1969.)*

environment, reticular input is more important for behavioral and autonomic regulation of body temperature.[55]

The structure, location, and properties of peripheral thermoreceptors are well documented. Thermal sensors are free nerve endings and are categorized as warm or cold. Cold receptors are found immediately beneath the epidermis, whereas warm receptors are located slightly deeper in the dermis. The hallmark of both types of receptors is their extremely high rate sensitivity (Figure 6-4). Although the static firing rate of cold receptors is usually less than 10 impulses per second, under conditions of rapid temperature change, firing rates are often higher by an order of magnitude. Cold receptors are excited by cooling and inhibited by warming, and they have static maxima at about 25°C (77.0°F); these receptors are active from about 10°C (50.0°F) to 40°C (104.0°F). Warm receptors are excited by warming and inhibited by cooling, and they have static maxima at more than 40°C; they are active from about 30°C (86.0°F) to 45°C (113.0°F). At both ends of the spectrum, more extreme temperatures activate neuronal responses that are subjectively reported as "cold pain" and "warm pain."[87]

Over the past two decades, work with the use of cloning and ion channel characterization has provided insight into molecular mechanisms of central and peripheral temperature transduction. A family of related temperature-activated transient receptor potential (TRP) ion channels is highly sensitive to temperature.[35] Although originally identified in the context of noxious heat sensation, TRP channels have been found to be ubiquitous and have multiple roles in cardiovascular, metabolic, volume regulatory, and many other integrative physiologic mechanisms.[61,246]

In terms of thermal sensation, the cloned receptors TRPV3 and TRPV4 respond over a range similar to that of the warm receptors previously described,[80] whereas TRPM8 responds similarly to the cool receptors. TRPM8 also responds to menthol, eucalyptol, and icillin.[136,169] TRPV1, TRPV2, and TRPA1 respond similarly to the heat-pain–sensitive and cold-pain–sensitive neurons. The heat-pain channels (vanilloid receptor 1 [VR1]) also respond to low pH, ethanol, and capsaicin, which is the active ingredient in hot peppers.[167] In human skin circulation, the TRPV receptors appear to be involved in local thermal vasodilation (below the pain threshold), because stimulation of these receptors with local application of capsaicin shifts thermal responsiveness of the local cutaneous vasodilator response.[214] However, neurogenic vasodilation in response to whole-body heating does not appear to be affected by acute or chronic local capsaicin treatment.[39] TRP channels are also involved in activation of brown adipose tissue thermogenesis during cold exposure, and as such have been proposed as a target for weight loss with capsaicin or capsaicin derivatives.[243] As examples of the ubiquitous, integrative nature of TRP superfamily, TRPM2, TRPM4, and TRPM5 respond to warm temperatures and are also involved in insulin secretion[226] and taste.[220] However, they are not regarded as warm receptors for thermal sensation, because sensory neurons do not appear to express those subtypes. In addition to TRP channels, some members of the TREK/TRAAK K(2P) potassium channel subfamily also appear to be involved in warmth and cold perception.[7,125,155]

Psychophysical and physiologic studies indicate that thermal receptors are not uniformly distributed across the body surface and that there are many more cold receptors.[87] Cold receptors are abundant in the face and trunk areas, especially in the lips; however, they are less numerous in the feet and lower legs. The face and fingers have a greater number of receptors that respond to warmth.[176,219] Threshold temperature for the perception of thermal sensation follows the anatomic distribution and is not uniform across the body. The face, particularly near the mouth, is exquisitely sensitive because of a high density of thermal receptors, whereas by comparison the extremities have a lower density of receptors and therefore poor sensitivity. Other regions of the body are intermediate in sensitivity.[217]

Because peripheral thermal input is intimately involved in regulation of body temperature, heating and cooling different body sites can differentially affect the magnitude of the restorative physiologic response produced. In one study, cooling the forehead was found to be more than three times as effective (per unit area) for decreasing ongoing sweating as cooling the lower leg.[53] Another study evaluated regional trunk and appendage

sensitivity to cooling by assessing the magnitude of the gasping response that occurs at the onset of immersion.[26] In this case, exposing various parts of the body to water at 15°C (59.0°F) indicated that the upper torso had the greatest cold receptor density or sensitivity (or both). The lower torso was somewhat less sensitive, with the arms and legs exhibiting similar but considerably lower sensitivity.

## CENTRAL THERMAL SENSORS

Many sites within the body are capable of eliciting generalized thermoregulatory responses. Such areas include the abdominal viscera, spinal cord, hypothalamus, and lower portions of the brainstem.[16,85] The specific mechanisms by which heating or cooling these areas elicits thermoregulatory responses are incompletely understood. Although some central nuclei contain neurons that are clearly temperature sensitive,[15,17] responses in other areas may result from modulation of synaptic connections rather than from stimulation of neurons that change their firing rate in response to temperature. Input from central, temperature-sensitive neurons is not rate sensitive; rather, it is a direct reflection of the absolute temperature.[15,17] The area that has the highest thermal sensitivity and has received the most experimental attention is the preoptic area/anterior hypothalamus (POAH). Heating or cooling this portion of the brainstem elicits the entire array of autonomic and behavioral heat loss and heat gain responses, respectively.[84] Neurons in this portion of the brain exhibit both warm sensitivity and cold sensitivity.[15,16] Data from hypothalamic slice preparations with the use of synaptic blockers indicate that warm sensitivity may be an inherent property of some of the POAH neurons, whereas cold sensitivity in this area of the brain requires synaptic input.[15,16,57]

Figure 6-5 illustrates the effects of temperature on the firing rates of three representative types of hypothalamic neurons. The high level of temperature sensitivity shown by one of the cells (labeled *C*) results from the temperature-dependent characteristic of the prepotential. Voltage-clamp experiments indicate that the altered rate of depolarization is most likely the result of an effect on hyperpolarizing ($K^+$) conductances.[79] Work involving the use of hypothalamic slices has also established that about one-half of the thermosensitive neurons also respond to nonthermal stimuli, such as osmotic pressure, glucose concentration, and steroid hormone concentration.[205] Such neurons could form the basis for the interactions between the homeostatic systems described later in this chapter.

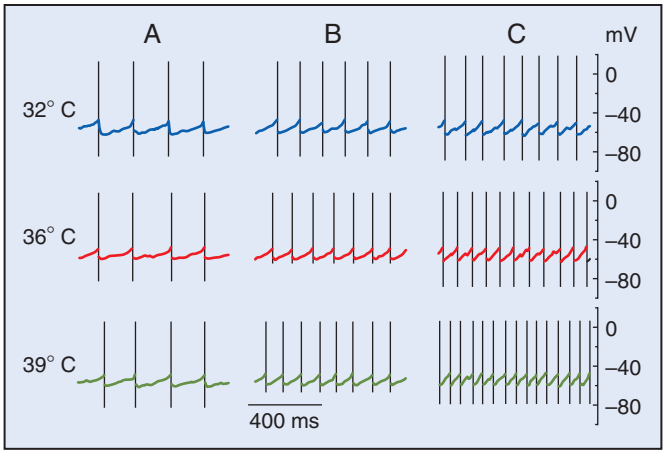



**FIGURE 6-5** Effects of temperature on the activity of three different types of hypothalamic neurons. **A,** Low-slope temperature-insensitive neuron. **B,** Moderate-slope temperature-insensitive neuron. **C,** Warm-sensitive neuron. The thermosensitivity in each case was 0.06 **(A),** 0.5 **(B),** and 1.1 impulses $s^{-1} \bullet °C^{-1}$ **(C).** All three types of neurons displayed depolarizing prepotentials, and action potentials occurred when the prepotentials reached threshold. As exemplified in **C,** putative post-synaptic potentials (especially inhibitory ones) were often observed in all neuronal types. *(From Griffin JD, Kaple ML, Chow AR, et al: Cellular mechanisms for neuronal thermosensitivity in the rat hypothalamus,* J Physiol *492:231, 1996.)*

Figure 6-6 illustrates the response of a warm-sensitive POAH neuron in a slice preparation. This cell is excited by increased temperature, low glucose, or increased osmotic pressure.[17] Because TRPV protein expression has been detected in the POAH, it was proposed that the TRPV channels may underlie the

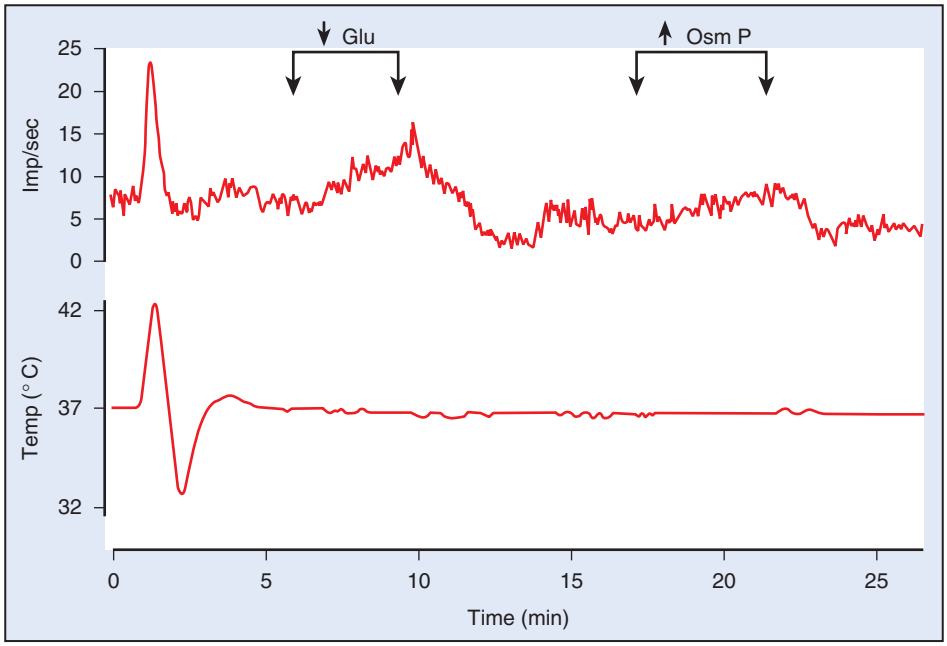



**FIGURE 6-6** Response of a warm-sensitive preoptic nucleus–anterior hypothalamic area neuron to changes in temperature, glucose concentration, and osmotic pressure. *Downward arrows* indicate media changes. *(From Boulant JA, Silva NL: Neuronal sensitivities in preoptic tissue slices: Interactions among homeostatic systems,* Brain Res Bull *20:871, 1988.)*

thermosensitivity found in POAH neurons,[167] and that both TRPV1 and TRPV2 channels may be active within the physiologic range of temperature.[109,172] However, some evidence is contrary to the proposal of TRPV1 as a thermosensor.[181]

## CENTRAL NEURAL STRUCTURES RESPONSIBLE FOR CONTROLLING THE LEVEL OF BODY TEMPERATURE

As mentioned previously, the brain is capable of accurately regulating body temperature under a wide range of conditions. Although almost all portions of the CNS can potentially be involved, the most critical neuroanatomic structures for thermoregulation include the spinal cord, brainstem, hypothalamus, and septum. The preoptic area and anterior hypothalamus are particularly important for both integration and sensing of internal temperature.[15,17,84] Recent advances in neurophysiologic, neuroanatomic, and imaging techniques have been used to extend our understanding of the systems involved in regulation of body temperature.[139,140,244] In this context, the median preoptic nucleus, medullary raphe region, and dorsomedial hypothalamus have been identified as important areas for integration of thermoregulatory signals with cardiovascular, volume regulatory, and other related physiologic systems.[134,137,148] Other notable advances include demonstration of the relative independence of populations of neurons that control separate effector systems[107,135,247] and elucidation of a pathway that conveys cold-sensitive afferent (feed-forward) information to the hypothalamus.[149]

Figure 6-7 presents a schematic model for regulation of body temperature, with credit to many others in the field besides the authors listed. For ease of understanding, many aspects of the system's complexity have been simplified or modified. The multiple inputs to this system not shown include those mentioned in the previous discussion of central thermoreceptors (e.g.,

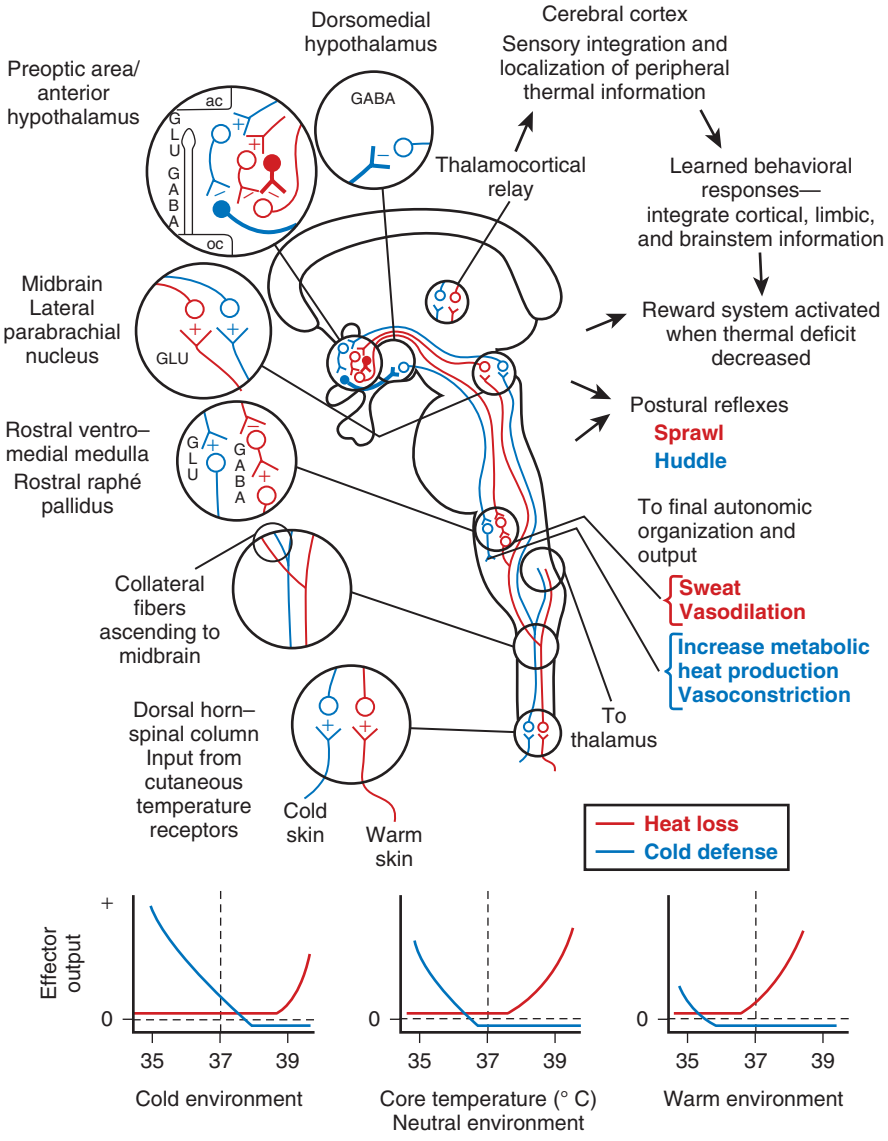



**FIGURE 6-7** Simplified schematic diagram of the basic parts of the nervous system responsible for regulating internal body temperature. Details of how this system functions are given in the text. *ac,* Anterior commissure; *GLU,* glutaminergic synapse; *GABA,* GABAergic synapse (GABA, γ-aminobutyric acid); *oc,* optic chiasm. *(Anatomic, neurophysiologic, and conceptual concepts represented in this image are from Boulant JA: Neuronal basis of Hammel's model for set-point thermoregulation,* J Appl Physiol *100:1347, 2006; Hammel HT: Regulation of internal body temperature,* Annu Rev Physiol *30:641, 1968; and Morrison SF, Nakamura K, Madden CJ: Central control of thermogenesis in mammals,* Exp Physiol *93:773, 2008. These articles should be consulted for a more rigorous explanation of the details of the thermoregulatory system.)*

glucose concentration, osmotic pressure) as well as factors covered later in this chapter (e.g., time of day, hormone levels, pyrogen titer, oxygen concentration of blood). In addition, thermoreceptors from many locations in the body provide input to this system. The key sensing elements of Figure 6-7 involve the peripheral warm and cold receptors and the central thermodetectors, the latter depicted by solid cell bodies and bold axons. Peripheral input originates in the skin and enters the CNS via the spinal or trigeminal dorsal horns; this information ascends to both the midbrain and the thalamus. The thalamic neurons that receive thermal information project to the sensory cortex and subserve sensory integration and localization of peripheral thermal information. They are also likely involved to some degree in learned behavioral thermoregulatory responses.

Thermal afferent pathways reaching the midbrain are involved in the feed-forward aspect of regulation.[149] Axons of the cell bodies in the midbrain synapse on cells in the midline subregion of the preoptic area. These preoptic cells receive excitatory input from peripheral warm and cold sensors, but they inhibit the cells on which they synapse. The systems that subserve heat loss and cold defense appear to inhibit each other reciprocally and receive output from a unitary integrating system. However, as mentioned previously, the systems are actually functionally separate to a large degree. In the schema of Figure 6-7, both systems depend on inherently warm-sensitive cells that have a high spontaneous firing rate at normal body temperatures. These cells inhibit the succeeding neurons, but the connections are such that, in a cold environment or when the body temperature is below normal, cold defense responses are disinhibited and heat loss responses are further suppressed. The opposite would occur in a warm environment or when the body becomes excessively hot.

The output of these systems under different conditions is illustrated in the panels below the neuroanatomic diagram of Figure 6-7. The middle graph illustrates the situation for a person with a body temperature of 37°C (98.6°F) in a thermoneutral environment. At 37°C, both systems are inhibited, and there is no effector response. If the body cools or becomes warmer, the inherently temperature-sensitive neurons disinhibit either the cold defense or the heat loss system. The graph on the left illustrates the action of the feed-forward cold neurons in a cold environment. Although the inherently thermosensitive neurons do not change their firing rate as a result of a local temperature that stays constant, input from the peripheral cold-sensitive pathway disinhibits the cold defense system. A similar situation—but in reverse—occurs when a person encounters a warm environment; this situation is depicted in the right graph. The error signal or output driving force is shown as the difference between the horizontal dashed line and the effector output at a given body temperature. The system is extremely accurate, and the error signal created by peripheral feed-forward input is usually just sufficient to counteract the sensed disturbance and to maintain body temperature at a constant level.

In addition to autonomic responses that are organized and transmitted from the brainstem (e.g., sweating, shivering), various complex whole-animal responses are also activated by the thermoregulatory system. Postural reflexes (e.g., huddling, sprawling) and learned behavioral thermoregulatory responses are initiated by cold and warm error signals. Although the mechanism is not entirely understood, appropriate behavior reduces the error signal and activates the reward system, which likely culminates in the release of dopamine in the nucleus accumbens of the septum by cell bodies located in the ventral midbrain.[96]

# EFFECTOR RESPONSES

## VASCULAR ADJUSTMENTS

Cardiovascular responses to thermal stress are largely geared toward changing blood flow to the skin surface, thereby increasing or decreasing convective heat transfer to the skin and to the external environment, as appropriate for the internal and external thermal environments.[20,37,38,101] In general terms, an important function of the circulatory system is to maintain a relatively homogeneous internal body temperature. Heat from metabolically active organs is convectively distributed to portions of the body where less heat is produced. More frequently appreciated are alterations of blood flow patterns that increase or decrease the overall thermal conductivity of the body during exposure to hot or cold environments, respectively. Some of these alterations in conductivity result from the preferential shunting of peripheral blood flow superficial or deep relative to the subcutaneous fat layer. Fat has about one-half the tissue conductivity of muscle and typically has a much lower rate of blood perfusion. Nevertheless, shunting blood away from major portions of the body is at least as important for determining overall conductivity as the conductive property of the tissue itself. For example, during immersion in cold water, muscle accounts for about 90% of the total tissue insulation of the forearm.[60] Thus, directing blood away from poorly insulated (and more highly conductive) regions reduces heat loss and preserves core temperature.

The cutaneous microcirculation is the primary circulation responsible for controlling heat transfer to the environment.[37,38,101] Microcirculatory units contain capillaries, arterioles, venules, metarterioles, and arteriovenous anastomoses (AVAs). The skin has a compliant vascular bed, with the majority of cutaneous blood volume contained in a plexus of veins just under the surface. The slow linear velocity of flow in this venous plexus allows for substantial heat transfer to occur between the skin and environment, particularly when skin blood flow is elevated.[186]

The major systemic neural control of skin blood flow occurs through two branches of the sympathetic nervous system: noradrenergic vasoconstrictor nerves and a non-noradrenergic active vasodilator system.[37,101] The vasoconstrictor system exhibits tonic activity and is responsible for most of the smaller, daily changes in skin blood flow that occur during minor changes in environment or activity.[194] This system is also responsible for the dramatic decreases in skin blood flow that occur with cold exposure, when skin blood flow can approach zero. Vasoconstrictor nerves release norepinephrine, which interacts primarily on the vascular smooth muscle with $\alpha_1$- and $\alpha_2$-adrenergic receptors to cause vasoconstriction. Glabrous skin (i.e., palms, lips, soles) contains numerous AVAs and is innervated only by sympathetic vasoconstrictor fibers. Therefore, all the dramatic changes in skin blood flow that can occur in these regions are controlled by changes in vasoconstrictor neural activity.

Nonglabrous (i.e., hairy) skin is innervated by sympathetic vasoconstrictor and vasodilator fibers and contains few AVAs. In contrast to the vasoconstrictor system, the active vasodilator system in human skin does not exhibit tonic activity and is only activated during increases in internal temperature. The vasodilator system operates through cholinergic nerve co-transmission. Although several candidate vasodilators have been studied, the specific vasodilator substance has not been identified; vasoactive intestinal polypeptide is a likely candidate.[8,235] Additionally, nitric oxide has an important role in active vasodilation, contributing about 30% to the total neurogenic vasodilation seen during whole-body heat stress.[111,112] Active vasodilation accounts for 80% to 90% of the increases in skin blood flow during heat stress, with about 10% to 20% caused by withdrawal of tonic activity of vasoconstrictor nerves.[101] Thermoregulatory vasodilation can result in skin blood flow values up to 8 L/min and 60% of cardiac output, making the skin circulation extremely relevant to systemic hemodynamics, particularly during severe heat stress.[37,186]

Cutaneous vascular responses to temperature are affected by excessive exposure to ultraviolet B (UVB) radiation. Moderate sunburn impairs the vasoconstrictor response to cold; an associated uncontrolled increase in thermal conduction is still present 1 week after exposure, although the original erythema will have disappeared.[164]

### CENTRAL SIGNAL

Vascular changes are bioenergetically the least costly thermoregulatory autonomic effector response. Because of the high sensitivity of the vasomotor system, ambient temperatures between the thresholds for sweating and shivering are often referred to as being in the zone of vasomotor regulation, or the "neutral zone" of human temperature regulation.[194] In dogs,

manipulation of hypothalamic temperature in this range confirms a high level of vasomotor activity between the thresholds for the activation of panting and shivering.[86] Within the vasomotor zone (i.e., skin temperatures of 33° to 35°C [91.5° to 95.1°F]), core and skin temperatures linearly combine to control skin blood flow. Skin blood flow responds accurately and rapidly to changes in skin temperature, which leads to a very stable core temperature.[21,194]

Although most peripheral arterioles are well supplied with adrenergic receptors, thermoregulatory innervation is not homogeneously distributed. For example, the density of thermosensory innervation in the lips, ears, and distal extremities is higher than in other areas; immersing the feet in cold water thus leads to marked vasoconstriction in the hands and forearms, but not in the abdomen or upper arms.[78]

### LOCAL MODULATION

In addition to systemic (whole-body) stimuli that elicit cutaneous vasoconstriction and vasodilation through changes in whole-body temperature, local temperature of the skin can substantially change skin blood flow through local mechanisms that do not require intact neural input.[101] Local warming of the skin elicits substantial, rapid vasodilation and can cause maximal vasodilation when temperature is held at 42° to 44° C for 25 to 30 minutes. This local warming response occurs in two phases: an initial peak that occurs within the first few minutes of heating and that depends on local sensory innervation, and a slower, prolonged phase that reaches a plateau at 25 to 30 minutes. The plateau phase of vasodilation largely depends on nitric oxide (40% to 70%, depending on the population studied).[37,101]

Local cooling can decrease superficial cutaneous blood flow to almost zero.[38,101] Although vascular beds on the skin surface constrict in response to cooling, other vascular beds dilate when cooled.[66,67] The specific response to cold shown by cutaneous vessels follows from the observed distribution and properties of the α-adrenergic vascular receptors. Local temperature affects the $\alpha_2$- and $\alpha_1$-adrenergic receptors in a reciprocal manner. Although cooling augments the response of the $\alpha_2$-receptors, it either inhibits or does not affect the response of the $\alpha_1$-receptors.[46,67] Although initial work was done on canine vessels, subsequent studies that involved α-adrenergic agonists and antagonists have demonstrated that a similar mechanism exists in human fingers.[62,67]

The responsiveness of cutaneous blood vessels is diminished in people with type 2 diabetes mellitus, both in terms of local responses to temperature and responses to whole-body heating,[208,209] resulting in impaired ability to thermoregulate in the heat. The increased incidence of type 2 diabetes among the general population may therefore presage a greater number of patients exhibiting severe hyperthermia.[38]

## EVAPORATIVE COOLING

At high workloads and at environmental temperatures approaching 37°C (98.6°F), the only way to maintain thermal balance is to augment evaporative cooling by activating the eccrine sweat glands. This sympathetic, cholinergically innervated organ system is spread over the entire body surface, but it is more profuse in some areas than in others. A person who is acclimatized to heat can sustainably produce as much as 1 to 2 L of sweat per hour.[2] High rates of sweating occur on the forehead, neck, anterior and posterior portions of the trunk, and dorsal surfaces of the hands and forearms. Lower rates occur on the medial femoral regions, lateral trunk areas, and palms and soles.[151] Sweat is secreted in these latter two areas in response to a combination of stimuli, including both nonthermal (emotional, exercise) and thermal inputs.[20,187] Because sweating is cholinergically mediated, it can be completely abolished by atropine. Sweat gland activity interacts with the regional vasculature; metabolic products of active sweat glands increase blood flow in areas of active sweating. In well-hydrated individuals, the degree of anhidrosis is correlated with the severity of generalized autonomic failure.[78,128] Several reviews discuss the many aspects of sweating disorders.[44,128,213,229]

### CENTRAL SIGNAL

By controlling the local milieu at different skin sites, it has been possible to separate the central thermoregulatory drive to sweat glands from local effects on the glands themselves. The central thermoregulatory system provides a proportional output that is influenced by both internal and whole-body skin temperatures. Per each degree increase above thermoneutral values, internal temperature is about 10 times as important as mean skin temperature for eliciting an output to the sweat glands.[144,146]

### LOCAL MODULATION

Local effects are also important for determining the output of sweat glands. Sweat gland temperature exerts a multiplicative effect on sweat secretion; the $Q_{10}$ for this augmentation is about 3.70. In addition, skin wetness has an important local effect on sweat glands; the wetter the skin, the greater the suppression of sweating.[145]

Moderate sunburn disrupts evaporative cooling. This effect is locally mediated and involves decreases in both responsiveness and capacity of the sweat glands.[163]

## METABOLIC ADJUSTMENTS

Heat is an inevitable byproduct of the inefficiencies of the body's metabolic reactions. When oxidizing foodstuffs to carbon dioxide and water during production and transport of adenosine triphosphate (ATP) to the functional systems of the cells, about 75% of the original chemical potential energy is given off as heat. With the exception of chemical energy sources that are excreted or used to perform physical work, the remaining 25% of the original energy is also converted to heat when ATP is used in the numerous metabolic reactions of the body.[198] Mammals, compared with poikilotherms such as reptiles or fish, use much more ATP to maintain ionic and electrochemical balances of the cells,[216] as well as for other necessary functions. This leads to greatly increased metabolic heat production (relative to poikilotherms), which forms the basis of homeothermy. It also creates the need to maintain a substantial thermal gradient between the body and the environment to dissipate the high levels of heat that are continually produced.

An increased rate of metabolism above basal levels is critical for maintenance of body temperature in cold environments. The elevated heat production is derived from shivering and nonshivering responses. Shivering is muscular contraction for the specific purpose of producing heat, consisting of simultaneous rhythmic excitation of agonistic and antagonistic skeletal muscles. Under normal circumstances, carbohydrate oxidation provides the major substrate for shivering. In glycogen-depleted individuals, shivering levels are maintained by the greatly increased oxidation of lipid and protein reserves.[83] Nonshivering heat production (or nonshivering thermogenesis) is associated with the presence of uncoupling protein 1 (UCP-1) in brown adipose tissue and is under strong sympathetic neural regulation in humans and other species.[139,140] UCP-1 is a transmembrane protein located in the mitochondrial inner membrane, which, on activation by the sympathetic nervous system, allows for protons to reenter the mitochondrial matrix without passing through ATP synthase. Because energy released during substrate oxidation is not conserved as ATP, heat is generated. Although brown adipose tissue was previously believed to be of little importance in adult humans, recent research has indicated the presence and physiologic significance of active brown adipose tissue in adults.[56,139,140,189]

Hormonal responses contribute importantly to increases in metabolism with cold exposure. Evidence shows that both epinephrine and thyroid hormones are released in humans exposed to cold environments.[69,211] Both these hormones augment overall tissue metabolism. Circulating epinephrine and norepinephrine are increased as part of the overall sympathoexcitatory response to body cooling. These hormones interact with β-adrenergic receptors on brown adipose tissue and in skeletal muscle to increase mitochondrial uncoupling, thereby increasing nonshivering thermogenesis.[233,234]

Thyroid hormone acts by both accelerating ATP turnover and reducing efficiency of ATP synthesis, contributing about 30% of resting metabolic heat production.[204] Thyroid hormone levels are ultimately controlled by thyrotropin-releasing hormone (TRH), which is synthesized and released in the paraventricular nucleus of the hypothalamus (PVN). Cold exposure increases biosynthesis, processing, and release of TRH through α- and β-adrenergic mechanisms, and a subsequent increase in thyroid hormone levels appears to increase thermogenesis in part through binding to thyroid hormone receptors on brown adipose tissue.[65]

Basal metabolic rate (BMR), when calculated on a weight-specific basis, decreases with body size. This relationship holds within as well as across species. BMR relates to size according to the following equation.[197]

$$\dot{V}O_2 = (0.676)M_b^{0.75}$$

Where $\dot{V}O_2$ is oxygen consumption in L/hr and $M_b$ is body mass in kg.

### CENTRAL SIGNAL

Of the various thermoregulatory outputs, metabolism is the easiest to evaluate quantitatively; the most complete documentation is available for this response, and most models of the thermoregulatory system are based on this information. Experiments on medium-size mammals have allowed for separate thermal manipulation of various parts of the brain, body core, and skin. This work has made it clear that the thermoregulatory centers act as a proportional controller, and that skin temperature provides a feed-forward input to the system.[84,100] Thus, greater decreases in either core or skin temperature (or both) below neutral values elicit proportionally larger compensatory increases in metabolism. In addition to an impaired ability to generate metabolic heat, hypothyroidism is also associated with a decrease in regulated core temperature of about 1°C (1.8°F).[240]

Evidence indicates that humans have a control system similar to that of medium-sized mammals such as dogs or wolves. In a summary of their data and of that collected previously, Hong and Nadel[92] noted that the central output for shivering is augmented by an increased rate of skin cooling. They also concluded that a given decrease in core temperature elicits 10 to 20 times the metabolic response of an equivalent decrease in mean skin temperature. Exercise is not incompatible with shivering, but increased levels of exercise exert increasing degrees of suppression on the shivering response, possibly as a consequence of an increased arousal response.[92]

### LOCAL MODULATION

Although the central and local effects of decreased core temperature on shivering have not been directly partitioned, both inputs are important. Slight decreases in core temperature create large compensatory responses, as delineated previously. However, even moderate hypothermia decreases the metabolic response to cold, and with severe hypothermia (~30°C [86.0°F] core temperature), the shivering response is lost altogether.[20] This decrement likely involves impaired transmission of neural signals, because the muscles themselves are quite responsive below this temperature. For example, in vitro studies show that limb muscles and diaphragm muscles develop peak tensions that are not greatly affected by temperatures as low as 25°C (77.1°F), and fatigue resistance is considerably increased at 25°C.[173,199] Likewise, altering the local skin and superficial muscle temperature of the anterior thigh through a range of temperatures between 12° and 40°C (53.6° and 104.0°F) for 30 minutes had minimal effect on subsequent isometric peak torque production during isometric knee extensions to exhaustion.[225] Additionally, time to fatigue was longer at the coolest temperature.

## BEHAVIORAL ADJUSTMENTS

In most wilderness situations, a variety of ambient temperatures is available, and external insulation is easily adjusted. Under these conditions (particularly in cold environments), the choice of thermal microenvironment and clothing provides a much higher gain than any of the autonomic effector systems discussed previously. Whole-body adjustments are achieved by all motile animals and are particularly well developed in vertebrates.[52] In addition to moving the body, the somatic effectors are important for optimizing autonomic responses to thermal stress. Thus, spreading out the arms and legs during heat stress increases the surface area available for the autonomic augmentation of conductive, convective, evaporative, and radiative heat losses.

Cabanac[28] found that internal body temperature determined whether a particular surface temperature was perceived as pleasant or unpleasant. When individuals were hypothermic, a warm stimulus applied to the hand was experienced as pleasant and a cold stimulus as unpleasant. The opposite responses were observed in hyperthermic persons. An overall sensation of "thermal pleasantness" is obtained when environmental conditions are appropriate for maintaining a normal body temperature with no fluid or energy expenditure. However, altered body temperature did not affect the discriminative (cortically mediated) aspects of the thermal stimuli; participants had no problem correctly identifying the actual peripheral temperature. This study also confirmed the intimate relationship between the thermoregulatory network and the pleasure-pain system.[165]

### CENTRAL SIGNAL

Compared with the knowledge about autonomic thermoregulation, we know little about the neural mechanisms that underlie behavioral thermoregulation. As noted in previous sections, the POAH plays a key role in autonomic thermoregulation. It is also important for behavioral thermoregulation, because local heating and cooling of this area lead to the appropriate behavioral response.[31,190] Although animals with lesions of the POAH are severely compromised in their ability to use autonomic thermoregulatory effectors, their ability behaviorally to thermoregulate is relatively intact.[32,191] These results indicate that the preoptic area is not as crucial for behavioral thermoregulatory processes as for autonomic processes. Alternatively, lesions of the lateral hypothalamus, which is involved in various reward systems, result in the loss of behavioral thermoregulation.[192]

Recent studies involving positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have demonstrated that temperature signals from the body surface reach the insular cortex.[50,93,161] However, insular activation correlates with the discrimination between hot and cold rather than with thermal pleasure, so this system is likely minimally involved with behavioral thermoregulatory processes. Also, thermal pleasantness is clearly important for behavioral thermoregulation. In other studies involving fMRI, it has been shown that activation of the amygdala, mid-orbitofrontal and pregenual cingulate cortices, and striatum is correlated with thermally related pleasant and unpleasant feelings.[107,180]

Because behavioral processes are usually activated by feed-forward signals before body core temperature changes, signals from the skin are clearly important. In a study involving persons who were given the choice of moving between 8°C (46°F) and 46°C (115°F), behavior (i.e., moving between environments) was the primary method of thermoregulation.[196] Physiologic (autonomic) responses occurred but were minimal and secondary to choice of environment. Furthermore, skin temperature was the primary driver of these behavioral choices, because core temperature changes were minimal throughout the study.[196] Although feed-forward information from the skin appears to predominate in this type of behavioral thermoregulation, severe deviations in core temperature disrupt ability of feed-forward information to contribute to appropriate behavioral responses. When this occurs, the person no longer feels too hot or too cold, and the desire to take corrective action is lost.

Regional differences exist in the contribution of the body surface to thermal comfort.[150] Facial cooling produces the most pleasant experiences during mild heat exposure, whereas during cold exposure, local warming of the chest and abdomen leads to the most pleasant sensations. This would induce people

preferentially to cool the head in the heat and to huddle or add clothing to warm the torso in the cold.

### LOCAL MODULATION

As with shivering, most problems that involve behavioral temperature regulation probably originate with disruption of central control mechanisms. Skeletal muscle function is fairly resistant to impairment by thermal mechanisms, as described previously. If this occurs, however, a major disruption of the body's thermal defense ensues.

## IMPORTANT MODIFICATIONS OF THERMOREGULATORY RESPONSES

In addition to establishing the status of the body temperature when the regulatory system is functioning normally, monitoring body temperature provides a significant diagnostic indicator for many pathologic conditions. Whether the goal is to stabilize or monitor the body temperature, it is necessary to understand the many conditions that affect both the regulated temperature and effectiveness of the thermoregulatory system.

### NORMAL VARIATIONS IN REGULATED TEMPERATURE AND ABILITY TO MAINTAIN BODY TEMPERATURE

The same body temperature can represent a different set of conditions even under regularly encountered circumstances. Some of these conditions are noted here.

#### Level of Activity

Activity normally leads to increases in body temperature. However, the level of activity does not appear to provide direct input to central thermoregulatory nuclei. Unlike the feed-forward input received from peripheral temperature, the magnitude of the error signal for increased heat dissipation is determined simply by the increase in body temperature.[218] A person who is exercising heavily (or who has just exercised) in a neutral environment will have an unusually high body temperature, whereas a person who is sleeping or resting quietly will have a relatively low body temperature. Core temperature increases at the onset of exercise. The time course and magnitude of the temperature increase during exercise depends on several factors, including absolute exercise intensity (metabolic heat production), environment, body mass, and body surface area.[98]

#### Circadian Changes

Body temperature shows cyclic changes throughout the day. Some of this variation is the result of the daily cycle of activity, as described previously. However, there also exists a circadian rhythm for the regulated body temperature.[3-5] This sinusoidal rhythm accounts for much of the observed variations in body temperature. In a study that involved 700 observations of 148 healthy individuals, the daily mean oral reading was 36.8°C (98.2°F). However, this was only a midpoint; the mean early-morning low was 36.4°C (97.6°F), and the mean late-afternoon high was 36.9°C (98.4°F).[153] These diurnal changes definitely reflect alterations in the controller, because the body temperature thresholds for eliciting sweating and peripheral vasodilation are significantly lower in the early morning than in the afternoon or evening, whereas the sensitivities and maximal response levels remain unchanged.[3-5] The body's biologic clock may directly modulate the body temperature rhythm. The suprachiasmatic nucleus in the hypothalamus is the main pacemaker for the circadian system of the body. The core molecular mechanisms of the circadian clock consist of autoregulatory transcription and translation loops by the clock genes and show a periodicity of approximately 24 hours. Removing the circadian clock abolishes the body temperature rhythm as well as the circadian influences on thermoregulatory responses.[147,227]

Thermoregulatory responses to exercise are affected by the circadian clock as well. At the daily low (5:00 AM), the perceived exertion for a standardized task is the greatest, and thermoregulation is less effective than at the time of maximum temperature (5:00 PM). At the time when the body temperature is rising at the fastest rate (11:00 AM), heat loss mechanisms are less responsive; alternatively, at 11:00 PM, when the body temperature is falling at the fastest rate, heat loss mechanisms are much more responsive.[230] Results of studies involving heat dissipation mechanisms during passive heat exposure or exercise suggest that the threshold for the onset of heat dissipation responses is shifted over the circadian cycle.[3-5,215] Sensitivity (responsiveness) of the sweating signal with respect to increases in core temperature does not appear to change over the course of the day;[5,215] results regarding cutaneous vasodilator sensitivity were less consistent, with some studies showing changes[3,4] while others did not.[215] An excellent overview of body temperature cycles is available.[177]

#### Interindividual Differences

Most oral temperature measurements are between 36.0°C (96.9°F) and 37.1°C (98.9°F) in the early morning. Corresponding values for the late afternoon are 36.3°C (97.4°F) and 37.4°C (99.4°F). On the basis of interindividual differences and diurnal changes, it has been suggested that the upper limit for a normal oral temperature should be 37.2°C (98.9°F) in early morning, which then increases gradually to 37.8°C (99.9°F) by early afternoon and remains at that level until early evening.[129] These values delineate the 99th percentile for body temperature observed during the respective time periods.

Alternatively, it is important to be aware that the normal body temperature of some individuals falls outside of population norms. We are anecdotally aware of three individuals whose core temperature is consistently 35.5° to 36.5°C (95.9° to 97.7°F). These individuals state that occasionally they have felt ill with a fever, but were told by a physician that their temperature of 37°C (98.6°F) was normal. For these individuals, however, it was *not* normal; a core temperature of 37°C (98.6°F) in fact represented a febrile state. Many individuals with atypical body temperatures are aware of their condition, and it is prudent to ask about this possibility.

#### Age

The circadian rhythm of body temperature develops soon after birth. Although newborns display small-amplitude rhythms, the patterns are not circadian. Circadian rhythmicity begins to develop during the second and third weeks of life, and, after a progressive increase in amplitude, the typical adult temperature rhythms are reached by age 2 years.[177] Under thermoneutral conditions, rectal temperatures of older adults are similar to those of younger people, whereas oral and axillary temperatures are slightly lower.[105] A recent overview of circadian temperature and aging is available.[231]

Of the major regulatory systems, temperature regulation is unique in the extent to which the effector organs are shared with other systems. This makes developmental assessments difficult because functional changes may be secondary to changes in primary systems, such as the skeletal muscles or the blood vessels. Other difficulties, as detailed by Cooper,[48] include inconsistencies between chronologic age and physiologic viability and the increased incidence of interfering disease states and cerebral microinfarcts as aging progresses.

Thermoregulatory capacities of young people show a progressive increase, but these are not fully developed until after puberty. Effectors that are more important to infants than to adults include certain behavioral responses (including calling for help) and the ability to activate thermogenic brown adipose tissue. Shivering is not present in infants; it develops fully only after several years of nervous system maturation. Metabolism in infants is increased to some degree by the increase in motor activity that accompanies cold stress.[113]

Sweating is present and effective in children, but the typical high capacity for evaporative heat loss that is present in adults is attained only following the changes that occur with puberty.[64] Factors that affect loss of body heat during cold stress throughout the adult years have been investigated with a multiple regression analysis. Fitness, fatness, and age from the 20s to the early 50s

were evaluated. Fitness had no effect, but fatness impaired heat loss. Aging during this period was correlated with progressive weakening of the vasoconstrictor response to cold.[25]

Individuals in their late 60s and beyond have a definite decrease in thermoregulatory capacity. Sweating is lessened in response to passive heating,[97] vascular responses to heating and cooling are significantly reduced,[91,110,113] and a distinct shivering tremor is rarely observed.[113] In older adults, thermoregulatory sympathetic nerve impulses to the skin are reduced by 60%,[77] several mechanisms of cutaneous vasoconstriction and vasodilation are impaired,[91] and resting metabolic rate is lower than in younger individuals.[236]

Young children and older adults are particularly vulnerable to thermal extremes and should be given treatment priority when possible. Both groups are susceptible to climatic heat injury. If core temperatures exceed 40°C (104°F) and are accompanied by an altered mental status, treatment should be immediate, even at the risk of misdiagnosing a febrile condition. As for all such cases, most clothing should be removed; if available, ice should be placed around the groin, in the axillae, and around the neck. Cool water should be sprayed on the skin and the individual then fanned. Blood gas and electrolyte status should be determined and any appropriate treatment measures taken.[34]

### Sex and Reproductive Hormone Status

Women have a number of physiologic and morphologic characteristics that could theoretically produce differences in the regulation of body temperature. These include smaller blood volume, lower hemoglobin concentration, smaller heart, smaller lean body mass, greater percentage of subcutaneous and total body fat, greater surface area–to–mass ratio (due to smaller overall body size), thinner extremities, and cyclic changes in sex hormone levels. In general, however, historical studies that originally suggested major differences in thermoregulation between men and women were poorly controlled or unclear in data presentation.[43] Most reports have shown that when age, thermal acclimation, body size, maximal aerobic capacity, cardiovascular responses during exercise, and relative workload are matched, sex differences in thermoregulation are minimal.[71] In particular, a recent, well controlled comparison of thermoregulatory responses between men and women during exercise concluded that female sex was associated with a slight impairment of thermoregulatory heat dissipation only at very high exercise intensities,[72] and the impairment was not such that it would cause an increase in dangerous levels of hyperthermia in women.

The menstrual cycle, oral contraceptives, menopause, and pregnancy are all associated with important effects on the thermoregulatory system. Relative to the early follicular phase of the menstrual cycle, core temperature is typically 0.3°C (0.5°F) lower during the late follicular (preovulatory) phase, when estrogen is elevated unopposed by progesterone, and 0.5° to 0.7°C (1.0° to 1.3°F) higher in the midluteal phase, when both progesterone and estrogen are elevated.[115,116,215] Thermoregulatory control mechanisms are similarly shifted across the menstrual cycle, such that heat dissipation responses, including cutaneous vasodilation and sweating, are initiated at lower temperatures during the preovulatory phase and higher temperatures during the midluteal phase.[40,116,215] These influences are also seen with the exogenous hormones in oral contraceptives.[40,42] Such data support the idea that estrogen tends to promote peripheral vasodilation and a lower body temperature, whereas progesterone tends to promote increased body temperature.[41,116]

The effects of reproductive hormones on thermoregulation in postmenopausal women undergoing hormone replacement therapy are generally consistent with those just described in younger women. Administered estrogen acts to lower the core temperature at which heat loss effector mechanisms are activated and results in a lowered core temperature.[22,222] The addition of exogenous progestins reverses these effects.[22] Although less work has been done on the thermoregulatory effects of testosterone, epidemiologic studies indicate that lower testosterone concentration may be associated with a sensation of cold.[76]

During menopause, fluctuating hormone levels are thought to contribute to hot flashes or "flushes," which involve increases in sweating, vasodilation, and heart rate.[126,127] Heat and exercise may be particularly stressful during and after these episodes. An increase in body temperature caused by heat exposure or exercise could also trigger a hot flash.[117] The integrative mechanism for the thermal responses appears to involve estrogen activating central (POAH) warm-sensitive neurons, which then trigger heat dissipation responses.[205] Hot flashes may be associated with activation of the insular cortex,[68] as well as circulating serotonin levels.[133] Additionally, nitric oxide has been shown to contribute to the peripheral vasodilator response.[94]

Pregnancy is of special concern to the physician in the wilderness. This concern does not apply to well-hydrated women who are exercising at submaximal levels, because the thermoregulatory system makes adaptive adjustments as pregnancy proceeds. In the course of a pregnancy, basal body temperature shows a continuous decline, and heat loss responses are elicited at progressively lower levels so that, near term, the steady-state temperature during exercise is about 1°C (1.8°F) lower than before conception.[124] This reduces thermal stress on the fetus, which is typically 0.5°C (0.9°F) warmer than the mother.[47,212]

However, concern is warranted if hyperthermia develops in pregnant women. Animal experiments and epidemiologic analysis both indicate that, during pregnancy, it is dangerous for body temperature to exceed 39°C (102.2°F). During the first half of pregnancy, excessive body temperature is likely to produce birth defects; during the latter half, birth weight is more likely to be affected. The fifth week after conception, which is the period of neural tube closure, is a particularly vulnerable time for the fetus.[124] Because women in the early stages of pregnancy may be unaware of their condition, it is critical that heat stress be promptly treated in women of childbearing age. When exercising, it is important that pregnant or potentially pregnant women acclimatize gradually to extreme thermal environments, remain well hydrated, wear loose-fitting clothing, exercise at a comfortable pace, and avoid swimming in warm water or immersing themselves in hot tubs.[212] A program of water aerobics for pregnant women was reported to decrease requests for analgesia when these women gave birth, and it was not found to be detrimental to the health of the mother or the child.[6]

## INDUCED ALTERATIONS OF THE REGULATED TEMPERATURE

The optimal body temperature is not always the same. In certain conditions of stress or vulnerability, the regulated temperature of the body may be altered; this is often an adaptive response to a particular perturbation or physiologic/pathophysiologic state. In such circumstances, altered body temperature may be beneficial and should not necessarily be manipulated until the underlying condition is improved.

### FEVER

The association between illness and increased body temperature has been recognized for thousands of years. Febrile body temperatures for resting young adults include a morning temperature of 37.3°C (99.2°F) or higher, which increases gradually to 37.8°C (100.0°F) for early afternoon and evening. Such elevated temperature needs to reflect a regulated increase to be considered a true fever.

Pathogens that cause fevers interact with components of the immune system such as macrophages, T cells, monocytes, and Kupffer cells as well as with glial, epithelial, and many other types of cells. This interaction stimulates the cells to produce pyrogenic cytokines,[131] including interleukin-1 (IL-1), interleukin-6, and macrophage inflammatory protein-1. The thermoregulatory "resetting" that results in a regulated increase in body temperature is initiated by activation of the complement cascade in the liver, which then initiates afferent neural signaling to the hypothalamus via a prostaglandin $E_2$–dependent vagal mechanism.[13,185] Aspirin and related drugs block fever by inhibiting prostaglandin synthesis.[13,185] In addition to causing fever, IL-1 and other cytokines have many other effects, including decreased appetite,

hypoferremia, activation of B and T lymphocytes, and increased slow-wave sleep.[114]

The increase in body temperature during fever helps with many immune functions; neutrophil migration, release of reactive oxygen intermediates and nitric oxide by neutrophils, and interferon production are all augmented. The most important aspect of fever may be to increase greatly the temperature of the peripheral tissues by selecting a warmer microclimate, adding insulation, and making postural changes. As peripheral temperatures increase from typical levels (i.e., 29° to 33°C [84.2° to 91.4°F]) to those that approximate core temperature, the activation, proliferation, and effector production in peripheral cells involved in cell-mediated and humoral immunity are greatly increased and show temperature coefficients ($Q_{10}$) of 100 to 1000. By contrast, the $Q_{10}$ for the effectiveness of the newly created effectors themselves, as well as for antigen-nonspecific defense systems, are much lower, at about 1.5 to 5.36.[184]

The presence and beneficial effects of fever have been documented in a variety of cold-blooded and warm-blooded vertebrates and even in some invertebrates. Under most conditions, it is probably not advisable to alleviate a fever. Exceptions include malignant hyperthermia and particularly high fevers during pregnancy. In addition, for patients with limited fluid, oxygen transport, or cardiopulmonary reserves, a febrile response should be treated with antipyretics.[110] Consequences of the decreased immune response can be treated after the emergency.

### ALCOHOL, ANESTHETICS, AND TOXINS

Increases in the blood concentrations of ethanol, anesthetics, and a number of toxic substances lead to substantial decreases in body temperature.[54,200] In many cases, this fall is caused by a decrease in the regulated temperature. In the case of high concentrations of alcohol and certain toxins, the reduction appears to be an adaptive adjustment that promotes survival. These chemicals disrupt protein structures within the cell membrane, and this effect is counteracted by a lower temperature.[54] Indeed, mouse studies have shown that lowered body temperature counteracts ethanol toxicity.[132] In humans as well, a decrease in the regulated temperature is caused by increases in blood ethanol concentration. After ingestion of ethanol (3.0 mL/kg body weight) at 33°C (91.4°F), sweat rate increased and body temperature fell. Although skin temperature did not increase, individuals reported a warm sensation that paralleled the increase in sweat rate.[242] At 18°C (64.4°F), body temperature decreased continuously before and after the drinking of alcohol, with no facilitation of metabolic heat production. During this period, the thermal discomfort sensation became more intense, although the discrimination of cold was impaired after the ingestion of ethanol.[241,242] However, lower blood ethanol levels associated with moderate consumption in humans have minimal and inconsistent effects on thermal balance of the whole body.[58,103]

Excellent overviews of the effects of general anesthetics on perioperative thermoregulation are available.[201,202] Many of these substances (e.g., halothane, fentanyl and nitrous oxide, enflurane, isoflurane) in anesthetic doses act in a similar manner. Heat loss thresholds are increased by about 1°C (1.8°F), and heat maintenance thresholds are lowered by approximately 2.5°C (4.5°F). Interestingly, in the typical clinical dose range, the gain (sensitivity) of the effector responses is near normal. In the conditions under which general anesthetics are normally administered, body temperature decreases significantly. An initial rapid drop is caused by redistribution of heat; cool blood from the periphery lowers central core temperature. A second and slower decrease results from a fall in body heat content. Finally, a plateau is reached, either because heat production and heat loss are passively balanced, or because heat maintenance thresholds are reached. During postanesthetic recovery, there is vigorous shivering. Anesthetic-induced hypothermia is reduced in patients with higher preoperative systolic blood pressure. This difference is associated with higher preoperative plasma norepinephrine levels, which may intensify the vasoconstriction response.[108] Cutaneous warming before and during anesthesia prevents the development of hypothermia and decreases the incidence of infectious complications.[118,201]

### SEVERE HYPOXIA AND ENDOTOXIN SHOCK

When inspired oxygen concentration falls to between 10% and 12%, a substantial decrease in the regulated temperature occurs. This reaction has been documented with the use of behavioral responses in fish, amphibians, reptiles, and mammals.[74,237] For humans who are exercising in 28°C (82.4°F) water under eucapnic conditions, decreasing inspired oxygen to 12% lowers the core temperature thresholds for vasoconstriction and shivering and increases the rate of core cooling by 33%.[104] The value of the resultant lowered body temperature is clear: the affinity of hemoglobin for oxygen is increased, and overall metabolic rate is decreased. The mechanism underlying the change in the regulated temperature may involve differential sensitivities of central neurons; hypoxia specifically increases activity of warm-sensitive neurons in the POAH.[221]

A somewhat similar regulated hypothermic response occurs when an animal is exposed to very high levels of pyrogens; the same response occurs under less extreme conditions in weak or malnourished animals. The lowered body temperature may serve to decrease the energy costs of maintaining a high body temperature for a severely compromised animal.[183]

## ALTERED SYSTEM RESPONSIVENESS AND CAPACITIES

A number of situations alter responsiveness of the thermoregulatory system. Awareness of these conditions is important when assessing the thermoregulatory capabilities of a particular person and when determining possible causes for hyperthermia or hypothermia.

### THERMAL ACCLIMATION

Thermoregulation is affected by chronic exposure to very cold or hot environments as well as by chronic exercise in cool or warm ambient temperatures. Such exercise in a cool environment greatly increases responsiveness of the sweat glands; if exercise is in the heat, the central temperature at which sweating is initiated is also lowered. The net consequence of these adjustments is that a heat-acclimated and exercise-acclimated individual can work at a given level with far less increase in core temperature.[146] A regimen of exercise in humid heat appears to decrease resting core temperature in acclimated individuals.[168] Repeated acute increases in both core and skin temperatures contribute to various changes involved in heat acclimation.[175] Physical training also increases skin blood flow at any given increase in core temperature.[100] Although acclimation to warm conditions produces many changes in the cardiovascular system, basic baroreflex responses are not altered.[239]

Heat acclimation may result in protective cellular adaptations. Intracellular heat shock protein (HSP) 72 is likely involved in the maintenance of cellular protein conformation and homeostasis during hyperthermia, inflammation, and injury.[141] Consistent with this, a 10-day program of heat and exercise acclimation increased HSP-72 levels in peripheral blood mononuclear cells.[238]

Chronic cold exposure alters many thermoregulatory systems. These effects can accrue to both evolutionary change and long-term individual thermal acclimation. In many cases, resting metabolic rate is increased after repeated cold exposure;[24] however, repeated exposure to very cold environments may produce the opposite effect. For example, eighty 30-minute sessions at 5°C (41°F) decreased the metabolic response to a standard cold-air test and often led to lower internal temperatures in these cold-acclimated individuals.[89]

On initial exposure of extremities to cold, substantial cutaneous vasoconstriction is observed. At some point, however, cold-induced removal of the superficial α-receptor inhibition leads to transient vasodilation of the fingers, which occurs in a cyclic

pattern.[1,159] This so-called cold-induced vasodilation warms the extremities, protects against frostbite, decreases pain, and improves manual dexterity during prolonged cold exposure.[1,90] This response has a genetic component; for individuals who are not cold acclimated, this response is very strong among Inuit Eskimos, moderate among whites, and minimal among Chinese from Hong Kong.[78] No differences appear to exist between men and women in the cold-induced vasodilation response.[228] Individual differences in the vasodilation response to cold determine the relative likelihood of the development of frostbite. An environmental influence in this response is also likely; fishermen in northeastern Canada did not exhibit vasoconstriction of the fingers when exposed to cold.[78]

## COMPETITION WITH OTHER HOMEOSTATIC SYSTEMS

In addition to a constant core temperature, the body has many other requirements. When fluid balance or energy requirements are not met, thermoregulatory responses can be compromised. For heat production and heat conservation, an adequate energy supply, patent nervous system, and functional effector organs are critical. Thus, hypoglycemia decreases the core temperature at which shivering is initiated while leaving the thresholds for sweating and vasodilation unaffected.[166] Competition between skin and muscle for blood flow during hyperthermic exercise is another consideration. During exercise, cutaneous vasodilation is elicited later, at a higher internal temperature than in resting hyperthermia, resulting in lower skin blood flow for a given internal temperature during exercise than at rest.[99] The arterial baroreflex is another nonthermal reflex that can alter skin blood flow responses to thermal stimuli. Activation of the baroreflex using lower-body negative pressure (LBNP) causes decreases in skin blood flow in both normothermic and hyperthermic individuals.[102]

During exercise, heat is generated by activity of the muscles. About 80% of the energy consumption is converted into heat, with only about 20% going to the actual work produced by contraction of the muscles. High muscle temperature increases efficiency of muscle contraction.[10,11] However, an excessive rise in body temperature impairs endurance performance and leads to more rapid fatigue. Some controversy surrounds the concept of a "critical core temperature" (~40°C [104°F]) at which fatigue occurs to protect the brain from neuronal damage caused by high internal temperatures.[75] Support for this includes observations that time to exhaustion during heavy exercise is affected by the initial body temperature.[75,152,154] In a heat acclimation study, individuals exercised until exhaustion at 60% of their maximum $\dot{V}O_2$ for 9 to 12 consecutive days at 40°C (104°F).[154] The time to exhaustion became progressively longer with acclimation, but core temperature at exhaustion remained at about 40°C. When body temperature was altered by water immersion before bicycle ergometer exercise at 40°C, time to exhaustion became progressively longer as initial body temperature was progressively lowered. Again, body temperature at exhaustion remained at approximately 40°C.[75]

Recent evidence suggests that the story may not be as "simple" as one core temperature that causes fatigue at the central level. In a field study, runners with rectal temperature above 40°C performed similar to runners with rectal temperature of 40°C or lower at the end of 8-km (4.8-mile) time trials.[63] With high skin temperatures, cardiovascular mechanisms, including redistribution of blood flow from the core to the periphery, and associated decreases in stroke volume maximize cardiovascular strain in high environmental temperatures. These mechanisms appear to be as important as the core temperature itself (or more so) with regard to development of fatigue. The integrative contributions of various mechanisms of fatigue are detailed in a recent review.[156]

For maintenance of exercise performance and body temperature in a warm environment, body water status is critical.[45,195] It is common for a person who is working in the heat to lose 1 L of water per hour. Even when fluids are readily available, maintaining a euhydrated state may be difficult. For hypohydration during continued activity, each percent decrease in body weight leads to a core temperature increase of about 0.15°C (0.27°F). This decreased heat dissipation is mediated by two mechanisms. At a given core temperature, hypertonicity decreases the sweating response, and hypovolemia reduces skin blood flow.[45,195] During compensable heat stress, in which a steady-state core temperature can be maintained, hyperhydration has no effect on thermoregulation.[119] During uncompensable exercise heat stress, in which core temperature continues to rise, hyperhydration slightly increases the time to exhaustion, but only by delaying hypohydration; thermoregulation is not affected.[120] It is important to be alert to the possibility of dehydration in many atypical situations. For example, swimmers training in an outdoor pool with a water temperature of 26°C (78.8°F) lost sufficient fluid (2.5% of their body weight) in 3 hours to compromise thermoregulatory responses.[210]

Exposure to hypoxia can alter thermoregulatory vascular responses, in part because hypoxia itself is a vasodilator.[207] During exposure to cold, augmented vasoconstriction appears to defend core temperature such that the rate of body cooling is unaffected.[206] Paradoxically, in a hot environment, hypoxia may reduce the cutaneous vasodilator response for a given level of hyperthermia.[188] This may be caused by the sympathoexcitatory influence of hypoxia.[82] However, regional differences in the influence of hypoxia on blood flow and vascular tone make mechanistic interpretation challenging.

## ALCOHOL, DRUGS, ANESTHETICS, AND TOXINS

Although moderate doses of anesthetics and toxins may elicit adaptive changes in the regulated body temperature, elevated doses of these substances impair or abolish both autonomic and behavioral aspects of thermoregulation. Body temperature then changes passively, depending on the thermal environment. This can be particularly dangerous when elevated levels of alcohol or similar substances are combined with heat stress. Impaired ability to dissipate heat is then combined with the enhanced toxicity of increased tissue temperature.

Drugs that increase metabolic heat production (e.g., amphetamines, ecstasy [3,4-methylenedioxymethamphetamine], cocaine) are also particularly dangerous to use in the heat. In addition, cocaine interferes with heat dissipation mechanisms and with the perception of warmth.[23,51]

# REFERENCES

***Complete references used in this text are available online at expertconsult.inkling.com.***

## REFERENCES


1. Adams T, Smith RE. Effect of chronic local cold exposure on finger temperature responses. J Appl Physiol 1962;17:317–22.
2. Allan JR, Wilson CG. Influence of acclimatization on sweat sodium concentration. J Appl Physiol 1971;30(5):708–12.
3. Aoki K, Kondo N, Shibasaki M, et al. Circadian variation in skin blood flow responses to passive heat stress. Physiol Behav 1997; 63(1):1–5.
4. Aoki K, Kondo N, Shibasaki M, et al. Control of circadian variation in skin blood flow response to heat stress. Jpn J Physiol 1998;48(1): 95–8.
5. Aoki K, Kondo N, Shibasaki M, et al. Circadian variation of sweating responses to passive heat stress. Acta Physiol Scand 1997;161(3): 397–402.
6. Baciuk EP, Pereira RI, Cecatti JG, et al. Water aerobics in pregnancy: Cardiovascular response, labor and neonatal outcomes. Reprod Health 2008;5:10.
7. Bagriantsev SN, Clark KA, Minor DL Jr. Metabolic and thermal stimuli control K(2P)2.1 (TREK-1) through modular sensory and gating domains. EMBO J 2012;31(15):3297–308.
8. Bennett LA, Johnson JM, Stephens DP, et al. Evidence for a role for vasoactive intestinal peptide in active vasodilatation in the cutaneous vasculature of humans. J Physiol 2003;552(Pt 1):223–32.
9. Benzinger TH. Peripheral cold- and central warm-reception, main origins of human thermal discomfort. Proc Natl Acad Sci U S A 1963; 49:832–9.
10. Bishop D. Warm up I: Potential mechanisms and the effects of passive warm up on exercise performance. Sports Med 2003; 33(6):439–54.
11. Bishop D. Warm up II: Performance changes following active warm up and how to structure the warm up. Sports Med 2003;33(7): 483–98.
12. Blatteis CM. Methods of body temperature measurement. In: Blatteis CM, editor. Physiology and pathophysiology of temperature regulation. Singapore: World Scientific; 1998.
13. Blatteis CM. The onset of fever: new insights into its mechanism. Prog Brain Res 2007;162:3–14.
14. Boller M, Lampe JW, Katz JM, et al. Feasibility of intra-arrest hypothermia induction: A novel nasopharyngeal approach achieves preferential brain cooling. Resuscitation 2010;81(8):1025–30.
15. Boulant JA. Neuronal basis of Hammel's model for set-point thermoregulation. J Appl Physiol (1985) 2006;100(4):1347–54.
16. Boulant JA, Curras MC, Dean JB. Neurophysiological aspects of thermoregulation. In: Wang LCH, editor. Advances in comparative and environmental physiology, vol. 4. Berlin: Springer-Verlag; 1989.
17. Boulant JA, Silva NL. Neuronal sensitivities in preoptic tissue slices: Interactions among homeostatic systems. Brain Res Bull 1988;20(6): 871–8.
18. Brengelmann GL. Body temperature regulation. In: Patton HD, Fuchs AF, Hille B, editors. Textbook of physiology: Circulation, respiration, body fluids, metabolism and endocrinology, vol. 2. 21st ed. Philadelphia: WB Saunders; 1989.
19. Brengelmann GL. Specialized brain cooling in humans? FASEB J 1993;7(12):1148–52, discussion 1152-1143.
20. Brengelmann GL, Brown AC. Temperature regulation. In: Ruch TC, Patton HD, editors. Physiology and biophysics. 19th ed. Philadelphia: WB Saunders; 1965.
21. Brengelmann GL, Savage MV. Temperature regulation in the neutral zone. Ann N Y Acad Sci 1997;813:39–50.
22. Brooks EM, Morgan AL, Pierzga JM, et al. Chronic hormone replacement therapy alters thermoregulatory and vasomotor function in postmenopausal women. J Appl Physiol (1985) 1997;83(2):477–84.
23. Brown PL, Kiyatkin EA. Brain hyperthermia induced by MDMA (ecstasy): modulation by environmental conditions. Eur J Neurosci 2004;20(1):51–8.
24. Bruck K, Hinckel P. Thermoafferent networks and their adaptive modifications. In: Schonbaum E, Lomax P, editors. Thermoregulation: physiology and biochemistry. New York: Pergamon Press; 1990.
25. Budd GM, Brotherhood JR, Hendrie AL, Jeffery SE. Effects of fitness, fatness, and age on men's responses to whole body cooling in air. J Appl Physiol (1985) 1991;71(6):2387–93.
26. Burke WE, Mekjavic IB. Estimation of regional cutaneous cold sensitivity by analysis of the gasping response. J Appl Physiol (1985) 1991;71(5):1933–40.
27. Burton AC. Human calorimetry: The average temperature of the tissues of the body. J Nutr 1935;9:261.
28. Cabanac M. Physiological role of pleasure. Science 1971;173(4002): 1103–7.
29. Cabanac M. Selective brain cooling in humans: "fancy" or fact? FASEB J 1993;7(12):1143–6, discussion 1146-1147.
30. Cabanac M, Caputa M. Natural selective cooling of the human brain: Evidence of its occurrence and magnitude. J Physiol 1979;286: 255–64.
31. Carlisle HJ. Behavioural significance of hypothalamic temperature-sensitive cells. Nature 1966;209(5030):1324–5.
32. Carlisle HJ. Effect of preoptic and anterior hypothalamic lesions on behavioral thermoregulation in the cold. J Comp Physiol Psychol 1969;69(2):391–402.
33. Casa DJ, Becker SM, Ganio MS, et al. Validity of devices that assess body temperature during outdoor exercise in the heat. J Athl Train 2007;42(3):333–42.
34. Caspani ML, Savioli M, Crotti S, et al. Heat stress: Characteristics, pathophysiology and avoidable mistakes. Minerva Anestesiol 2004; 70(7–8):617–24.
35. Caterina MJ, Leffler A, Malmberg AB, et al. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science 2000;288(5464):306–13.
36. Cetas TC. Thermometers. In: Mackowiak PA, editor. Fever: Basic mechanisms and management. 2nd ed. Philadelphia: Lippincott-Raven; 1997.
37. Charkoudian N. Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans. J Appl Physiol (1985) 2010;109(4):1221–8.
38. Charkoudian N. Skin blood flow in adult human thermoregulation: How it works, when it does not, and why. Mayo Clin Proc 2003; 78(5):603–12.
39. Charkoudian N, Fromy B, Saumet JL. Reflex control of the cutaneous circulation after acute and chronic local capsaicin. J Appl Physiol (1985) 2001;90(5):1860–4.
40. Charkoudian N, Johnson JM. Altered reflex control of cutaneous circulation by female sex steroids is independent of prostaglandins. Am J Physiol 1999;276(5 Pt 2):H1634–40.
41. Charkoudian N, Johnson JM. Female reproductive hormones and thermoregulatory control of skin blood flow. Exerc Sport Sci Rev 2000;28(3):108–12.
42. Charkoudian N, Johnson JM. Modification of active cutaneous vasodilation by oral contraceptive hormones. J Appl Physiol (1985) 1997; 83(6):2012–18.
43. Charkoudian N, Stachenfeld NS. Reproductive hormone influences on thermoregulation in women. Compr Physiol 2014;4(2):793–804.
44. Cheshire WP, Freeman R. Disorders of sweating. Semin Neurol 2003;23(4):399–406.
45. Cheuvront SN, Kenefick RW, Montain SJ, Sawka MN. Mechanisms of aerobic performance impairment with heat stress and dehydration. J Appl Physiol (1985) 2010;109(6):1989–95.
46. Chotani MA, Flavahan S, Mitra S, et al. Silent alpha(2C)-adrenergic receptors enable cold-induced vasoconstriction in cutaneous arteries. Am J Physiol Heart Circ Physiol 2000;278(4):H1075–83.
47. Clapp JF 3rd. The changing thermal response to endurance exercise during pregnancy. Am J Obstet Gynecol 1991;165(6 Pt 1):1684–9.
48. Cooper KE. Thermoregulation in the elderly. In: Bender BS, Scarpace PJ, editors. Physiology and pathophysiology of temperature regulation. Singapore: World Scientific; 1998.
49. Cossins AR, Bowler K. Temperature biology of animals. New York: Chapman & Hall; 1987.
50. Craig AD, Chen K, Bandy D, Reiman EM. Thermosensory activation of insular cortex. Nat Neurosci 2000;3(2):184–90.
51. Crandall CG, Vongpatanasin W, Victor RG. Mechanism of cocaine-induced hyperthermia in humans. Ann Intern Med 2002;136(11): 785–91.
52. Crawshaw LI. Temperature regulation in vertebrates. Annu Rev Physiol 1980;42:473–91.
53. Crawshaw LI, Nadel ER, Stolwijk JA, Stamford BA. Effect of local cooling on sweating rate and cold sensation. Pflugers Arch 1975; 354(1):19–27.
54. Crawshaw LI, Wallace H, Crabbe J. Ethanol, body temperature and thermoregulation. Clin Exp Pharmacol Physiol 1998;25(2):150–4.
55. Crawshaw LI, Wollmuth LP, O'Connor CS. Body temperature regulation in vertebrates: Comparative aspects and neuronal elements. In: Schonbaum E, Lomax P, editors. Thermoregulation: Physiology and biochemistry. New York: Pergamon Press; 1990.
56. Cypess AM, Lehman S, Williams G, et al. Identification and importance of brown adipose tissue in adult humans. N Engl J Med 2009; 360(15):1509–17.
57. Dean JB, Boulant JA. Effects of synaptic blockade on thermosensitive neurons in rat diencephalon in vitro. Am J Physiol 1989;257(1 Pt 2): R65–73.
58. Desruelle AV, Boisvert P, Candas V. Alcohol and its variable effect on human thermoregulatory response to exercise in a warm environment. Eur J Appl Physiol Occup Physiol 1996;74(6):572–4.
59. Doufas AG. Consequences of inadvertent perioperative hypothermia. Best Pract Res Clin Anaesthesiol 2003;17(4):535–49.

60. Ducharme MB, Tikuisis P. In vivo thermal conductivity of the human forearm tissues. J Appl Physiol (1985) 1991;70(6):2682–90.
61. Earley S, Brayden JE. Transient receptor potential channels in the vasculature. Physiol Rev 2015;95(2):645–90.
62. Ekenvall L, Lindblad LE, Norbeck O, Etzell BM. Alpha-adrenoceptors and cold-induced vasoconstriction in human finger skin. Am J Physiol 1988;255(5 Pt 2):H1000–3.
63. Ely BR, Ely MR, Cheuvront SN, et al. Evidence against a 40 degrees C core temperature threshold for fatigue in humans. J Appl Physiol (1985) 2009;107(5):1519–25.
64. Falk B, Bar-Or O, Calvert R, MacDougall JD. Sweat gland response to exercise in the heat among pre-, mid-, and late-pubertal boys. Med Sci Sports Exerc 1992;24(3):313–19.
65. Fekete C, Lechan RM. Central regulation of hypothalamic-pituitary-thyroid axis under physiological and pathophysiological conditions. Endocr Rev 2014;35(2):159–94.
66. Flavahan NA, Cooke JP, Shepherd JT, Vanhoutte PM. Human postjunctional alpha-1 and alpha-2 adrenoceptors: Differential distribution in arteries of the limbs. J Pharmacol Exp Ther 1987;241(2):361–5.
67. Flavahan NA, Lindblad LE, Verbeuren TJ, et al. Cooling and alpha 1- and alpha 2-adrenergic responses in cutaneous veins: Role of receptor reserve. Am J Physiol 1985;249(5 Pt 2):H950–5.
68. Freedman RR, Benton MD, Genik RJ 2nd, Graydon FX. Cortical activation during menopausal hot flashes. Fertil Steril 2006;85(3):674–8.
69. Fregly M. Activity of the hypothalamic-pituitary-thyroid axis during exposure to cold. In: Schonbaum E, Lomax P, editors. Thermoregulation: Physiology and biochemistry. New York: Pergamon Press; 1990.
70. Frohlich D, Wittmann S, Rothe G, et al. Mild hyperthermia down-regulates receptor-dependent neutrophil function. Anesth Analg 2004;99(1):284–92.
71. Fu Q, Levine BD. Cardiovascular response to exercise in women. Med Sci Sports Exerc 2005;37(8):1433–5.
72. Gagnon D, Kenny GP. Sex differences in thermoeffector responses during exercise at fixed requirements for heat loss. J Appl Physiol (1985) 2012;113(5):746–57.
73. Gagnon D, Lemire BB, Jay O, Kenny GP. Aural canal, esophageal, and rectal temperatures during exertional heat stress and the subsequent recovery period. J Athl Train 2010;45(2):157–63.
74. Gautier H, Bonora M, M'Barek SB, Sinclair JD. Effects of hypoxia and cold acclimation on thermoregulation in the rat. J Appl Physiol (1985) 1991;71(4):1355–63.
75. Gonzalez-Alonso J, Teller C, Andersen SL, et al. Influence of body temperature on the development of fatigue during prolonged exercise in the heat. J Appl Physiol (1985) 1999;86(3):1032–9.
76. Gotmar A, Hammar M, Fredrikson M, et al. Symptoms in peri- and postmenopausal women in relation to testosterone concentrations: Data from The Women's Health in the Lund Area (WHILA) study. Climacteric 2008;11(4):304–14.
77. Grassi G, Seravalle G, Turri C, et al. Impairment of thermoregulatory control of skin sympathetic nerve traffic in the elderly. Circulation 2003;108(6):729–35.
78. Grayson J. Responses of the microcirculation to hot and cold environments. In: Schonbaum E, Lomax P, editors. Thermoregulation: Physiology and biochemistry. New York: Pergamon Press; 1990.
79. Griffin JD, Kaple ML, Chow AR, Boulant JA. Cellular mechanisms for neuronal thermosensitivity in the rat hypothalamus. J Physiol 1996;492(Pt 1):231–42.
80. Guler AD, Lee H, Iida T, et al. Heat-evoked activation of the ion channel, TRPV4. J Neurosci 2002;22(15):6408–14.
81. Hadad E, Rav-Acha M, Heled Y, et al. Heat stroke: a review of cooling methods. Sports Med 2004;34(8):501–11.
82. Halliwill JR, Minson CT. Effect of hypoxia on arterial baroreflex control of heart rate and muscle sympathetic nerve activity in humans. J Appl Physiol (1985) 2002;93(3):857–64.
83. Haman F, Peronnet F, Kenny GP, et al. Effects of carbohydrate availability on sustained shivering I. Oxidation of plasma glucose, muscle glycogen, and proteins. J Appl Physiol (1985) 2004;96(1):32–40.
84. Hammel HT. Regulation of internal body temperature. Annu Rev Physiol 1968;30:641–710.
85. Hardy JD. Body temperature regulation. In: Mountcastle VB, editor. Medical physiology, vol. 2. 2nd ed. St Louis: Mosby; 1980.
86. Hellstrom B, Hammel HT. Some characteristics of temperature regulation in the unanesthetized dog. Am J Physiol 1967;213(2):547–56.
87. Hensel H. Cutaneous thermoreceptors. In: Iggo A, editor. Handbook of sensory physiology, vol. 2. Somatosensory systems. Berlin: Springer-Verlag; 1973.
88. Hensel H. Temperature receptors in the skin. In: Hardy JD, Gagge AP, Stolwijk JA, editors. Physiological and Behavioral Temperature Regulation. Springfield, IL: Thomas; 1970. p. 442–62.
89. Hesslink RL Jr, D'Alesandro MM, Armstrong DW 3rd, Reed HL. Human cold air habituation is independent of thyroxine and thyrotropin. J Appl Physiol (1985) 1992;72(6):2134–9.
90. Heus R, Daanen HA, Havenith G. Physiological criteria for functioning of hands in the cold: a review. Appl Ergon 1995;26(1):5–13.
91. Holowatz LA, Thompson-Torgerson C, Kenney WL. Aging and the control of human skin blood flow. Front Biosci (Landmark Ed) 2010;15:718–39.
92. Hong SI, Nadel ER. Thermogenic control during exercise in a cold environment. J Appl Physiol Respir Environ Exerc Physiol 1979;47(5):1084–9.
93. Hua le H, Strigo IA, Baxter LC, et al. Anteroposterior somatotopy of innocuous cooling activation focus in human dorsal posterior insular cortex. Am J Physiol Regul Integr Comp Physiol 2005;289(2):R319–25.
94. Hubing KA, Wingo JE, Brothers RM, et al. Nitric oxide synthase inhibition attenuates cutaneous vasodilation during postmenopausal hot flash episodes. Menopause 2010;17(5):978–82.
95. Ikeda T, Sessler DI, Marder D, Xiong J. Influence of thermoregulatory vasomotion and ambient temperature variation on the accuracy of core-temperature estimates by cutaneous liquid-crystal thermometers. Anesthesiology 1997;86(3):603–12.
96. Ikemoto S. Dopamine reward circuitry: Two projection systems from the ventral midbrain to the nucleus accumbens–olfactory tubercle complex. Brain Res Rev 2007;56(1):27–78.
97. Inoue Y, Nakao M, Araki T, Murakami H. Regional differences in the sweating responses of older and younger men. J Appl Physiol (1985) 1991;71(6):2453–9.
98. Jay O, Bain AR, Deren TM, et al. Large differences in peak oxygen uptake do not independently alter changes in core temperature and sweating during exercise. Am J Physiol Regul Integr Comp Physiol 2011;301(3):R832–41.
99. Johnson JM. Nonthermoregulatory control of human skin blood flow. J Appl Physiol (1985) 1986;61(5):1613–22.
100. Johnson JM. Physical training and the control of skin blood flow. Med Sci Sports Exerc 1998;30(3):382–6.
101. Johnson JM, Minson CT, Kellogg DL Jr. Cutaneous vasodilator and vasoconstrictor mechanisms in temperature regulation. Compr Physiol 2014;4(1):33–89.
102. Johnson JM, Niederberger M, Rowell LB, et al. Competition between cutaneous vasodilator and vasoconstrictor reflexes in man. J Appl Physiol 1973;35(6):798–803.
103. Johnston CE, Bristow GK, Elias DA, Giesbrecht GG. Alcohol lowers the vasoconstriction threshold in humans without affecting core cooling rate during mild cold exposure. Eur J Appl Physiol Occup Physiol 1996;74(3):293–5.
104. Johnston CE, White MD, Wu M, et al. Eucapnic hypoxia lowers human cold thermoregulatory response thresholds and accelerates core cooling. J Appl Physiol (1985) 1996;80(2):422–9.
105. Jones SR. Fever in the elderly. In: Mackowiak PA, editor. Fever: Basic mechanisms and management. 2nd ed. Philadelphia: Lippincott-Raven; 1997.
106. Kanosue K, Crawshaw LI, Nagashima K, Yoda T. Concepts to utilize in describing thermoregulation and neurophysiological evidence for how the system works. Eur J Appl Physiol 2010;109(1):5–11.
107. Kanosue K, Sadato N, Okada T, et al. Brain activation during whole body cooling in humans studied with functional magnetic resonance imaging. Neurosci Lett 2002;329(2):157–60.
108. Kasai T, Hirose M, Matsukawa T, et al. Preoperative blood pressure and catecholamines related to hypothermia during general anesthesia. Acta Anaesthesiol Scand 2003;47(2):208–12.
109. Kauer JA, Gibson HE. Hot flash: TRPV channels in the brain. Trends Neurosci 2009;32(4):215–24.
110. Kayman H. Management of fever: Making evidence-based decisions. Clin Pediatr (Phila) 2003;42(5):383–92.
111. Kellogg DL Jr, Crandall CG, Liu Y, et al. Nitric oxide and cutaneous active vasodilation during heat stress in humans. J Appl Physiol (1985) 1998;85(3):824–9.
112. Kellogg DL Jr, Zhao JL, Wu Y, Johnson JM. Nitric oxide and receptors for VIP and PACAP in cutaneous active vasodilation during heat stress in humans. J Appl Physiol (1985) 2012;113(10):1512–18.
113. Khan F, Spence VA, Belch JJ. Cutaneous vascular responses and thermoregulation in relation to age. Clin Sci (Lond) 1992;82(5):521–8.
114. Kluger MJ. Is fever beneficial? Yale J Biol Med 1986;59(2):89–95.
115. Kolka MA, Stephenson LA. Control of sweating during the human menstrual cycle. Eur J Appl Physiol Occup Physiol 1989;58(8):890–5.
116. Kolka MA, Stephenson LA. Resetting the thermoregulatory set-point by endogenous estradiol or progesterone in women. Ann N Y Acad Sci 1997;813:204–6.
117. Kronenberg F. Hot flashes: Phenomenology, quality of life, and search for treatment options. Exp Gerontol 1994;29(3–4):319–36.

118. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. N Engl J Med 1996;334(19):1209–15.
119. Latzka WA, Sawka MN, Montain SJ, et al. Hyperhydration: Thermoregulatory effects during compensable exercise-heat stress. J Appl Physiol (1985) 1997;83(3):860–6.
120. Latzka WA, Sawka MN, Montain SJ, et al. Hyperhydration: Tolerance and cardiovascular effects during uncompensable exercise-heat stress. J Appl Physiol (1985) 1998;84(6):1858–64.
121. Lee JY, Wakabayashi H, Wijayanto T, Tochihara Y. Differences in rectal temperatures measured at depths of 4-19 cm from the anal sphincter during exercise and rest. Eur J Appl Physiol 2010;109(1): 73–80.
122. Lenhardt R, Sessler DI. Estimation of mean body temperature from mean skin and core temperature. Anesthesiology 2006;105(6): 1117–21.
123. Leslie K, Sessler DI. Perioperative hypothermia in the high-risk surgical patient. Best Pract Res Clin Anaesthesiol 2003;17(4):485–98.
124. Lindqvist PG, Marsal K, Merlo J, Pirhonen JP. Thermal response to submaximal exercise before, during and after pregnancy: a longitudinal study. J Matern Fetal Neonatal Med 2003;13(3):152–6.
125. Lolicato M, Riegelhaupt PM, Arrigoni C, et al. Transmembrane helix straightening and buckling underlies activation of mechanosensitive and thermosensitive K(2P) channels. Neuron 2014;84(6):1198–212.
126. Low DA, Davis SL, Keller DM, et al. Cutaneous and hemodynamic responses during hot flashes in symptomatic postmenopausal women. Menopause 2008;15(2):290–5.
127. Low DA, Hubing KA, Del Coso J, Crandall CG. Mechanisms of cutaneous vasodilation during the postmenopausal hot flash. Menopause 2011;18(4):359–65.
128. Low PA. Evaluation of sudomotor function. Clin Neurophysiol 2004; 115(7):1506–13.
129. MacKenzie MA. Poikilothermia in man: Pathophysiological aspects and clinical implications [thesis]. Nijmegen, The Netherlands: University of Nijmegen; 1996.
130. Mackowiak PA. Clinical thermometric measurements. In: Mackowiak PA, editor. Fever: Basic mechanisms and management. 2nd ed. Philadelphia: Lippincott-Raven; 1997.
131. Mackowiak PA, Bartlett JG, Borden EC, et al. Concepts of fever: Recent advances and lingering dogma. Clin Infect Dis 1997;25(1): 119–38.
132. Malcolm RD, Alkana RL. Temperature dependence of ethanol lethality in mice. J Pharm Pharmacol 1983;35(5):306–11.
133. Maswood N, Cosmi S, Alfinito PD, et al. The role of the selective serotonin reuptake inhibitor fluoxetine in temperature regulation in ovariectomized rat models. Neuroendocrinology 2006;84(5):330–8.
134. McAllen RM, Farrell M, Johnson JM, et al. Human medullary responses to cooling and rewarming the skin: A functional MRI study. Proc Natl Acad Sci U S A 2006;103(3):809–13.
135. McAllen RM, Tanaka M, Ootsuka Y, McKinley MJ. Multiple thermoregulatory effectors with independent central controls. Eur J Appl Physiol 2010;109(1):27–33.
136. McKemy DD, Neuhausser WM, Julius D. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature 2002;416(6876):52–8.
137. McKinley MJ, Yao ST, Uschakov A, et al. The median preoptic nucleus: Front and centre for the regulation of body fluid, sodium, temperature, sleep and cardiovascular homeostasis. Acta Physiol (Oxf) 2015;214(1):8–32.
138. Mitchell D, Maloney SK, Jessen C, et al. Adaptive heterothermy and selective brain cooling in arid-zone mammals. Comp Biochem Physiol B Biochem Mol Biol 2002;131(4):571–85.
139. Morrison SF, Madden CJ. Central nervous system regulation of brown adipose tissue. Compr Physiol 2014;4(4):1677–713.
140. Morrison SF, Nakamura K, Madden CJ. Central control of thermogenesis in mammals. Exp Physiol 2008;93(7):773–97.
141. Moseley PL. Heat shock proteins and heat adaptation of the whole organism. J Appl Physiol (1985) 1997;83(5):1413–17.
142. Mount LE. Adaptation to thermal environment: Man and his productive animals. Baltimore: University Park Press; 1979.
143. Mount LE. The climatic physiology of the pig. London: Edward Arnold; 1968.
144. Nadel ER, Bullard RW, Stolwijk JA. Importance of skin temperature in the regulation of sweating. J Appl Physiol 1971;31(1):80–7.
145. Nadel ER, Mitchell JW, Saltin B, Stolwijk JA. Peripheral modifications to the central drive for sweating. J Appl Physiol 1971;31(6):828–33.
146. Nadel ER, Pandolf KB, Roberts MF, Stolwijk JA. Mechanisms of thermal acclimation to exercise and heat. J Appl Physiol 1974; 37(4):515–20.
147. Nagashima K, Matsue K, Konishi M, et al. The involvement of *Cry1* and *Cry2* genes in the regulation of the circadian body temperature rhythm in mice. Am J Physiol Regul Integr Comp Physiol 2005;288(1): R329–35.
148. Nakamura K. Central circuitries for body temperature regulation and fever. Am J Physiol Regul Integr Comp Physiol 2011;301(5): R1207–28.
149. Nakamura K, Morrison SF. A thermosensory pathway that controls body temperature. Nat Neurosci 2008;11(1):62–71.
150. Nakamura M, Yoda T, Crawshaw LI, et al. Regional differences in temperature sensation and thermal comfort in humans. J Appl Physiol (1985) 2008;105(6):1897–906.
151. Newburgh LH. Physiology of heat regulation and the science of clothing. Philadelphia: WB Saunders; 1949.
152. Nielsen B, Hales JR, Strange S, et al. Human circulatory and thermoregulatory adaptations with heat acclimation and exercise in a hot, dry environment. J Physiol 1993;460:467–85.
153. Nielsen B, Kaciuba-Uscilko H. Temperature regulation in exercise. In: Blatteis CM, editor. Physiology & pathophysiology of temperature regulation. Singapore: World Scientific; 1998.
154. Nielsen B, Strange S, Christensen NJ, et al. Acute and adaptive responses in humans to exercise in a warm, humid environment. Pflugers Arch 1997;434(1):49–56.
155. Noel J, Zimmermann K, Busserolles J, et al. The mechano-activated $K^+$ channels TRAAK and TREK-1 control both warm and cold perception. EMBO J 2009;28(9):1308–18.
156. Nybo L, Rasmussen P, Sawka MN. Performance in the heat-physiological factors of importance for hyperthermia-induced fatigue. Compr Physiol 2014;4(2):657–89.
157. Nybo L, Secher NH. Counterpoint: humans do not demonstrate selective brain cooling during hyperthermia. J Appl Physiol (1985) 2011; 110(2):571–3, discussion 581-572.
158. Nybo L, Secher NH, Nielsen B. Inadequate heat release from the human brain during prolonged exercise with hyperthermia. J Physiol 2002;545(Pt 2):697–704.
159. O'Brien C. Reproducibility of the cold-induced vasodilation response in the human finger. J Appl Physiol (1985) 2005;98(4): 1334–40.
160. O'Brien DL, Rogers IR, Holden W, et al. The accuracy of oral predictive and infrared emission detection tympanic thermometers in an emergency department setting. Acad Emerg Med 2000;7(9):1061–4.
161. Olausson H, Charron J, Marchand S, et al. Feelings of warmth correlate with neural activity in right anterior insular cortex. Neurosci Lett 2005;389(1):1–5.
162. Olsen TS, Weber UJ, Kammersgaard LP. Therapeutic hypothermia for acute stroke. Lancet Neurol 2003;2(7):410–16.
163. Pandolf KB, Gange RW, Latzka WA, et al. Human thermoregulatory responses during heat exposure after artificially induced sunburn. Am J Physiol 1992;262(4 Pt 2):R610–16.
164. Pandolf KB, Gange RW, Latzka WA, et al. Human thermoregulatory responses during cold water immersion after artificially induced sunburn. Am J Physiol 1992;262(4 Pt 2):R617–23.
165. Panksepp J. Hypothalamic integration of behavior: Rewards, punishments and related psycho-biological processes. In: Morgane PJ, Panksepp J, editors. Handbook of the hypothalamus, vol. 3, part B. New York: Marcel Dekker; 1981.
166. Passias TC, Meneilly GS, Mekjavic IB. Effect of hypoglycemia on thermoregulatory responses. J Appl Physiol (1985) 1996;80(3): 1021–32.
167. Patapoutian A, Peier AM, Story GM, Viswanath V. ThermoTRP channels and beyond: Mechanisms of temperature sensation. Nat Rev Neurosci 2003;4(7):529–39.
168. Patterson MJ, Stocks JM, Taylor NA. Humid heat acclimation does not elicit a preferential sweat redistribution toward the limbs. Am J Physiol Regul Integr Comp Physiol 2004;286(3):R512–18.
169. Peier AM, Moqrich A, Hergarden AC, et al. A TRP channel that senses cold stimuli and menthol. Cell 2002;108(5):705–15.
170. Petersen MH, Hauge HN. Can training improve the results with infrared tympanic thermometers? Acta Anaesthesiol Scand 1997;41(8): 1066–70.
171. Polderman KH. Application of therapeutic hypothermia in the intensive care unit: Opportunities and pitfalls of a promising treatment modality. Part 2. Practical aspects and side effects. Intensive Care Med 2004;30(5):757–69.
172. Premkumar LS, Ahern GP. Induction of vanilloid receptor channel activity by protein kinase C. Nature 2000;408(6815):985–90.
173. Prezant DJ, Richner B, Valentine DE, et al. Temperature dependence of rat diaphragm muscle contractility and fatigue. J Appl Physiol (1985) 1990;69(5):1740–5.
174. Ramanathan NL. A new weighting system for mean surface temperature of the human body. J Appl Physiol 1964;19:531–3.
175. Regan JM, Macfarlane DJ, Taylor NA. An evaluation of the role of skin temperature during heat adaptation. Acta Physiol Scand 1996; 158(4):365–75.

176. Rein H. Uber die tophographie der warmempfindung. Beziehungen zwischen innervation und rezeptorischen endorganen. Z Biol 1925; 82:513.
177. Reinberg A, Smolensky M. Chronobiology and thermoregulation. In: Schonbaum E, Lomax P, editors. Thermoregulation: physiology and biochemistry. New York: Pergamon Press; 1990.
178. Robinson J, Charlton J, Seal R, et al. Oesophageal, rectal, axillary, tympanic and pulmonary artery temperatures during cardiac surgery. Can J Anaesth 1998;45(4):317–23.
179. Rogers IR, O'Brien DL, Wee C, et al. Infrared emission tympanic thermometers cannot be relied upon in a wilderness setting. Wilderness Environ Med 1999;10(3):201–3.
180. Rolls ET, Grabenhorst F, Parris BA. Warm pleasant feelings in the brain. Neuroimage 2008;41(4):1504–13.
181. Romanovsky AA, Almeida MC, Garami A, et al. The transient receptor potential vanilloid-1 channel in thermoregulation: A thermosensor it is not. Pharmacol Rev 2009;61(3):228–61.
182. Romanovsky AA, Quint PA, Benikova Y, Kiesow LA. A difference of 5 degrees C between ear and rectal temperatures in a febrile patient. Am J Emerg Med 1997;15(4):383–5.
183. Romanovsky AA, Shido O, Sakurada S, et al. Endotoxin shock: Thermoregulatory mechanisms. Am J Physiol 1996;270(4 Pt 2): R693–703.
184. Rosenspire AJ, Kindzelskii AL, Petty HR. Cutting edge: Fever-associated temperatures enhance neutrophil responses to lipopolysaccharide: a potential mechanism involving cell metabolism. J Immunol 2002;169(10):5396–400.
185. Roth J, Blatteis CM. Mechanisms of fever production and lysis: Lessons from experimental LPS fever. Compr Physiol 2014;4(4): 1563–604.
186. Rowell LB. Human cardiovascular adjustments to exercise and thermal stress. Physiol Rev 1974;54(1):75–159.
187. Saad AR, Stephens DP, Bennett LA, et al. Influence of isometric exercise on blood flow and sweating in glabrous and nonglabrous human skin. J Appl Physiol (1985) 2001;91(6):2487–92.
188. Sagawa S, Shiraki K, Konda N. Cutaneous vascular responses to heat simulated at a high altitude of 5,600 m. J Appl Physiol (1985) 1986; 60(4):1150–4.
189. Saito M, Okamatsu-Ogura Y, Matsushita M, et al. High incidence of metabolically active brown adipose tissue in healthy adult humans: effects of cold exposure and adiposity. Diabetes 2009;58(7): 1526–31.
190. Satinoff E. Behavioral thermoregulation in response to local cooling of the rat brain. Am J Physiol 1964;206:1389–94.
191. Satinoff E, Rutstein J. Behavioral thermoregulation in rats with anterior hypothalamic lesions. J Comp Physiol Psychol 1970;71(1): 77–82.
192. Satinoff E, Shan SY. Loss of behavioral thermoregulation after lateral hypothalamic lesions in rats. J Comp Physiol Psychol 1971;77(2): 302–12.
193. Sato KT, Kane NL, Soos G, et al. Reexamination of tympanic membrane temperature as a core temperature. J Appl Physiol (1985) 1996; 80(4):1233–9.
194. Savage MV, Brengelmann GL. Control of skin blood flow in the neutral zone of human body temperature regulation. J Appl Physiol (1985) 1996;80(4):1249–57.
195. Sawka MN. Physiological consequences of hypohydration: Exercise performance and thermoregulation. Med Sci Sports Exerc 1992;24(6): 657–70.
196. Schlader ZJ, Perry BG, Jusoh MR, et al. Human temperature regulation when given the opportunity to behave. Eur J Appl Physiol 2013; 113(5):1291–301.
197. Schmidt-Nielsen K. Animal physiology: Adaptation and environment. 5th ed. Cambridge: Cambridge University Press; 1997.
198. Schonbaum E, Lomax P. Temperature regulation and drugs: an introduction. In: Schonbaum E, Lomax P, editors. Thermoregulation: Physiology and biochemistry. New York: Pergamon Press; 1990.
199. Segal SS, Faulkner JA, White TP. Skeletal muscle fatigue in vitro is temperature dependent. J Appl Physiol (1985) 1986;61(2):660–5.
200. Sessler DI. Mild perioperative hypothermia. N Engl J Med 1997; 336(24):1730–7.
201. Sessler DI. Perianesthetic thermoregulation and heat balance in humans. FASEB J 1993;7(8):638–44.
202. Sessler DI. Perioperative thermoregulation and heat balance. Ann N Y Acad Sci 1997;813:757–77.
203. Shibasaki M, Kondo N, Tominaga H, et al. Continuous measurement of tympanic temperature with a new infrared method using an optical fiber. J Appl Physiol (1985) 1998;85(3):921–6.
204. Silva JE. The thermogenic effect of thyroid hormone and its clinical implications. Ann Intern Med 2003;139(3):205–13.
205. Silva NL, Boulant JA. Effects of testosterone, estradiol, and temperature on neurons in preoptic tissue slices. Am J Physiol 1986;250 (4 Pt 2):R625–32.
206. Simmons GH, Barrett-O'Keefe Z, Minson CT, Halliwill JR. Cutaneous vascular and core temperature responses to sustained cold exposure in hypoxia. Exp Physiol 2011;96(10):1062–71.
207. Simmons GH, Minson CT, Cracowski JL, Halliwill JR. Systemic hypoxia causes cutaneous vasodilation in healthy humans. J Appl Physiol (1985) 2007;103(2):608–15.
208. Sokolnicki LA, Roberts SK, Wilkins BW, et al. Contribution of nitric oxide to cutaneous microvascular dilation in individuals with type 2 diabetes mellitus. Am J Physiol Endocrinol Metab 2007;292(1): E314–18.
209. Sokolnicki LA, Strom NA, Roberts SK, et al. Skin blood flow and nitric oxide during body heating in type 2 diabetes mellitus. J Appl Physiol (1985) 2009;106(2):566–70.
210. Soler R, Echegaray M, Rivera MA. Thermal responses and body fluid balance of competitive male swimmers during a training session. J Strength Cond Res 2003;17(2):362–7.
211. Solianik R, Skurvydas A, Vitkauskiene A, Brazaitis M. Gender-specific cold responses induce a similar body-cooling rate but different neuroendocrine and immune responses. Cryobiology 2014;69(1):26–33.
212. Soultanakis-Aligianni HN. Thermoregulation during exercise in pregnancy. Clin Obstet Gynecol 2003;46(2):442–55.
213. Stashak AB, Brewer JD. Management of hyperhidrosis. Clin Cosmet Investig Dermatol 2014;7:285–99.
214. Stephens DP, Charkoudian N, Benevento JM, et al. The influence of topical capsaicin on the local thermal control of skin blood flow in humans. Am J Physiol Regul Integr Comp Physiol 2001;281(3): R894–901.
215. Stephenson LA, Kolka MA. Menstrual cycle phase and time of day alter reference signal controlling arm blood flow and sweating. Am J Physiol 1985;249(2 Pt 2):R186–91.
216. Stevens ED. The evolution of endothermy. J Theor Biol 1973;38(3): 597–611.
217. Stevens JC, Choo KK. Temperature sensitivity of the body surface over the life span. Somatosens Mot Res 1998;15(1):13–28.
218. Stolwijk JA, Nadel ER. Thermoregulation during positive and negative work exercise. Fed Proc 1973;32(5):1607–13.
219. Strughold H, Porz R. Die dichte der kaltpunkte auf der haut der menschlichen korpers. Z Biol 1931;91:563.
220. Talavera K, Yasumatsu K, Voets T, et al. Heat activation of TRPM5 underlies thermal sensitivity of sweet taste. Nature 2005;438(7070): 1022–5.
221. Tamaki Y, Nakayama T. Effects of air constituents on thermosensitivities of preoptic neurons: Hypoxia versus hypercapnia. Pflugers Arch 1987;409(1–2):1–6.
222. Tankersley CG, Nicholas WC, Deaver DR, et al. Estrogen replacement in middle-aged women: Thermoregulatory responses to exercise in the heat. J Appl Physiol (1985) 1992;73(4):1238–45.
223. Thomas KA, Savage MV, Brengelmann GL. Effect of facial cooling on tympanic temperature. Am J Crit Care 1997;6(1):46–51.
224. Thompson HJ, Tkacs NC, Saatman KE, et al. Hyperthermia following traumatic brain injury: A critical evaluation. Neurobiol Dis 2003;12(3): 163–73.
225. Thornley LJ, Maxwell NS, Cheung SS. Local tissue temperature effects on peak torque and muscular endurance during isometric knee extension. Eur J Appl Physiol 2003;90(5–6):588–94.
226. Togashi K, Hara Y, Tominaga T, et al. TRPM2 activation by cyclic ADP-ribose at body temperature is involved in insulin secretion. EMBO J 2006;25(9):1804–15.
227. Tokizawa K, Uchida Y, Nagashima K. Thermoregulation in the cold changes depending on the time of day and feeding condition: Physiological and anatomical analyses of involved circadian mechanisms. Neuroscience 2009;164(3):1377–86.
228. Tyler CJ, Reeve T, Cheung SS. Cold-induced vasodilation during single digit immersion in 0 degrees C and 8 degrees C water in men and women. PLoS ONE 2015;10(4):e0122592.
229. Vinik AI, Nevoret M, Casellini C, Parson H. Neurovascular function and sudorimetry in health and disease. Curr Diab Rep 2013;13(4): 517–32.
230. Waterhouse J, Edwards B, Bedford P, et al. Thermoregulation during mild exercise at different circadian times. Chronobiol Int 2004;21(2): 253–75.
231. Weinert D. Circadian temperature variation and ageing. Ageing Res Rev 2010;9(1):51–60.
232. White MD, Greiner JG, McDonald PL. Point: Humans do demonstrate selective brain cooling during hyperthermia. J Appl Physiol (1985) 2011;110(2):569–71, discussion 581-562.
233. Wijers SL, Schrauwen P, van Baak MA, et al. Beta-adrenergic receptor blockade does not inhibit cold-induced thermogenesis in humans: Possible involvement of brown adipose tissue. J Clin Endocrinol Metab 2011;96(4):E598–605.
234. Wikstrom JD, Mahdaviani K, Liesa M, et al. Hormone-induced mitochondrial fission is utilized by brown adipocytes as an amplification pathway for energy expenditure. EMBO J 2014;33(5):418–36.

235. Wilkins BW, Chung LH, Tublitz NJ, et al. Mechanisms of vasoactive intestinal peptide-mediated vasodilation in human skin. J Appl Physiol (1985) 2004;97(4):1291–8.
236. Wilson MM, Morley JE. Invited review: Aging and energy balance. J Appl Physiol (1985) 2003;95(4):1728–36.
237. Wood SC. Interactions between hypoxia and hypothermia. Annu Rev Physiol 1991;53:71–85.
238. Yamada PM, Amorim FT, Moseley P, et al. Effect of heat acclimation on heat shock protein 72 and interleukin-10 in humans. J Appl Physiol (1985) 2007;103(4):1196–204.
239. Yamazaki F, Hamasaki K. Heat acclimation increases skin vasodilation and sweating but not cardiac baroreflex responses in heat-stressed humans. J Appl Physiol (1985) 2003;95(4):1567–74.
240. Yang Y, Gordon CJ. Regulated hypothermia in the hypothyroid rat induced by administration of propylthiouracil. Am J Physiol 1997; 272(5 Pt 2):R1390–5.
241. Yoda T, Crawshaw LI, Nakamura M, et al. Effects of alcohol on thermoregulation during mild heat exposure in humans. Alcohol 2005;36(3):195–200.
242. Yoda T, Crawshaw LI, Saito K, et al. Effects of alcohol on autonomic responses and thermal sensation during cold exposure in humans. Alcohol 2008;42(3):207–12.
243. Yoneshiro T, Saito M. Transient receptor potential activated brown fat thermogenesis as a target of food ingredients for obesity management. Curr Opin Clin Nutr Metab Care 2013;16(6):625–31.
244. Yoshida K, Li X, Cano G, et al. Parallel preoptic pathways for thermoregulation. J Neurosci 2009;29(38):11954–64.
245. Young CC, Sladen RN. Temperature monitoring. Int Anesthesiol Clin 1996;34(3):149–74.
246. Yue Z, Xie J, Yu AS, et al. Role of TRP channels in the cardiovascular system. Am J Physiol Heart Circ Physiol 2015;308(3):H157–82.
247. Zhang YH, Yanase-Fujiwara M, Hosono T, Kanosue K. Warm and cold signals from the preoptic area: Which contribute more to the control of shivering in rats? J Physiol 1995;485(Pt 1):195–202.
248. Zweifler RM, Voorhees ME, Mahmood MA, Parnell M. Rectal temperature reflects tympanic temperature during mild induced hypothermia in nonintubated subjects. J Neurosurg Anesthesiol 2004;16(3): 232–5.

CHAPTER 7

# Accidental Hypothermia

DANIEL F. DANZL AND MARTIN R. HUECKER

Although used for medical purposes for millennia, cold modalities were not scientifically evaluated until the 18th century. The hemostatic, analgesic, and therapeutic effects of cold on various conditions were well known. Biblical references cite truncal rewarming of King David by a damsel; various remedies were mentioned by Hippocrates, Aristotle, and Galen.[253] Folklore from Maine still recounts the buggy ride of "Frozen Charlotte."

The effects of cold on human performance are perhaps best documented in military history.[65,226] Frosty conditions have decided many battles. Numerous casualties occur even in training. Most cold injuries currently encountered affect destitute urban people and wilderness or sports enthusiasts, such as skiers, hunters, sailors, climbers, and swimmers.[6,278] The popularity of Arctic and mountain expeditions increases the number of persons at risk.[3,145] Among those challenging the environment are climbers of Mt Everest, Mt Hood, and Denali.[122,212,236]

## EPIDEMIOLOGY

In most countries, deaths from primary hypothermia are considered violent and classified as accidental, homicidal, or suicidal.[41] Deaths from secondary hypothermia are usually considered natural complications of systemic disorders, including trauma, carcinoma, and sepsis. The true incidence of secondary hypothermia throughout the world is unknown because hypothermic persons found indoors usually have other serious and diverting medical illnesses. In addition, delays are common between hospital admission and death, so secondary hypothermia is significantly underreported. In contrast, death certificate data more accurately quantify primary hypothermia.[81]

Hypothermia occurs in various locations and in all seasons.[33,222,293,340] In a multicenter survey of 428 cases of civilian accidental hypothermia, 69 occurred in Florida.[62,319] Urban settings account for the majority of cases in most industrialized countries.[62,279,309] An annual average of more than 1300 deaths is attributed to primary hypothermia in the United States. About one-half these fatalities are in patients older than 65, and 67% are males.[17]

The reason for any year-to-year decline in fatalities is unknown. Of note, the incidence of secondary hypothermia fatalities is much greater, but there are no reliable histologic criteria to confirm that hypothermia is the cause of death.

### CLASSIFICATIONS

*Accidental hypothermia* is best defined as the unintentional decrease of about 2°C (3.6°F) in the "normal" core temperature of 37.2° to 37.7°C (99.0° to 99.9°F) without disease in the preoptic and anterior hypothalamic nuclei (Table 7-1). Classically, hypothermia is defined as a core temperature below 35°C (95°F).[78] Hypothermia is both a symptom and a clinical disease entity. When sufficient heat cannot be generated to maintain homeostasis and core temperature drops below 30°C (86°F), the patient becomes poikilothermic and cools to the ambient temperature.[182,61]

Among clinical classifications, the most practical division includes healthy patients with simple environmental exposure (primary), those with specific diseases that produce hypothermia (secondary), and those with predisposing conditions. Other divisions that reflect the etiology of hypothermia include immersion versus nonimmersion and acute versus chronic heat loss.[204,228]

Various physiologic stressors and other factors can impair thermoregulation.[286] Age extremes, state of health and nutrition, type of exposure, and a multitude of intoxicants or medications can jeopardize thermostability by decreasing heat production or increasing heat loss. Physiologic stressors also include dehydration, sleep deprivation, and fatigue. These challenges increase heat loss through evaporation, radiation, conduction, and convection, and compensatory responses often fail.[204] The resulting mortality rates range to well over 50% in many clinical series, depending largely on the severity of risk factors and on patient selection criteria.[62,222,270,340]

For safety, experimental investigations of induced hypothermia in human volunteers usually terminate cooling at about 35°C (95°F). Naturally, this precludes analysis of some of the more significant pathophysiologic features of moderate or severe hypothermia. Design limitations also occur in studies of anesthetized animals, because the results of these experiments require varying degrees of extrapolation to humans. For example, large differences exist both in the cardiovascular responses to interventions and in the amounts of peripheral musculature that are present, particularly in nonporcine animal models. As a result, clinical treatment recommendations must be predicated on the degree and duration of hypothermia and on the predisposing factors that are subsequently identified.[34,78,120,229]

## NORMAL PHYSIOLOGY OF TEMPERATURE REGULATION

Warm-blooded animals maintain a precariously dynamic equilibrium between heat production and heat loss.[152,153] The normal diurnal variation in humans is only 1°C (1.8°F). Because physiologic changes occurring in humans are modified by predisposing or contributory factors, the normal responses to severe temperature depression require significant extrapolation.[208,237]

Basal heat production usually averages 40 to 60 kilocalories per square meter (kcal/$m^2$) of body surface area per hour, which approximates the heat from a 100-watt incandescent bulb. This increases with shivering thermogenesis,[220] food ingestion, fever, activity, and cold stress. Normal thermoregulation in vertebrates involves transmitting cold sensation to hypothalamic neurons via the lateral spinothalamic tracts and the thalamus (Figure 7-1). Table 7-2 lists the physiologic characteristics of the four zones of hypothermia.

## PATHOPHYSIOLOGY

### NERVOUS SYSTEM

Numbing cold depresses the central nervous system (CNS), producing impaired memory and judgment, slurred speech, and decreased consciousness. During cold-weather expeditions, leaders are prone to impaired judgment, risk-taking behavior, and the attendant trauma. Temperature-dependent enzyme systems in the brain do not function properly at cold temperatures that are well tolerated by the kidneys. As a result, most patients are comatose below 30°C (86°F), although some remain amazingly alert.[138]

Neurons are initially stimulated by a 1°C (1.8°F) drop in temperature, but the brain does not always cool uniformly during accidental hypothermia. After the initial increase, there is a linear decrease in cerebral metabolism by 6% to 10% per degree Celsius from 35°C (95°F) to 25°C (77°F). Hypothermia can initially afford cerebral protection because of the diminished cerebral metabolic requirements for oxygen.[104] The electroencephalogram

**TABLE 7-1** Fahrenheit-to-Celsius Conversion Scale

| Fahrenheit† | Celsius* | Fahrenheit† | Celsius* |
|---|---|---|---|
| **95** | **35.00** | 63 | 17.22 |
| 94 | 34.44 | 62 | 16.67 |
| 93 | 33.89 | 61 | 16.11 |
| 92 | 33.33 | 60 | 15.56 |
| 91 | 32.78 | **59** | **15.00** |
| 90 | 32.22 | 58 | 14.44 |
| 89 | 31.67 | 57 | 13.89 |
| 88 | 31.11 | 56 | 13.33 |
| 87 | 30.56 | 55 | 12.78 |
| **86** | **30.00** | 54 | 12.22 |
| 85 | 29.44 | 53 | 11.67 |
| 84 | 28.89 | 52 | 11.11 |
| 83 | 28.33 | 51 | 10.56 |
| 82 | 27.78 | **50** | **10.00** |
| 81 | 27.22 | 49 | 9.44 |
| 80 | 26.67 | 48 | 8.89 |
| 79 | 26.11 | 47 | 8.33 |
| 78 | 25.56 | 46 | 7.78 |
| **77** | **25.00** | 45 | 7.22 |
| 76 | 24.44 | 44 | 6.67 |
| 75 | 23.89 | 43 | 6.11 |
| 74 | 23.33 | 42 | 5.56 |
| 73 | 22.78 | **41** | **5.00** |
| 72 | 22.22 | 40 | 4.44 |
| 71 | 21.67 | 39 | 3.89 |
| 70 | 21.11 | 38 | 3.33 |
| 69 | 20.56 | 37 | 2.78 |
| **68** | **20.00** | 36 | 2.22 |
| 67 | 19.44 | 35 | 1.67 |
| 66 | 18.89 | 34 | 1.11 |
| 65 | 18.33 | 33 | 0.56 |
| 64 | 17.78 | **32** | **0.00** |

*C = (F – 32) × 5/9
†F = 9/5 C + 32

is abnormal below 33.5°C (92.3°F) and becomes silent at 19° to 20°C (66.2° to 68°F). The triphasic waves typically noted in hypothermia are also observed in various metabolic, toxic, and diffuse encephalopathies. Visual evoked potentials, another objective measure of cerebral function, become smaller as the mercury drops. After cerebral cortical function becomes impaired, lower brainstem functions are also deranged.

Cerebrovascular autoregulation is protectively intact until the temperature drops below 25°C (77°F). Although vascular resistance is increased, blood flow is disproportionately redistributed to the brain. In canine studies, blood flow in the brain, muscle, kidneys, and myocardium recovers quickly to control levels after rewarming. Flow deficits persist in the pulmonary, digestive, and endocrine systems for up to 2 hours after rewarming.

Chilling the peripheral nervous system increases muscle tension and preshivering tone, eventually leading to shivering. Shivering, which is also centrally controlled, is a more efficient heat producer than are voluntary muscle contractions of the extremities.

## CARDIOVASCULAR SYSTEM

Many cardiovascular responses caused by or associated with hypothermia are well described.[184] Cold stress increases consumption of myocardial oxygen. Autonomic nervous system stimulation causes tachycardia and peripheral vasoconstriction, both of which increase systemic blood pressure and cardiac afterload.

As core temperature drops, there should be a fairly linear decrease in pulse rate. After premonitory tachycardia, decremental bradycardia produces a 50% decrease in heart rate at 28°C (82.4°F). Because this bradycardia is caused by decreased spontaneous depolarization of pacemaker cells, it is refractory to atropinization. If there is a "relative" tachycardia not consistent with the degree of hypothermia, the clinician should consider occult trauma with hypovolemia, drug ingestion, and hypoglycemia.

During hypothermic bradycardia, unlike normothermia, systole is more prolonged than diastole. In addition, the conduction system is more sensitive to cold than is the myocardium, so the cardiac cycle is lengthened. Cold-induced changes in pH, oxygen, electrolytes, and nutrients also alter electrical conduction.[203]

Hypothermia progressively decreases mean arterial pressure and the cardiac index. Cardiac output drops to about 45% of normal at 25°C (77°F). Systemic arterial resistance, determined by invasive hemodynamic monitoring, is increased. Even after rewarming, cardiovascular function may remain temporarily depressed, with impaired myocardial contractility, metabolism, and peripheral vascular function.

Mild, steady hypothermia in patients with poikilothermic thermoregulatory disorders causes electrocardiographic (ECG) alterations and conduction abnormalities.[9,71] First the PR, then the QRS, and most characteristically the QTc intervals are prolonged.

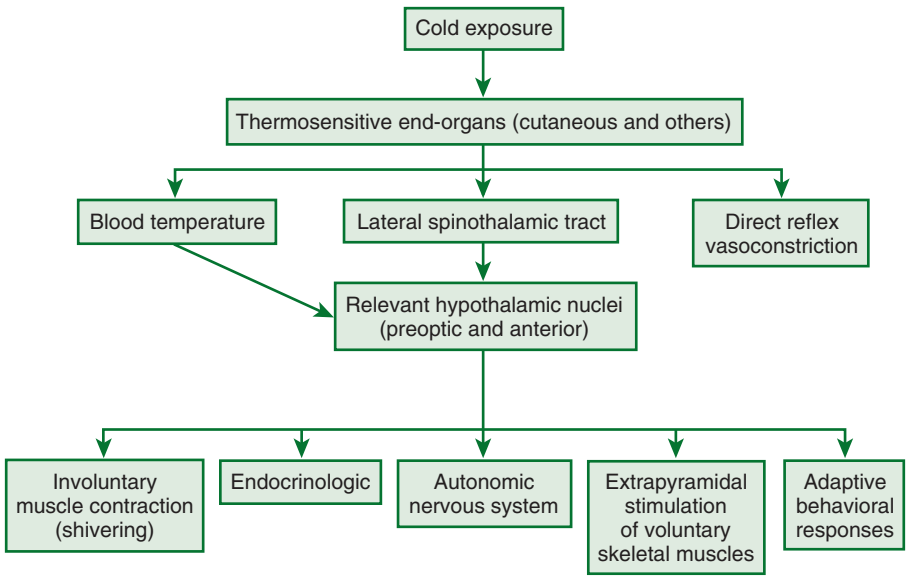



**FIGURE 7-1** Physiology of cold exposure.

**TABLE 7-2** Characteristics of the Four Zones of Hypothermia

| Stage | Core Temperature °C | Core Temperature °F | Characteristics |
|---|---|---|---|
| Mild | 37.6 | 99.7 ±1 | Normal rectal temperature |
| | 37.0 | 98.6 ±1 | Normal oral temperature |
| | 36.0 | 96.8 | Increases in metabolic rate, blood pressure, and preshivering muscle tone |
| | 35.0 | 95.0 | Urine temperature 34.8°C (94.6°F); maximal shivering thermogenesis |
| | 34.0 | 93.2 | Development of amnesia, dysarthria, and poor judgment; maladaptive behavior; normal blood pressure; maximal respiratory stimulation; tachycardia, then progressive bradycardia |
| | 33.30 | 91.4 | Development of ataxia and apathy; linear depression of cerebral metabolism; tachypnea, then progressive decrease in respiratory minute volume; cold diuresis |
| Moderate | 32.0 | 89.6 | Stupor; 25% decrease in oxygen consumption |
| | 31.0 | 87.8 | Extinguished shivering thermogenesis |
| | 30.0 | 86.0 | Development of atrial fibrillation and other arrhythmias; poikilothermia; cardiac output two-thirds normal; insulin ineffective |
| | 29.0 | 84.2 | Progressive decrease in level of consciousness, pulse, and respiration; pupils dilated; paradoxical undressing |
| Severe | 28.0 | 82.4 | Decreased ventricular fibrillation threshold; 50% decrease in oxygen consumption and pulse; hypoventilation |
| | 27.0 | 80.6 | Loss of reflexes and voluntary motion |
| | 26.0 | 78.8 | Major acid-base disturbances; no reflexes or response to pain |
| | 25.0 | 77.0 | Cerebral blood flow one-third normal; loss of cerebrovascular autoregulation; cardiac output 45% of normal; pulmonary edema may develop[106,258,264] |
| | 24.0 | 75.2 | Significant hypotension and bradycardia |
| | 23.0 | 73.4 | No corneal or oculocephalic reflexes; areflexia |
| | 22.0 | 71.6 | Maximal risk of ventricular fibrillation; 75% decrease in oxygen consumption |
| Profound | 20.0 | 68.0 | Lowest temperature for mechanical resumption of cardiac electromechanical activity; pulse 20% of normal |
| | 19.0 | 66.2 | Electroencephalographic silencing |
| | 18.0 | 64.4 | Asystole |
| | 13.7 | 56.7 | Lowest adult accidental hypothermia survival[106] |
| | 15.0 | 59.0 | Lowest infant accidental hypothermia survival[264] |
| | 10.0 | 50.0 | 92% decrease in oxygen consumption |
| | 9.0 | 48.2 | Lowest therapeutic hypothermia survival[237] |

Clinically invisible increased preshivering muscle tone can obscure the P waves; ST-segment and T-wave abnormalities are inconsistent.[9,326] Of note, standard surface ECG electrodes, when attached to dry skin, will accurately reflect cardiac electrical activity. Needle electrodes are not necessary to detect weak ECG signals.[170]

The *J wave* (Osborn wave or hypothermic hump; Figure 7-2), first described by Tomaszewski in 1938, occurs at the junction of the QRS complex and the ST segment. It is not prognostic but is potentially diagnostic.[108,177] J waves occur at any temperature below 32.2°C (90°F) and are most frequently seen in leads II and $V_6$. When core temperature falls below 25°C (77°F), J waves are found in the precordial leads (especially $V_3$ or $V_4$). The size of the J waves also increases with temperature depression, but is unrelated to arterial pH.[350] J waves are usually upright in aVL, aVF, and the left precordial leads.[4,158,241]

J waves may represent hypothermia-induced ion fluxes, resulting in delayed depolarization or early repolarization of the left ventricle, or there may be an unidentified hypothalamic or neurogenic factor. J waves are *not* pathognomonic of hypothermia but occur also with CNS lesions, focal cardiac ischemia, and sepsis.[158] J waves may also be present in young, healthy persons. When pronounced, J waveform abnormalities can simulate myocardial infarction. Computer software that can successfully recognize and suggest the diagnosis of hypothermia is not widely available (see Figure 7-2).[180,213,234]

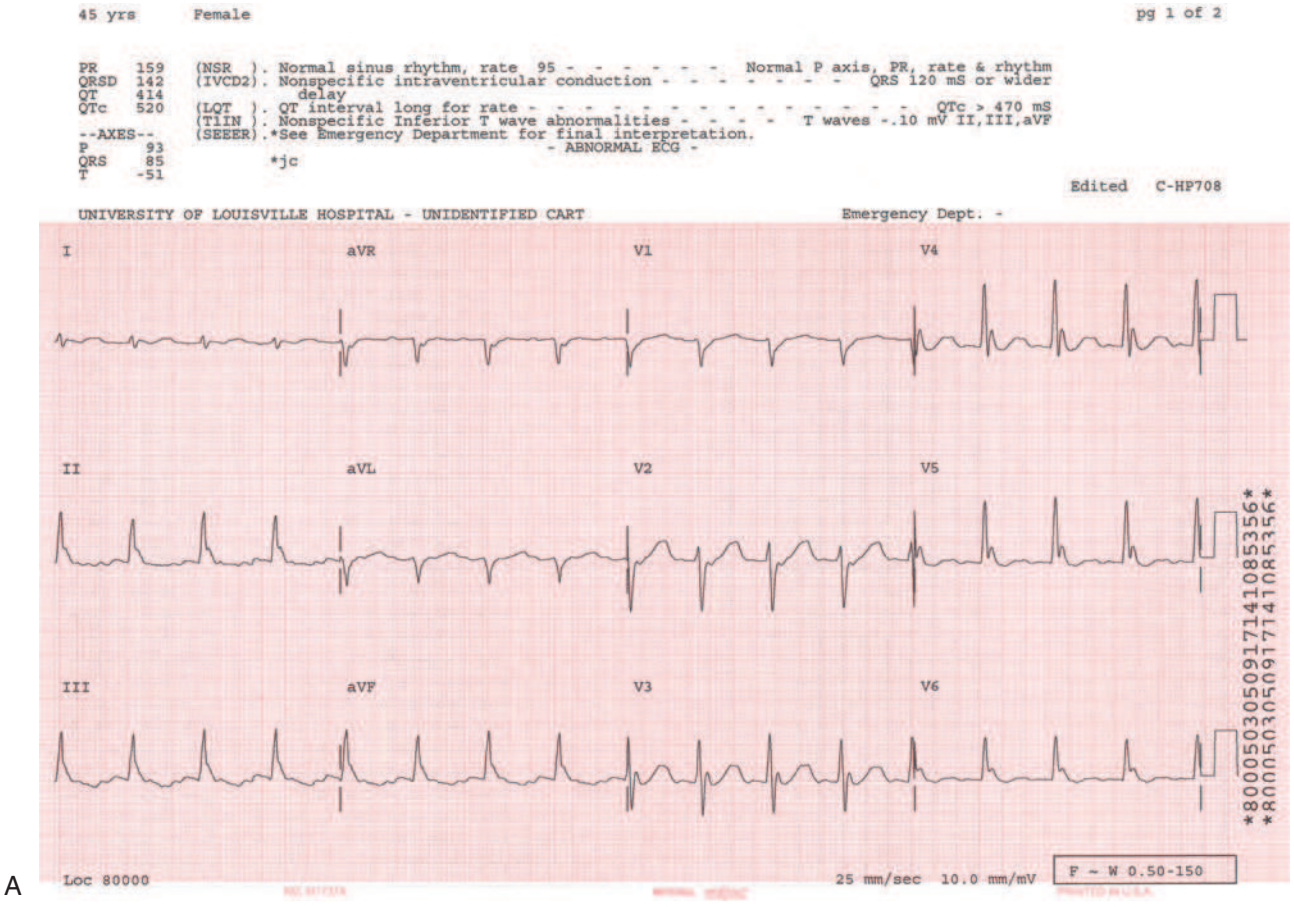
The prehospital capability to differentiate between J waves and injury current is particularly important in rural and wilderness settings with long patient transport times.[60] Thrombolysis is unstudied in accidental hypothermia but would be expected to exacerbate coagulopathies.[105]

Below 32.2°C (90°F), all types of atrial and ventricular arrhythmias are encountered.[45,77] The His-Purkinje system is more sensitive to cold than is the myocardium. As a result, conduction velocity decreases and electrical signals can disperse. Because conduction time is prolonged more than the absolute refractory period, reentry currents can produce circus rhythms (movements) that initiate ventricular fibrillation (VF).

In addition to causing bradycardia, widening the QRS complex, and prolonging the QT interval, hypothermia increases the duration of action potentials (Figure 7-3).[20] During rewarming, nonuniform myocardial temperatures can disperse conduction and further increase the action potential duration, another mechanism to develop the unidirectional blocks that facilitate reentrant arrhythmias. At temperatures between 25° and 20°C (77° and 68°F), myocardial conduction time is prolonged further than the absolute refractory period. Another arrhythmogenic mechanism is development of independent electrical foci that precipitate arrhythmias.

Various electrolyte abnormalities can further complicate the situation during hypothermic conditions, because they exacerbate the effects of prolonged action potentials. Most conspicuously, hypothermia-induced cellular calcium loading mimics digitalis toxicity and may predispose to a forme fruste of torsades de pointes.

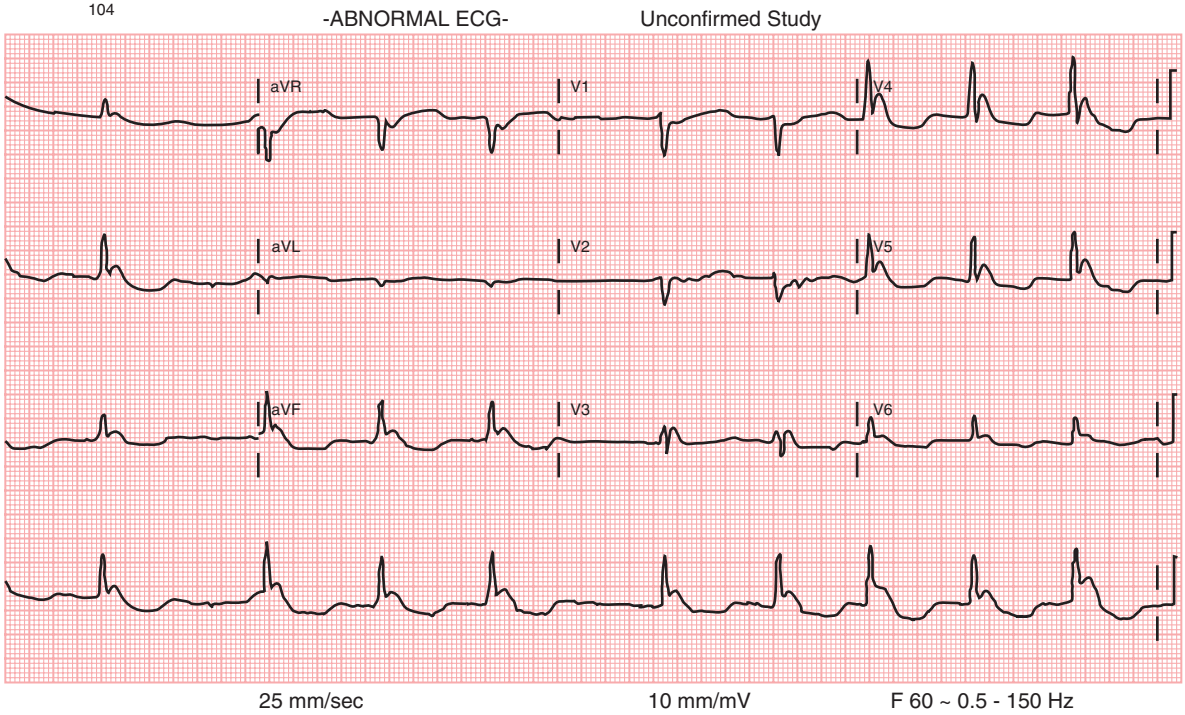
Hypothermia-induced VF and asystole often occur spontaneously below 25°C (77°F). The VF threshold and transmembrane resting potential are decreased. Because the heart is cold, the conduction delay is facilitated by the large dispersion of repolarization, and the action potential is prolonged. The increased temporal dispersion of the recovery of excitability is linked to VF. Nature's model of resistance to VF is the heart of hibernating animals during rewarming.[151] Animals with this capacity seem to be protected by a shortened QT duration and a calcium channel handling system that prevents intracellular calcium overload.




A

64 ATRIAL FIBRILLATION
229 NONSPECIFIC INTRAVENTRICULAR CONDUCTION DELAY
114 INFERIOR INJURY, PROBABLE EARLY ACUTE INFARCT
412 ST ELEVATION, PROBABLE ANTERIOR INJURY
426 LATERAL LEADS ARE ALSO INVOLVED
–AXIS– Standard 12 Lead Report
Abnormal ECG
68
104

Req MD:
Acct No:
Field2:
Field3:
Field4:




B

**FIGURE 7-2** The J or Osborn wave of hypothermia. Note that the obvious J waves are usually misinterpreted by the computer as injury current or nonspecific interventricular conduction delay (**A** and **B**).

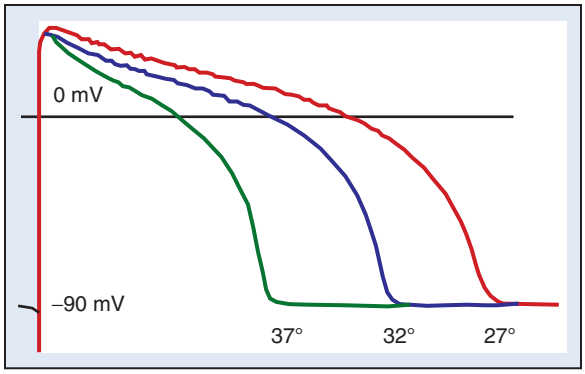



**FIGURE 7-3** Example of the effects of temperature on action potentials in cardiac cells.

Asystole and VF may both result from hypovolemia, tissue hypoxia, therapeutic manipulations, acid-base fluxes, autonomic dysfunction, and coronary vasoconstriction coupled with increased blood viscosity. Other causes may include rough handling or jostling, sudden vertical positioning, and acute metabolic stress from exertion or very rapid rewarming.

## CORE TEMPERATURE AFTERDROP

Core temperature afterdrop refers to the continued decline in a hypothermic patient's temperature after removal from the cold. Contributing to afterdrop is the simple temperature equilibration between the warmer core and cooler periphery. Circulatory changes account for another set of observations. The countercurrent cooling of blood that perfuses cold extremities results in core temperature decline until the existing temperature gradient is eliminated. In cold-water immersion, collapse after rescue may also result from abrupt hypotension following loss of hydrostatic squeeze contributed by the water.

The incidence and magnitude of core temperature afterdrop vary widely in clinical experiments and in surgically induced hypothermia.[99,100] Hayward[123] measured his own esophageal, rectal, tympanic, and cardiac temperatures (via flotation tip catheter) during rewarming after being cooled in 10°C (50°F) water. On three different days, rewarming was achieved by shivering thermogenesis, heated humidified inhalation, and warm-bath immersion. Coincident with a 0.3°C (0.5°F) afterdrop during warm-bath immersion, his mean arterial pressure fell 30% and peripheral vascular resistance fell 50%. Therefore, the circulatory mechanism is another major contributor to afterdrop.

A human study of peripheral blood flow during rewarming from mild hypothermia suggests that minimal skin blood flow changes can also lead to afterdrop (Figure 7-4). The largest core temperature afterdrops occur when participants are rewarmed with plumbed garments and heating pads.

In summary, core temperature afterdrop appears to become most clinically relevant when a large temperature gradient exists between the periphery and the core, particularly in dehydrated, chronically cold patients. Both conductive and convective mechanisms are responsible for afterdrop.[100] Stimulating peripheral blood flow can increase afterdrop. Major afterdrops are also observed when frostbitten extremities are thawed before crystalloid volume resuscitation and thermal stabilization of the core temperature.

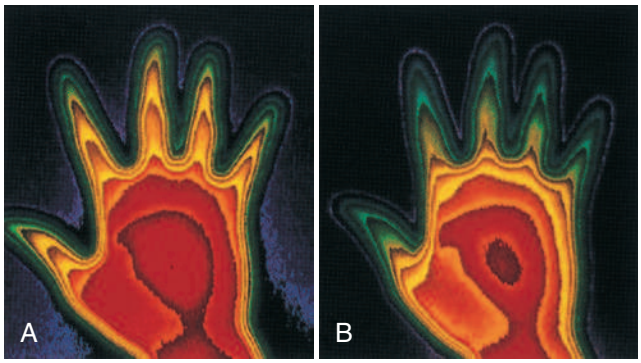



**FIGURE 7-4** Infrared scan of the palmar hand surface. *Blue,* 43°C (109.4°F); *red,* 68°C (154.4°F). **A,** At room temperature. **B,** After 5 minutes in a cold room, with evidence of vasoconstriction. *(Courtesy Naval Health Research Center, San Diego, Calif.)*

## RESPIRATORY SYSTEM

Any exposure to a large chill initially stimulates respiratory drive, which is followed by progressive depression of respiratory minute volume as cellular metabolism is depressed.[267] The respiratory rate often falls to 5 to 10 breaths/min below 30°C (86°F), and ultimately, brainstem neurocontrol of ventilation fails. An important physiologic observation is that carbon dioxide ($CO_2$) production drops 50% for each 8°C (14°F) fall in temperature. In severe hypothermia, $CO_2$ retention and respiratory acidosis reflect the aberrant responses to normothermic respiratory stimuli.[96]

Other pathophysiologic factors contributing to ventilation-perfusion mismatch include decreased ciliary motility, increased quantity and viscosity of secretions, hypothermic acute respiratory distress syndrome, and noncardiogenic pulmonary edema.[310] The thorax loses elasticity, and pulmonary compliance drops. The respiratory "bellows" stiffen and fail because of a decline in contractile efficiency of the intercostal muscles and diaphragm.

Box 7-1 lists pertinent, potentially protective or detrimental factors that affect tissue oxygenation in endothermic humans.

## RENAL SYSTEM

The kidneys respond briskly to hypothermia-induced changes in the vascular tree's capacitance. Peripheral vasoconstriction can result initially in a relative central hypervolemia, producing diuresis, even with mild dehydration. In addition, renal blood flow is depressed by 50% at 27° to 30°C (80.6° to 86°F), which decreases glomerular filtration rate. Nevertheless, there is an initial large diuresis of this dilute glomerular filtrate, which does not efficiently clear nitrogenous wastes.

The etiology of the cold diuresis is multifactorial.[110] Suggested mechanisms include inhibition of antidiuretic hormone (ADH) release and decreased renal tubular function. Neither hydration nor ADH infusions influence the diuretic response, which appears

**BOX 7-1 Oxygenation Considerations during Hypothermia**

**Detrimental Factors**

- Oxygen consumption increases with rise in temperature; use caution if rewarming is rapid; shivering also increases demand
- Decreased temperature shifts oxyhemoglobin dissociation curve to the left
- Ventilation-perfusion mismatch; atelectasis; decreased respiratory minute volume; bronchorrhea; decreased protective airway reflexes
- Decreased tissue perfusion from vasoconstriction; increased viscosity
- "Functional hemoglobin" concept: capability of hemoglobin to unload oxygen is lowered
- Decreased thoracic elasticity and pulmonary compliance

**Protective Factors**

- Reduction of oxygen consumption by 50% at 28°C (82.4°F), 75% at 22°C (71.6°F), and 92% at 10°C (50°F)
- Increased oxygen solubility in plasma
- Decreased pH and increased $PaCO_2$ shift oxyhemoglobin dissociation curve to right

to be an attempt to compensate for initial relative central hypervolemia that is caused by vasoconstrictive overload of capacitance vessels.

The diuresis may also be pressure related, caused by impaired autoregulation in the kidneys. Cold diuresis has circadian rhythmicity and correlates with periods of shivering. Cold-water immersion increases urine output 3.5 times, and the presence of ethanol impressively doubles this diuresis.

## COAGULATION

Coagulopathies often develop in hypothermic patients because of effects on the enzymatic nature of the activated clotting factors.[88] In vivo, clotting prolongation is proportional to the number of steps in the cascade. For example, at 29° C (84.2° F), a 50% to 60% increase in the partial thromboplastin time (PTT) would be expected. Kinetic tests of coagulation, however, are performed in the laboratory at 37° C (98.6° F). As the blood warms in the machine, the enzymes between the factors in the cascade are activated. The sample of warmed in vitro blood then clots normally.[79]

The reversible hemostatic defect created by hypothermia may not be reflected by the reported "normal" prothrombin time (PT), PTT,[272] or international normalized ratio (INR). This coagulopathy is basically independent of clotting factor levels and cannot be confirmed by laboratory studies performed at 37° C (98.6° F). Treatment is rewarming and not simply administration of clotting factors.[269] When rapid rewarming is difficult, concentrations of 0.01 to 1 nM of desmopressin may partially reverse hypothermia-induced coagulopathy in vitro.[351]

Thrombocytopenia as a cause of bleeding becomes progressively significant in severe hypothermia. Proposed mechanisms include direct bone marrow suppression and splenic or hepatic sequestration. Thromboxane $B_2$ production by platelets is also temperature dependent, so cooling skin temperature produces reversible platelet dysfunction. Thrombocytopenia is a common but poorly recognized corollary of hypothermia in neonates and older adults.

Coagulopathy in trauma patients is attributed to enzyme inhibition, platelet alteration, and fibrinolysis. The critical temperature at which enzyme activity slows significantly is 34° C (93.2° F).[334] In addition, clot strength weakens as a result of platelet malfunction. Fibrinolysis is not significantly affected at any temperature in the range measured (33° to 37° C [91.4° to 98.6° F]) (see Trauma, later).

Physiologic hypercoagulability also develops during hypothermia, with a sequence similar to that seen in disseminated intravascular coagulation (DIC). This produces a higher incidence of thromboembolism during hypothermia. Causes include thromboplastin release from cold tissue, simple circulatory collapse, and release of catecholamines and steroids. Because levels of fibrin split products can be normal, bleeding is not always considered a hematologic manifestation of DIC.

Whole-blood viscosity increases with the hemoconcentration seen after diuresis and the shift of fluid out of vascular compartments. Red blood cells (RBCs) simply stiffen and have diminished cellular deformability when chilled.[258] The elevated viscosity of hypothermia is also exacerbated by cryoglobulinemia. Cryofibrinogen is a cold-precipitated fibrinogen occasionally seen with carcinoma, sepsis, and collagen vascular diseases. Blood viscosity is increased by the transient increases in platelet and RBC counts seen with mild surface cooling. This explains the increased coronary and cerebral thromboses that occur in winter.[204]

# PREDISPOSING FACTORS

The factors that predispose to hypothermia can be separated into those that decrease heat production, increase heat loss, and impair thermoregulation.[204] There is significant overlap between these groups (Box 7-2).

## DECREASED HEAT PRODUCTION

Thermogenesis is decreased at both extremes of age.[54] In older adults, neuromuscular inefficiency and decreased physical activity impair shivering. Aging progressively diminishes homeostatic and cold-adaptive capabilities. Although most older adults have normal thermoregulation, they tend to develop conditions that impair heat conservation.[265]

**BOX 7-2 Factors Predisposing to Hypothermia**

**Decreased Heat Production**

***Endocrinologic Failure***
- Hypopituitarism
- Hypoadrenalism
- Hypothyroidism
- Lactic acidosis
- Diabetic and alcoholic ketoacidosis

***Insufficient Fuel***
- Hypoglycemia
- Malnutrition
- Marasmus
- Kwashiorkor
- Extreme physical exertion

***Neuromuscular Physical Exertion***
- Age extremes
- Impaired shivering
- Inactivity
- Lack of adaptation

**Impaired Thermoregulation**

***Peripheral Failure***
- Neuropathies
- Acute spinal cord transection
- Diabetes

***Central or Neurologic Failure***
- Cardiovascular accident
- Central nervous system (CNS) trauma
- Toxicologic effects
- Metabolic failure
- Subarachnoid hemorrhage
- Pharmacologic effects
- Hypothalamic dysfunction
- Parkinson's disease
- Anorexia nervosa
- Cerebellar lesion
- Neoplasm
- Congenital intracranial anomalies
- Multiple sclerosis
- Hyperkalemic periodic paralysis

**Increased Heat Loss**

***Environmental***
- Immersion
- Nonimmersion

***Induced Vasodilation***
- Pharmacologic effects
- Toxicologic effects

***Erythrodermas***
- Burns
- Psoriasis
- Ichthyosis
- Exfoliative dermatitis

***Iatrogenic***
- Emergency childbirth
- Cold infusions
- Heatstroke treatment

**Miscellaneous Associated Clinical States**
- Multisystem trauma
- Recurrent hypothermia
- Episodic hypothermia
- Shapiro syndrome
- Infections: bacterial, viral, parasitic
- Pancreatitis
- Carcinomatosis
- Cardiopulmonary disease
- Vascular insufficiency
- Uremia
- Paget's disease
- Giant cell arteritis
- Sarcoidosis
- Shaken baby syndrome
- Systemic lupus erythematosus
- Wernicke-Korsakoff syndrome
- Hodgkin's disease
- Shock
- Sickle cell anemia
- Sudden infant death syndrome

Older adults are physiologically less adept at increasing heat production and the respiratory quotient, which is the ratio of the volume of $CO_2$ produced to the volume of oxygen consumed per unit of time. Impaired thermal perception, possibly caused by decreased resting peripheral blood flow, leads to poor adaptive behavior. Metabolic studies also demonstrate that in severely hypothermic older adults, lipolysis occurs in preference to glucose consumption.[235,254]

Neonates have a large surface area–to–mass ratio, a relatively noninsulating subcutaneous tissue layer, and virtually no behavioral defense mechanisms. Newborn "unadapted" infants attempt to thermoregulate with initial vasoconstriction and acceleration of metabolic rate. In contrast, "adapted" infants who are older than 5 days can increase lipolysis immediately and "burn" oxidative brown adipose tissue.

No cause-and-effect relationship has been found between hypothermia and the mortality rate of premature infants.[282] Although the smaller infants in a neonatal intensive care unit are at the greatest risk for hypothermia, mortality is related to hypothermia only in larger neonates.

Emergency deliveries and resuscitations are responsible for most acute neonatal hypothermia. Other common risk factors are prematurity, low birth weight, inexperienced parents, perinatal morbidity, and low socioeconomic status. In babies with more chronically induced subacute hypothermia, lethargy, a weak cry, and failure to thrive are common.[314]

Many cold infants have "paradoxical rosy cheeks," looking surprisingly healthy. After the first few days of life, hypothermia frequently indicates septicemia and carries a high mortality rate. Low weight and malnutrition are common. Hypothermia in a low-birth-weight neonate should suggest the possibility of intracranial hemorrhage; hypothermia is also observed in shaken baby syndrome.

Endocrinologic failure, including hypopituitarism, hypoadrenalism, and myxedema, frequently decreases heat production. Interestingly, congenital adrenal hyperplasia with mineralocorticoid insufficiency is more common in cold climates, possibly an adaptive response to prolonged exposure to cold temperatures, because "normal" cold diuresis is reduced in these patients.

Hypothyroidism is often occult, with no history of cold intolerance, dry skin, lassitude, or arthralgias. A thyroid scar or any history of thyroid hormone replacement should be suggestive. The degree of temperature depression correlates fairly directly with mortality. About 80% of patients in myxedema coma, which is several times more common in female patients, are hypothermic.

The effects of insufficient nutrition extend from hypoglycemia to marasmus to kwashiorkor. Kwashiorkor is less often associated with hypothermia than is marasmus, because of the insulating effect of hypoproteinemic edema. Neuroglycopenia distorts hypothalamic function. Many alcoholic patients with hypothermia are hypoglycemic. Malnutrition decreases insulative subcutaneous fat and directly alters thermoregulation. Poor nutrition predisposes to hypothermia and its attendant clumsiness in older adult women with femoral neck fractures. Partly because of fuel depletion, hypothermia is as great a threat as hyperthermia in marathon races run in cool climates. Runners slowing from fatigue or injury late in a race are at serious risk for hypothermia.[155]

## INCREASED HEAT LOSS

Poorly acclimated and insulated individuals often have high diaphoretic, convective, and evaporative heat losses during exposure to cold. Because the skin functions as a radiator, any dermatologic malfunction increases heat loss. Such erythrodermas include psoriasis, exfoliative dermatitis, and toxic epidermal necrolysis.

Burns and inappropriate burn treatment cause excessive heat loss, as do other iatrogenic factors, including massive cold intravenous (IV) infusions and overcooling heatstroke patients. When $CO_2$ is used for abdominal insufflation before laparoscopy, warming the gas before administration helps prevent hypothermia.

Many pharmacologic and toxicologic agents both increase heat loss and impair thermoregulation.[152,153,320] The most common is ethanol, which interacts with every putative thermoregulatory neurotransmitter. Although ingestion of ethanol produces a feeling of warmth and perhaps visible flushing, it is the major cause of urban hypothermia.[62,222] In fatal cases of accidental hypothermia, many victims are under the influence of ethanol. In children with ethanol intoxication, hypothermia is common.

Ethanol is also a poikilothermia-producing agent that directly impairs thermoregulation at high or low temperatures. Body temperature is lowered both from cutaneous vasodilation with radiative heat loss and from impaired shivering thermogenesis. Chronic ethanol ingestion damages the mammillary bodies and posterior hypothalamus, which modulates shivering thermogenesis.[259] Ethanol also increases the risk for being exposed to the environment by modifying protective adaptive behavior. The ultimate example is *paradoxical undressing,* or removal of clothing in response to a cold stress.[110]

The neurophysiologic effects of ethanol are modified by duration and intensity of exercise, food consumption, and applied cold stress.[92] Aging increases sensitivity to the hypothermic actions of ethanol. Chronic ingestion yields tolerance to its hypothermic effects, and rebound hyperthermia may be seen during withdrawal. Conditions associated with ethanol ingestion that adversely affect heat balance include immobility and hypoglycemia.[345]

Inhibited hepatic gluconeogenesis coexists with malnutrition. Hypothermic alcoholic ketoacidosis occurs.[340] IV thiamine is diagnostic and therapeutic for Wernicke's encephalopathy, another cause of reversible hypothermia. The acute triad of global confusion, ophthalmoplegia, and truncal ataxia is often masked by hypothermia, and temperature depression may persist for weeks.

## IMPAIRED THERMOREGULATION

Various conditions that impair thermoregulation can be considered as having central, peripheral, metabolic, and pharmacologic or toxicologic effects.

### Central Effects

Central conditions may directly affect hypothalamic function and mediate vasodilation. Traumatic lesions include skull fractures, especially basilar, and intracerebral hemorrhages, most often chronic subdural hematomas. Pathologic lesions include neoplasms, congenital anomalies, and Parkinson's disease. Patients with Parkinson's or Alzheimer's disease, because of global neurologic impairment, are particularly at behavioral risk. Finally, cerebellar lesions also impede heat production because of inefficient choreiform shivering.

Hypothermia can occur with Reye's syndrome. In Hodgkin's disease, hypothermia is seen only in previously febrile patients with advanced disease. This is a disease-associated functional disorder of thermoregulation, similar to that seen in anorexia nervosa. Centrally induced hypothermia is completely antagonized with thyrotropin-releasing hormone.

### Peripheral Effects

Peripheral thermoregulation fails after acute spinal cord transection. Patients are functionally poikilothermic as soon as peripheral vasoconstriction is extinguished.[219] Other peripheral impediments to thermostability include neuropathies and diabetes mellitus. Hypothermia is more common in older adult diabetic patients than in the general population, even after excluding patients with diabetic metabolic emergencies. The common denominator in metabolic derangements may be abnormal plasma osmolality that interferes with hypothalamic function. Similar causes of hypothermia include hypoglycemia, diabetic ketoacidosis, and uremia. Remarkably, the pH was 6.67 in one hypothermic survivor with lactic acidosis, and 6.41 in another.[232]

### Pharmacologic or Toxicologic Effects

Numerous medications and toxins in therapeutic or toxic doses impair centrally mediated thermoregulation and vasoconstriction.[156,352] The usual offenders are barbiturates, benzodiazepines, antimanic agents, and antidepressants. Reduced core temperature may be a prodrome of lithium poisoning. Organophosphates, narcotics, glutethimide, bromocriptine, erythromycin, clonidine, fluphenazine, bethanechol, atropine, acetaminophen, and carbon monoxide (CO) all cause hypothermia. Hypothermia after acute CO poisoning is associated with increased mortality.

## RECURRENT HYPOTHERMIA

Recurrent and episodic hypothermia are widely reported. The recurrent variety is more common and is usually secondary to ethanol abuse, with one person having survived 12 episodes.[58] Severe, recurrent presentations are also caused by self-poisoning and anorexia nervosa.

Persons with episodic hypothermia can be divided into two groups, with significant overlap, as follows:

*Group 1:* Diaphoretic episodes precede the temperature decline, which lasts several hours. This group includes those with hypothalamic lesions and agenesis of the corpus callosum (Shapiro syndrome) and persons with spontaneous periodic hyperthermia. Resultant hyperhidrosis and hypothermia are successfully treated with clonidine, a centrally acting α-adrenergic agonist. The hypothermia of corpus callosum agenesis is also seen with hypercalcemia and status epilepticus. Since hypothermia does not result from experimental sectioning of the corpus callosum, associated lesions, including lipomas, probably cause thermoinstability. Spontaneous periodic hypothermia may reflect a diencephalic autonomic seizure disorder and can accompany paroxysmal hypertension. Vasomotor and thermoregulatory mechanisms are successfully treated with anticonvulsants. Florid psychiatric symptoms often mask these intermittent hypothermic episodes.

*Group 2:* This group consists of persons who remain cold for days to weeks, rather than hours. These people have more seizure disorders, and the central hypothalamic thermostat is set abnormally low.

Patients with intermittent hypothermia usually show some characteristics of both groups.[204] Circadian rhythm disturbances are also seen in persons with neurologic disorders who have chronic hypothermia.

## PREDISPOSING INFECTIONS OR CONDITIONS

Among the infestations and infections that may elevate or depress core temperature are septicemia, pneumonia, peritonitis, meningitis, encephalitis, bacterial endocarditis, typhoid, miliary tuberculosis, syphilis, brucellosis, and trypanosomiasis.[192] Other diseases, in addition to cerebrovascular and cardiopulmonary disorders, that produce secondary hypothermia include systemic lupus erythematosus, carcinomatosis, pancreatitis, and multiple sclerosis. Hypothalamic demyelination may explain episodic hypothermia observed in some patients with multiple sclerosis.

Hypothermia can also result from low cardiac output after a major myocardial infarction. Other causes include vascular insufficiency, giant cell arteritis, uremia, sickle cell anemia, Paget's disease, sarcoidosis, and sudden infant death syndrome. Magnesium sulfate infusion during preterm labor can produce hypothermia with fetal and maternal bradycardia, and hypothyroidism can be manifested as hypothermia after preeclampsia (see Box 7-2).

## TRAUMA

Hypothermia protects the brain from ischemia but can result in arrhythmias, acidosis, and coagulopathies and extracts a high metabolic cost during rewarming.[95] Hypothermia hinders protective physiologic responses to acute trauma and affects pharmacologic and therapeutic maneuvers necessary to treat injuries.[15,26]

An inverse relationship usually exists between the Injury Severity Score (ISS) and core temperature of traumatized patients on arrival in the emergency department (ED). This observation does not settle whether hypothermia is just another risk factor for increased mortality or reflects that the most severely injured patients are in hemorrhagic shock.[126,225] One study assessed the impact of hypothermia as an independent variable during resuscitation from major trauma.[95] Patients not aggressively rewarmed with continuous arteriovenous rewarming (CAVR) had increased fluid requirements, increased lactate levels, and increased acute mortality.

Of the clinical entities associated with hypothermia, traumatic conditions causing hypotension and hypovolemia most dramatically jeopardize thermostability. Hypothermia is often obscured by obvious hemorrhaging and injuries. Liberalized indications for Focused Assessment with Sonography for Trauma (FAST) ultrasound examinations can minimize unnecessary computed tomography (CT) imaging. On the other hand, traumatic neurologic deficits, including paresis and areflexia, can be misattributed to hypothermia. In trauma patients requiring surgery, the mean temperature loss was greater in the ED than in the operating room.[111,112] Thermal insults are often added during a trauma resuscitation. The patient is completely exposed for examination, and resuscitative procedures cause further heat loss.[287]

When stratifying patients with the anatomic ISS, hypothermic patients may have a higher mortality rate than similarly injured patients who remain normothermic. Caution is advised when using trauma revised injury severity score (TRISS) methodology. It is less valid during hypothermia because the physiologic components overestimate injury severity. To illustrate this point, some component of hypotension is normal for a given degree of hypothermia.[300]

Various adverse physiologic events accompany hypothermia with trauma.[201,202] Decreased skin and core temperatures without compensatory shivering thermogenesis occur in patients with major trauma as defined by the ISS.

Hypothermia directly causes coagulopathies in trauma patients through at least three avenues (see Coagulation, earlier).[32] The cascade of enzymatic reactions is impaired and plasma fibrinolytic activity is enhanced, producing a clinical presentation similar to that of DIC. Also, platelets are poorly functional and become sequestered.

Hypothermia is protective only when induced before shock occurs. This reduces adenosine triphosphate (ATP) utilization while ATP stores are still normal, as during elective surgery. ATP stores in traumatized patients are already depleted. Hypothermia worsens the effects of endotoxins on clotting time in vitro and may synergistically exacerbate the coagulopathy seen in trauma.[88] The average temperature of 123 initially normothermic trauma patients in whom lethal coagulopathies developed was 31.2°C (88.2°F). Postinjury life-threatening coagulopathy in the seriously injured patient who requires massive transfusion is predicted by persistent hypothermia and progressive metabolic acidosis.[55,89]

The appropriate target core temperature for a hypothermic patient with an isolated severe head injury is unclear. The target temperature could help balance neuroprotection against the adverse hematologic and physiologic consequences of hypothermia[18,210] (see Cerebral Resuscitation, later.)

# PRESENTATION

The patient's history may suggest hypothermia.[32] Diagnosis is simple when exposure is obvious, as with avalanche victims. Subtle presentations, however, predominate in urban settings. Patients often complain only of vague symptoms, including hunger, nausea, fatigue, and dizziness. Predisposing underlying illness or ethanol ingestion is also common, as are major trauma, immersion, overdose, cerebrovascular accident (CVA, stroke), and psychiatric emergencies (Box 7-3).

During the head, eye, ear, nose, and throat examination, abnormal findings can include decreased corneal reflexes, mydriasis, strabismus, flushing, erythropsia, facial edema, rhinorrhea, and epistaxis. Mild hypothermia usually does not depress pupillary light reflexes.

**BOX 7-3 Signs of Hypothermia**

**Head, Eye, Ear, Nose, Throat**
- Mydriasis
- Decreased corneal reflexes
- Extraocular muscle abnormalities
- Erythropsia
- Flushing
- Facial edema
- Epistaxis
- Rhinorrhea
- Strabismus

**Cardiovascular**
- Initial tachycardia
- Subsequent tachycardia
- Arrhythmias
- Decreased heart tones
- Hepatojugular reflux
- Jugular venous distention
- Hypotension
- Peripheral vasoconstriction

**Respiratory**
- Initial tachypnea
- Adventitious sounds
- Bronchorrhea
- Progressive hypoventilation
- Apnea

**Gastrointestinal**
- Ileus
- Constipation
- Abdominal distention or rigidity
- Poor rectal tone
- Gastric dilation in neonates or in adults with myxedema
- Vomiting

**Genitourinary**
- Anuria
- Polyuria
- Oliguria
- Testicular torsion

**Neurologic**
- Depressed level of consciousness
- Ataxia
- Dysarthria
- Amnesia
- Anesthesia
- Areflexia
- Poor suck reflex
- Hypoesthesia
- Antinociception
- Initial hyperreflexia
- Hyporeflexia
- Central pontine myelinolysis

**Psychiatric**
- Impaired judgment
- Perseveration
- Mood changes
- Peculiar "flat" affect
- Altered mental status
- Paradoxical undressing
- Neuroses
- Psychoses
- Suicide
- Organic brain syndrome
- Anorexia nervosa
- Depression
- Apathy
- Irritability

**Musculoskeletal**
- Increased muscle tone
- Shivering
- Rigidity or pseudo–rigor mortis
- Paravertebral spasm
- Opisthotonos
- Compartment syndrome

**Dermatologic**
- Erythema
- Pallor
- Cyanosis
- Icterus
- Scleral edema
- Ecchymosis
- Edema
- Pernio
- Frostnip
- Frostbite
- Panniculitis
- Cold urticaria
- Necrosis
- Gangrene

Cardiovascular findings after initial tachycardia include bradyarrhythmias and hypotension. Heart sounds may be muffled and distant. Tachypnea, an early respiratory finding, is usually followed by progressive hypoventilation with bronchorrhea and adventitious sounds. Because the gastrointestinal (GI) tract is depressed, abdominal distention or rigidity, ileus, obstipation, and poor rectal tone are often present. Gastric dilation is common in neonates and myxedematous adults. Urine output ranges from initial polyuria resulting from cold diuresis to anuria. The incidence of testicular torsion increases because of cremasteric contractions.

Diffuse neurologic abnormalities vary widely. Some persons can still converse at 32°C (89.6°F) and are normoreflexic. The level of consciousness generally declines proportionate to the degree of hypothermia. The presence of ataxia and dysarthria may mimic a CVA. Speed of reasoning and memory registration are also impaired. Amnesia, antinociception, anesthesia, or hypesthesia can develop. Cranial nerve abnormalities are present after bulbar damage from central pontine myelinolysis. These extraocular muscle movement abnormalities, as with extensor plantar responses, do not directly correlate with the degree of hypothermia.

Hyperreflexia predominates from 35° to 32.2°C (95° to 90°F) and is followed by hyporeflexia. The plantar response remains flexor until 26°C (78.8°F), when areflexia develops. The knee jerk is usually the last reflex to disappear and the first to reappear during rewarming. From 30° to 26°C (86° to 78.8°F), both contraction and relaxation phases of reflexes are prolonged equally. In myxedema, however, the relaxation phase of the ankle reflex is more prolonged than the contraction phase.[204] Spinal cord and other CNS lesions may be obscured by depressive neurologic changes that normally accompany hypothermia.

Psychiatric presentations and suicide attempts associated with hypothermia often are initially misdiagnosed. Preexisting psychiatric disorders can blossom in the cold, even if they were stabilized in temperate climates.[29] Mental status alterations include anxiety, impaired judgment, perseveration, neurosis, and psychosis.[145] Leaders of expeditions can become moody, apathetic, uncooperative, and risk taking. Older adult patients often withdraw in confusion, become silent, and display lassitude and poor judgment. A peculiar or flat affect is common, and psychomotor impairment can resemble organic brain syndrome.

Early in hypothermia, simply losing effective use of the hands can be devastating. Appropriate behavior adapted to the cold, such as seeking a heat source, is often lacking. An extreme example is paradoxical undressing.[167] The clothing is removed in a preterminal effort to address impending thermoregulatory collapse, and many persons are mistakenly identified as sexual assault victims. This phenomenon is also seen in hypothermic children. Undressing may result from Alzheimer's disease before the patient wanders into the cold.[165]

Musculoskeletal posturing can extend to pseudo–rigor mortis. Preshivering muscle tone is increased before core temperature drops to 35°C (95°F), and muscular rigidity, paravertebral spasm, and even opisthotonos may occur. Extremity compartment syndromes often develop because of associated conditions causing prolonged compression and immobility, in addition to compartment hypertension seen during reperfusion of frostbitten extremities.

Dermatologic presentations of hypothermia include erythema, pallor, edema, and scleral edema. Cold urticaria, frostnip, frostbite, and gangrene should also cause the clinician to consider this diagnosis. Pernio is also observed with chronic myelomonocytic leukemia.

# LABORATORY EVALUATION

## ACID-BASE BALANCE

The strategy for achieving and maintaining acid-base balance in hypothermia differs from that of normothermia.[68,121,141,162] After initial respiratory alkalosis from hyperventilation when a person first becomes chilled, a common underlying disturbance is mixed acidosis. The respiratory component of the acidosis is caused

mainly by direct respiratory depression. In addition, as body temperature decreases, solubility of $CO_2$ in blood increases. Further contributors to the metabolic component of this acidosis include impaired hepatic metabolism and acid excretion, lactate generation from shivering, and decreased tissue perfusion.[129] Nevertheless, reliable clinical prediction of the acid-base status in accidental hypothermia is not possible. In one series of 135 patients, 30% were acidotic and 25% alkalotic.[222]

Circulatory changes also prevent adequate mobilization and delivery of organic acids to buffer systems. As in normothermia, mixed venous blood may best reflect acid-base status during resuscitation. Despite flow changes in a canine model of moderate hypothermia, a significant correlation persists between arterial and mixed venous pH. The arteriovenous change in pH is 0.03 to 0.04 pH unit.

The buffering capacity of cold blood is also greatly impaired. In normothermia, when the arterial partial pressure of carbon dioxide ($PaCO_2$) increases 10 mm Hg, a decrease in pH of 0.08 unit occurs. At 28°C (82.4°F), the decrease in pH doubles to 0.16 unit.

The initial assumption was that 7.42 was the ideal "corrected" patient pH at all temperatures and that therapy should be directed at maintenance of the corrected arterial pH at 7.42.[339] A better intracellular pH reference is electrochemical neutrality, at which pH equals pOH. Because the neutral point of water at 37°C (98.6°F) is pH 6.8, Rahn[264] hypothesizes that this normal 0.6 unit pH offset in body fluids should be maintained at all temperatures. Because the neutral pH rises with cooling, so should blood pH (Figure 7-5).[268]

Relative alkalinity of tissues makes physiologic sense. Intracellular electrochemical neutrality ensures optimal function of enzyme systems and transport proteins at all temperatures and allows excretion of the neutral intracellular waste product urea.[13]

Depressed metabolism and $CO_2$ generation are physiologic responses to temperature depression, because each temperature has its associated metabolic rate. Ventilation is intrinsically adjusted to maintain a net charge on the defended parameter, the peptide-linked histidine-imidazole buffering system.

One homeostatic approach to maintain a steady pH is to keep the bicarbonate content constant. This is achievable only if total blood $CO_2$ content does not change. Because $CO_2$ solubility increases with temperature depression, alveolar ventilation must increase to compensate by lowering the $PaCO_2$. Active ectotherms exhibit this respiratory adaptation and do not depress their respiratory minute volume when cold. This response, termed the *ectothermic,* or *alpha-stat, strategy,* allows them to maintain total bicarbonate and $CO_2$ content while increasing pH. Hibernating mammals are far more acidic because of respiratory acidosis and use an acid-base strategy that suppresses metabolism, termed the *endothermic,* or *pH-stat, strategy.*

Induced hypothermia, which clearly differs from accidental hypothermia, might benefit from the alpha-stat approach, with improved neurologic outcome and myocardial function.[69,162,179,268] On the other hand, various animal models suggest that the pH-stat strategy may be preferable.[76] Accidental hypothermia in a human should not be considered a protective form of hibernation. The ectothermic (alpha-stat) approach appears to ensure adequate alveolar ventilation and acid-base balance at any temperature when the uncorrected pH is 7.42 and the uncorrected $PaCO_2$ is 40 mm Hg.[132,162,273]

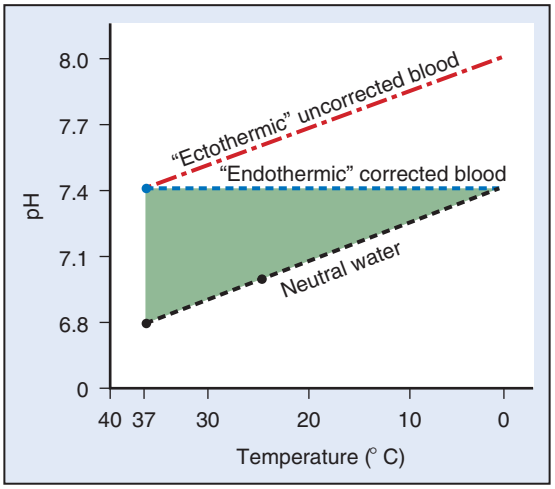



**FIGURE 7-5** Neutrality is the pH of water at any given temperature. At 25°C (77°F), the neutral pH of water is 7.0; at 37°C (98.6°F), it is 6.8. An ectotherm's physiologic 0.6 pH offset from neutral water progressively diminishes if the arterial blood gases are temperature corrected. After the in vitro sample is warmed in the analyzer to 37°C (98.6°F), do not mathematically correct the reported values to reflect the in vivo temperature.

## HEMATOLOGIC EVALUATION

Severity of blood loss is easily underestimated. Hematocrit value increases because of a decline in plasma volume that leads to a 2% increase per 1°C (1.8°F) fall in temperature. In addition, total RBC mass might already be low because of preexisting anemia, malnutrition, leukemia, uremia, or neoplasm.

The white blood cell count is frequently normal or low, even if sepsis is present. As a result, systemic leukopenia does not imply absence of infection, especially if the patient is at either age extreme; is debilitated, intoxicated, or myxedematous; or has secondary hypothermia.[192] The leukocyte count also drops during hypothermia because of direct bone marrow depression and hepatic, splenic, and splanchnic sequestration.

Serum electrolyte levels must be continuously monitored and rechecked during warming. There are no safe predictors of electrolyte values.[120] Serum electrolytes fluctuate with temperature, duration of exposure, and rewarming technique selected. Both membrane permeability and sodium-potassium pump efficiency also change with temperature. Isolated temperature depression has no consistent effect on sodium and chloride levels until well below 25°C (77°F). Plasma electrolyte levels are also affected by ongoing fluid shifts, prehydration, rehydration, and endocrine or GI dysfunction.

The plasma potassium level is independent of temperature. Empirical potassium supplementation during hypothermia often results in normothermic toxicity. From a clinical perspective, hypokalemia occurs as potassium moves into the musculature and not simply out of the body through kaliuresis. The physiologically illogical discrepancy of decreasing potassium level with decreasing pH results from greater intracellular than extracellular pH changes. Hypokalemia is much more common in prolonged or chronically induced hypothermia.

Systemic potassium deficiencies can also be exacerbated by prior diuretic therapy, alcoholism, diabetic ketoacidosis, hypopituitarism, and inappropriate antidiuretic hormone (ADH) secretion. Hypokalemic digitalis sensitivity can be masked by hypothermia, and gradual correction of persistent and severe hypokalemia during rewarming is necessary for optimal cardiac and GI function.

When hyperkalemia is identified, the physician should search for other causes of metabolic acidosis, crush injury or rhabdomyolysis, renal failure, postsubmersion hemolysis, or hypoaldosteronism. Temperature depression can increase hyperkalemic cardiac toxicity. An important caveat is that the well-known diagnostic ECG changes are often obscured by hypothermia, and VF can occur with serum potassium levels of less than 7 mEq/L.

Hypothermia has no consistent effect on magnesium or calcium levels. Severe hypophosphatemia can occur during treatment of profound hypothermia. Although increases in serum enzyme levels are not seen in mild experimental hypothermia, numerous serum enzymes are elevated when diffuse intracellular structural damage occurs in severe accidental hypothermia. Creatine kinase (CK) levels over 200,000 international units (IU) are observed, and rhabdomyolysis is often present.[58]

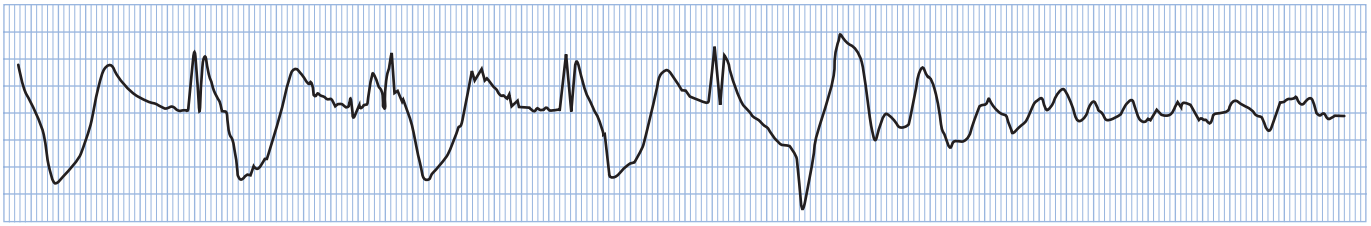


**FIGURE 7-6** In this patient, ventricular fibrillation developed during a code 3 transport by emergency medical services to the emergency department. Note the pronounced J waves after the QRS complexes.

Inhibition of cellular membrane transport decreases glucose utilization. In addition, insulin release and activity are greatly reduced below 30°C (86°F). Because target cells are insulin resistant, hyperglycemia is frequently seen initially. Markedly elevated glucose levels often correlate with hyperamylasemia and increased cortisol secretion.[340]

Acute hypothermia initially elevates the serum glucose level through catecholamine-induced glycogenolysis. Chronic exposure after exhaustion and glycogen depletion leads to hypoglycemia.[305] The symptoms often resemble those of hypothermia. Cold-induced renal glycosuria is common and does not imply normoglycemia or hyperglycemia. When hypoglycemia and central neuroglycopenia are present, correction improves the level of consciousness only to that expected for the current core temperature. Cholesterol and triglyceride levels are also often below normal.

Hyperglycemia that persists during and after rewarming should suggest diabetic ketoacidosis or hemorrhagic pancreatitis. Insulin is ineffective until the core temperature is well above 30° to 32°C (86° to 89.6°F) and therefore should be withheld to avoid iatrogenic hypoglycemia after rewarming. Although prior renal disease should be a consideration, blood urea nitrogen (BUN) and creatinine concentrations are often elevated because of decreased nitrogenous waste clearance by the cold diuresis. Ongoing fluid shifts render the BUN a poor reflection of circulatory volume status.[97]

The relationship between primary accidental hypothermia and hyperamylasemia appears to correlate with the severity of temperature depression, but preexisting or hypothermia-induced pancreatitis is present in up to 50% of patients. The abdominal examination is frequently unreliable. Therefore, lipase levels should be measured, except in minor cases.[51] Ischemic pancreatitis is attributable to microcirculatory collapse in hypothermia. Decreased pancreatic blood flow activates many proteolytic enzymes.

## TREATMENT

Four decisive factors should be considered when assessing nonperfusing, severely hypothermic patients at the site. Rescuers should reconsider the decision to resuscitate if there is evidence of asphyxia or lethal injuries. A rigid thorax precludes closed-chest cardiopulmonary resuscitation (CPR), and a probable field core temperature below 10° to 12°C (50° to 53.6°F) is ominous.

Pulses are difficult to palpate in vasoconstricted and extremely bradycardic patients. If possible, check for an organized rhythm on a cardiac monitor. Bedside echocardiography is an ideal tool to assess cardiac activity.[28,229]

The combination of cold and exhaustion is a common cause of hypothermia in the field.[142,223,224] The individual's cold tolerance depends on temperature, wind, clothing worn, and wetness. It does not take an extremely cold temperature to produce hypothermia after energy depletion. As mental function decreases, the hypothermic patient cannot respond to the rising threat. Judgment is impaired, and the patient seldom takes necessary precautions to prevent further disaster.[24]

Field presentation of patients who are awake covers a wide spectrum. Some persons are obtunded but conscious. Patients may or may not be shivering and often have a distant gaze and slurred speech.[98]

The type of power available in the transport vehicle determines the options for active rewarming. These include forced-air warming devices, heated IV fluids, and resistive and combustive heat.[99,101,106]

Comatose patients require careful handling because they are extremely likely to develop VF and asystole with rough handling (Figure 7-6). Gurneys should be carried or rolled slowly to avoid jostling, and "code 3, full lights and sirens" transport should be avoided if patients are perfusing spontaneously.

It is often impossible for rescuers to separate primary from secondary hypothermia when an unwitnessed cardiac arrest patient is found in a frigid environment. Patients with cold, stiff, and cyanotic primary hypothermia and fixed and dilated pupils have been "reanimated." A succinct summary of prehospital care of the hypothermic patient is rescue, examine, insulate, and transport.

The initial rescuer and first responder often encounter obstacles to preventing further heat loss.[224,335] In certain imposing geographic settings, treatment protocols are helpful to standardize treatment while tacitly acknowledging that available health care facilities may offer limited expertise and equipment. All treatment recommendations must be adapted to local rescue systems and facilities.[78,274] Aeromedical transport is often ideal in these circumstances.[347] In difficult environments, proper protocols with rehearsal and critique of mass casualty plans in the cold are very important.

The history obtained at the scene helps determine optimal treatment. The pertinent medical history regarding prior cardiopulmonary, endocrinologic, and neurologic conditions is particularly helpful. The circumstances of discovery, duration of exposure, associated injuries or frostbite, and obvious predisposing conditions should be recorded. No prognostic neurologic scale (e.g., Glasgow Coma Scale score) is valid during hypothermia, but trends are often useful.

Accurate field measurement of core temperature is difficult.[306] The International Commission for Mountain Emergency Medicine recommends tympanic or esophageal field measurements, although these have significant limitations. Never insert an esophageal probe unless the patient is already tracheally intubated.[62,274]

Prolonged field treatment should be avoided whenever possible, although the rescuer must attempt to prevent further heat loss (Box 7-4). The rescuer should anticipate the presence of an irritable myocardium, hypovolemia, and a large temperature gradient between the periphery and the core.[353]

The crux of the prehospital quandary surrounds the safety of providing prehospital heat. On the one hand, the original "metabolic icebox" concept[223,224] implies that the risk of inducing a nonperfusing rhythm in a hostile environment justifies simple stabilization of the core temperature; on the other hand, the warmer the heart, the better. Core temperature can decrease beyond reversal. Operant factors impacting the decision whether or not to provide prehospital heat include core temperature, fluid status, predisposing factors, extent of frostbite, length and type of exposure, available expertise and position of transport, and type of active rewarming available.

**BOX 7-4 Preparing Hypothermic Patients for Transport**

1. The patient must be dry. Gently remove or cut off wet clothing, and replace it with dry clothing or a dry insulation system. Keep the patient horizontal, and do not allow exertion or massage of the extremities.
2. Stabilize injuries (i.e., the spine; place fractures in the correct anatomic position). Open wounds should be covered before packaging.
3. Initiate heated intravenous infusions (IVs) if feasible; bags can be placed under the patient's buttocks or in a compressor system. Administer a fluid challenge.
4. Active rewarming should be limited to heated inhalation and truncal heat. Insulate hot-water bottles in stockings or mittens, and then place them in the patient's axillae and groin.
5. The patient should be wrapped. Begin building the wrap by placing a large plastic sheet on the available surface (floor, ground), and on it place an insulated sleeping pad. A layer of blankets, a sleeping bag, or "bubble wrap" insulating material is laid over the sleeping pad. The patient is then placed on the insulation. Heating bottles are put in place along with IVs, and the entire package is wrapped layer over layer, with the plastic as the final closure. The patient's face should be partially covered, but a tunnel should be created to allow access for breathing and monitoring.

The rescuer should stabilize injuries, protect the spine, splint fractures, and cover open wounds. Rescuer safety concerns typically include unstable snow or ice and falling rocks.[263]

Passive external rewarming with dry insulating materials minimizes conductive, convective, evaporative, and radiant heat losses. Remove any wet clothing from awake patients, and insulate them with sleeping bags, insulated pads, plastic "bubble wrap," metallized or regular blankets, or even newspaper. One device has a nylon shell and a polyester-pile liner to wick moisture. In a survey of common field rewarming methods used by mountain rescue teams, the most common techniques included chemical pads, sleeping bags, body-to-body contact, and hot-water bottles.[118]

If extrication will be delayed, give mildly hypothermic patients warm, sweet drinks, warm gelatin (Jell-O), Tang, juice, tea, or cocoa, because carbohydrates fuel shivering. Avoid heavily caffeinated drinks. A significant diuresis is usually associated with the cooling process, so the patient's fluid balance must be reassessed. Once mildly hypothermic patients are well hydrated, they can be walked out to safety.

Handle severely hypothermic patients gently, immobilizing them to prevent exertion. Although exercise can rewarm a person more rapidly than shivering, it also greatly increases afterdrop.[97,100] Patients *must* be kept in a horizontal position whenever possible to minimize orthostatic hypotension. Vigorously massaging cold extremities is also contraindicated, because skin rubbing, as with ethanol, suppresses shivering thermogenesis and increases cutaneous vasodilation.

Field management of the comatose patient first involves ventilation to raise oxygen saturation. Rescue breathing may be difficult because of chest stiffness and significant resistance to diaphragmatic motion. Forced ventilation increases oxygenation, which helps stabilize cardiac conduction. The single greatest factor in maintaining perfusion during severe hypothermia is oxygenation.[98] At altitude, a portable hyperbaric chamber may prove useful.[42]

During a storm, prolonged field rewarming may be the only viable option until meteorologic conditions become more favorable for land or, preferably, aeromedical evacuation.[347] Many prehospital medications freeze in solution. If this occurs, their pharmacologic activity after thawing is indeterminate (see Appendix at the end of this book).

The rescuer should administer an IV fluid challenge with 250 to 500 mL of heated (37° to 41° C [98.6° to 105.8° F]) 5% dextrose in normal saline solution. Empirical 50% dextrose is indicated only in select cases. The safety of several reversal agents, such as naloxone or flumazenil, used in the field is unknown. Concerns regarding these agents before warming include precipitation of acute withdrawal, seizures, and markedly increased oxygen utilization.

Most patients are volume depleted. Nevertheless, iatrogenic volume overload should be avoided, because myocardial contractility is impaired. Improvisation during transport is often helpful. For example, a plastic IV container can be placed under the patient's back, shoulders, or buttocks to add warmth and infusion pressure. Taping heat-producing packets to IV bags is another option. These heating agents may be chemical packets or phase-change crystals, which produce heat for up to several hours. A variety of hot-pack hypothermia devices are commercially available.

Intravenous fluid compressors are bulb-inflating cuffs that surround IV pouches to maintain flow. The Israeli army has a spring steel compressor system for IV bags. Portable IV fluid heaters are commercially available. The devices fit in-line and are DC powered. Commercial heaters are available that are powered by a battery or from a DC converter plugged into an AC outlet.

Some warmers run on 12 volts from any vehicle or portable battery. The current drain can be 4 amperes, and the insulation case may lose only 0.5° C (0.9° F) over 10 minutes. In a study comparing IV warming techniques, meals ready to eat (MRE) heat packs or a camp stove outperformed standard chemical heat packs.[257] Another option is an in-line battery-powered, disposable, lightweight fluid-warming device.

Peripheral vessels may be difficult to locate, and IV lines are difficult to maintain during transport. Ideally, IV fluids should be warmed to body temperature or slightly higher, but total body warming is not accomplished with IV fluids in the field. Using intraosseous infusions may provide a reasonable pathway for fluid replacement in the field when peripheral vessels have collapsed.

The methods selected to stabilize core temperature should be tailored to the severity of hypothermia and the field circumstances.[313] Gently removing or cutting off wet clothing while the patient remains prone may be the best option to limit heat loss and prevent orthostasis. Passive external rewarming with waterproof insulation suffices for mild chronic hypothermia. The addition of a vapor barrier will reduce evaporative heat loss.[127,128] Other common equipment types include duvets and plastic bubble wrap.[159]

In a series of patients requiring cardiopulmonary bypass (CPB), hypothermia was maintained during transport.[332] Whether supplemental active field rewarming should be initiated en route to the ED, and in which subsets of patients, is not definitively established. Intentionally maintaining hypothermia during gentle transport seems wise only for patients with an isolated closed-head injury. For long helicopter or ambulance transports, the ideal ambient temperature in the vehicle is unclear. Rescue personnel comfort is important to maximize performance, and it is unlikely that heating the interior above 25° C (77° F) will accelerate the rate of rewarming or induce vasodilation.

"Field rewarming" is a misnomer, because adding much heat to a hypothermic patient in the field is difficult.[82] Warmed IV solutions, heated sarongs, or heated humidified oxygen can provide only a small amount of heat input. Hot-water bottles or heat packs can be placed in the axillae, in the groin, and around the neck. Casualty evacuation bags are available in many models and designs. Some have more insulation than others, and some have specialized zippers and openings that allow access to the victim during transport. Most bags are windproof and waterproof. Experimentally, convective air warming is more effective than resistive heating[147] and might be a viable option in some transport situations.

Inhalation therapy is safe for active rewarming of patients with profound hypothermia in the field.[120] It helps prevent respiratory heat loss, which represents an important percentage of heat production when the core temperature is below 32° C (89.6° F). Technical difficulties can occur while using inhalation rewarming devices in volunteers, illustrating the importance of proper instruction for the rescuer.[302] Under certain conditions, the impact of field inhalation therapy on the rate of rewarming may not be

significant.[106] In shivering, mildly cold patients the thermal advantage is minimal.[74,218]

One rewarming device weighs 3 kg (6.6 lb), including oxygen tank, and consists of an oxygen cylinder, demand valve, 2-L reservoir bag, soda lime, and pediatric water canister. An in-line thermometer measures mean air temperature at the face mask. In the field, heat and moisture exchangers are practical, light, and inexpensive. They are, however, less efficient than active humidifiers.[195,196]

Commercially available lightweight, portable, noninvasive core-rewarming systems that deliver heated humidified air or oxygen at 42° to 44°C (107.6° to 111.2°F) are available. Some systems consist of a heating chamber connected by a corrugated hose to a one-way flow valve and an oronasal mask. The temperature is controlled by a transducer in the one-way flow valve that provides feedback to the electronic control circuits.

Although surface rewarming suppresses shivering, it may be the only option when the patient is isolated from medical care. Active external rewarming options include radiant heat, warmed objects placed on the patient, and body-to-body contact. Care must be exercised not to burn victims with hot objects, including commercially produced hot packs. Total-body-contact rewarming may carry some risk,[120] but logistical impediments limit the use of this method unless extrication will be significantly delayed. In a prospective prehospital rewarming study, hot-pack rewarming was the only technique that increased body temperature during transport.[335]

A hydraulic sarong or vest, in which heated water is circulated via a hand pump, is another option.[118] Immersion rewarming is dangerous in the field because monitoring and resuscitation capabilities are limited.

Charcoal heaters can deliver 100 watts for 8 hours. The charcoal "vest" burns a briquette and has a favorable heat-to-weight ratio, unlike most rewarming devices.[52] Battery polarity is critical to prevent CO exposure.[302] The battery must be inserted correctly to avoid a CO exhaust hazard. Do not use in an aircraft. These devices can circulate hot air within a blanket or sleeping bag and provide a comfortable, warm, and dry environment for transporting patients.

Another option is a modified forced-air warming system for field use.[75,101] It covers the patient's trunk and thighs and can adapt to various transport vehicle power sources. Experimentally, convective warming is more efficient than resistive heating.[147] The U.S. Army has a commercially available Hypothermia Prevention Management Kit. A heat-reflective shell and blanket with chemical heat packs provide 6 hours of heat.

## PREHOSPITAL LIFE SUPPORT

The Wilderness Medical Society has published evidence-based guidelines providing consensus suggestions for evaluation and treatment of hypothermic patients. The key factors to guide treatment are the level of consciousness, intensity of shivering, and cardiovascular stability.[353] An altered mental status or lack of shivering after minimal cold exposure should suggest secondary hypothermia. The value of characterizing the five stages of the "Swiss" hypothermia grading system is limited by the high variability of physiologic responses during hypothermia.[78,353]

A patent airway and the presence of respirations must be established (Figure 7-7). The patient may appear apneic if the respiratory minute ventilation is significantly depressed. A common error in tracheally intubated patients is excessive ventilation, which can induce hypocapnic ventricular irritability. The indications for prehospital endotracheal intubation are identical to those under normothermic conditions. Appropriate ventilation with 100% oxygen may protect the heart during extrication and transport. Avoid overinflation of the tracheal cuff with frigid ambient air. As the patient warms, air in the cuff can expand and kink the tube. Careful protection and fixation of the tubing of the cuff port during extremely cold conditions are necessary to prevent breakage and cuff leak.

The palpation of peripheral pulses is often difficult in vasoconstricted and bradycardic patients.[252] Apparent cardiovascular collapse may actually reflect cardiac output that can meet minimal metabolic demands. The rescuer should auscultate and palpate for at least 1 minute to find pulses if a cardiac monitor or portable ultrasound is unavailable. Iatrogenic VF can easily result from chest compressions that are not indicated.

When a cardiac monitor is available, use maximal amplification to search for QRS complexes. If the patient is in VF, the rescuer should attempt defibrillation initially with 2 watt sec/kg and up to 200 watt sec. The energy requirement for defibrillation does not increase in hypothermia. If the patient does not respond, generally defer further attempts, and assume that the patient must

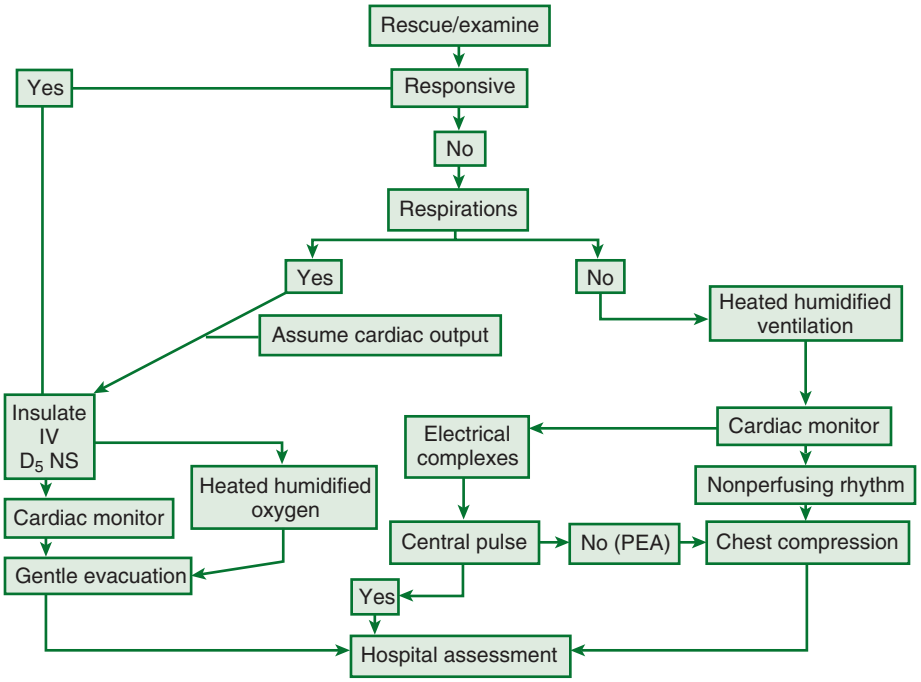



**FIGURE 7-7** Prehospital life support. *IV $D_5$ NS,* Intravenous 5% dextrose in normal saline; *PEA,* pulseless electrical activity.

be rewarmed at least past 30° C (86° F) before further attempts.[7] Effective CPR in deep accidental hypothermia is demonstrated in many cases. One patient fully recovered with extracorporeal rewarming after 130 minutes of CPR and 38 defibrillation attempts.[242]

Do not perform defibrillation if organized, narrow electrical complexes are seen on the monitor.[187] Most monitors and defibrillators are not tested for operation at temperatures below 15.5° C (59.9° F). Standard monitor leads do not always stick well to cold skin, so benzoin may be useful. If this fails, needle electrodes may be necessary. Another option is to puncture the Gelfoam conventional monitor pad with a small-gauge injection needle.[336]

Unresponsive patients should be carefully assessed for a central pulse before assuming they have pulseless electrical activity (PEA). The lowest temperature at which mechanical reestablishment of cardiac activity has been successful is 20° C (68° F),[64] and defibrillation attempts rarely succeed below 30° C (86° F). If resuscitation in the field is unsuccessful, rewarming and CPR should be continued during transport to the ED.[251]

## MANAGEMENT IN THE EMERGENCY DEPARTMENT

The history obtained from a hypothermic patient is often unreliable, so it is prudent to confirm hypothermia and monitor with continuous core temperature measurements. Diagnostic errors in the ED usually result from incomplete monitoring of vital signs. Doppler ultrasound may be necessary to locate a pulse and should be supported by continuous ECG monitoring. The physician should also address the requirements for resuscitation and initiate advanced life support when necessary (Box 7-5).[295]

### Temperature Measurement

Few emergency departments have a hypothermia protocol.[107] Most have adequate equipment for accurate core temperature measurement.[166,238] Rectal measurements are most practical clinically for mild cases but may not reflect cardiac or brain temperatures. An indwelling thermistor probe placed to a depth of 15 cm (6 inches) is fairly reliable unless adjacent to cold feces. Rectal temperature lags behind core temperature fluctuations and is also affected by lower-extremity temperatures (Table 7-3).[341]

Esophageal temperature measurements are far preferable in severe cases when airway protection is provided with endotracheal intubation. Esophageal temperature approximates cardiac temperature. Because the upper third of the esophagus is near the trachea, the probe may read falsely high during heated inhalation therapy if the probe is positioned too proximally. The probe does not have markings but should be placed 24 cm (9.5 inches) below the larynx into the lower third of the esophagus. The greatest discordance between rectal and esophageal temperatures is noted during the transition phase between cooling and rewarming.

Tympanic temperature theoretically approximates hypothalamic temperature and can be accurately measured with thermometers that are in contact with the tympanic membrane. These are usually impractical except in anesthetized patients. External auditory canal thermometers that measure infrared emission from the tympanic membrane are available. These are actually "epitympanic" thermometers.[355] Infrared external auditory canal thermometers are not very sensitive. Tympanic thermometers are inaccurate if the canal is full of cerumen or snow, or is not adequately sealed.[85]

Although bladder temperature measurement devices can be incorporated into the urinary drainage catheter, the readings are frequently unreliable. Measurements are falsely elevated with heated peritoneal lavage and, more often, low as a result of cold-induced diuresis and crystalloid resuscitation.

**TABLE 7-3 Core Temperature Measurements**

| Type | Advantages | Considerations |
|---|---|---|
| Rectal | Convenient<br>Continuous monitoring | Insert 15 cm (6 inches)<br>Lags during transition from cooling to rewarming<br>Falsely elevated with peritoneal lavage<br>Falsely low if probe is in cold feces or when lower extremities are frozen |
| Esophageal | Convenient<br>Continuous monitoring | Insert 24 cm (9.5 inches) below larynx<br>Tracheal misplacement<br>Aspiration<br>Falsely elevated with heated inhalation |
| Tympanic | Approximates hypothalamic temperature via internal carotid artery | Probe: tympanic membrane perforation; canal hemorrhage<br>Infrared: unreliable; cerumen effect |
| Bladder | Convenient<br>Continuous monitoring | Unreliable<br>Falsely elevated with peritoneal lavage<br>Falsely low with cold diuresis |

### Initial Stabilization

After core temperature measurement, all clothing should be gently removed or cut off with minimal patient manipulation.[251] Immediately insulate the patient with dry blankets. Apply a cardiac monitor, and insert IV catheters as needed. Arterial catheter insertion may help in managing select, profoundly hypothermic patients. Pulmonary artery catheters can precipitate cardiac arrhythmias and should be reserved for complex cases. Insertion of pulmonary artery catheters into cold vessels may perforate the pulmonary artery.[50] Central venous catheters should not be inserted into the right atrium, because this could precipitate arrhythmias. A better option is temporary catheterization of the femoral vein.

The accuracy of pulse oximetry during conditions of poor perfusion is unclear, because there are no studies in accidental hypothermia.[172] In one study of hypothermic patients on CPB, the finger probes were inaccurate.[46] The probe may be more reliable if a vasodilating cream is applied first. In addition, there is a lag time in pulse oximetry with hypoxic desaturation in anesthetized hypothermic individuals. There is less failure with forehead pulse oximetry compared to fingertip readings.[205]

In theory, combining pulse oximetry with near-infrared spectroscopy could provide tissue perfusion information during hypothermic vasoconstriction. More practically, an accurate core and peripheral muscle temperature would prove just as useful. The value of end-tidal $CO_2$ measurements to assess adequacy of tissue perfusion and tracheal tube placement is established at normal temperatures. Most of these devices, however, measure only the

**BOX 7-5 Resuscitation Requirements**

**Thermal Stabilization**
- Conduction
- Convection
- Radiation
- Evaporation
- Respiration

**Maintenance of Tissue Oxygenation**
- Adequate circulation
- Adequate ventilation

**Identification of Primary vs. Secondary Hypothermia**

**Rewarming Options**
- Passive external rewarming
- Active external rewarming
- Active core rewarming

$CO_2$ content of dehumidified air and thus cannot be used during airway rewarming.

Laboratory evaluations, except in some patients with mild hypothermia, include blood glucose, arterial blood gases, complete blood cell count, electrolytes, BUN, creatinine, serum calcium, serum magnesium, serum amylase and lipase, PT, PTT, INR, platelet count, and fibrinogen level. A toxicologic screen should be considered if the level of consciousness does not correlate with the degree of hypothermia. Selective studies of thyroid function, cardiac markers, and serum cortisol levels are indicated.[61]

The indications for radiography should be liberalized from normothermia. Radiologic evaluation of poorly responsive patients must include cervical and other spine images to detect occult trauma. Chest radiographs may predict lung collapse during rewarming when cardiomegaly and redistribution of vascularity are already present. Abdominal imaging should be obtained when the physical examination is unreliable. Bowel sounds are usually diminished or absent in severe hypothermia, and rectus muscle rigidity is frequently present. Pneumoperitoneum, pancreatic calcifications, or hemoperitoneum may be noted. Small bowel dilation is associated with cold-induced mesenteric vascular occlusion, and colonic dilation is often present in conjunction with myxedema coma. The use of FAST may be helpful.[58]

Nasogastric tube insertion should be performed after endotracheal intubation in moderate or severe hypothermia, because gastric dilation and poor GI motility are common. Indwelling bladder catheters with urine meters are needed to monitor urine output and the cold diuresis.

## FLUID RESUSCITATION

Most fluid shifts are reversed by rewarming, and mild hypothermia usually requires only modest amounts of crystalloids. In more severe cases, volume shifts and elevated blood viscosity from hemoconcentration, lowered temperature, increased vascular permeability, and low flow state mandate aggressive fluid resuscitation. The viscosity of blood increases 2% per degree Celsius drop in temperature; therefore, hematocrit values over 50% are commonly seen. Low circulatory plasma volume is often coupled with elevated total plasma volume during rewarming. Hemodilution is usually not a problem and is seen only during massive crystalloid resuscitation of actively hemorrhaging patients.[31,58]

Most patients are significantly dehydrated, with free water depletion elevating serum sodium concentration and osmolality. During the descent into a hypothermic state, normal physiologic cues for thirst become inactive, and access to water is often difficult. Because hypothermia results in natriuresis, saline depletion may be present. Further causes of sodium losses include prior diuretic therapy and GI losses. Preexisting total body sodium excess is seen with congestive heart failure, cirrhosis, and nephrosis. In these patients, serum sodium and osmolality values are often normal. Rarely, serum sodium level is low because of free water excess. Other causes include myxedema, panhypopituitarism, and inappropriate ADH secretion.

Most adult patients with a core temperature below 32.2°C (90°F) should receive an initial fluid challenge with 250 to 500 mL of warmed 5% dextrose in normal saline solution. Theoretically, Ringer's lactate solution should be avoided because a cold liver cannot metabolize lactate. In severe cases, some clinicians favor a mixture of crystalloids and colloids.

The patient should be monitored for standard clinical signs of fluid overload, including rales, jugular venous distention, hepatojugular reflux, and $S_3$ cardiac gallop. Persistent cardiovascular instability often reflects inadequate intravascular volume. As mentioned, a properly placed central venous pressure catheter, such as a femoral line that does not enter and irritate the right atrium, has a role. Pulmonary wedge pressure measurements are rarely indicated. The need for RBC transfusions is determined by the corrected hematocrit; blood dilution with warmed infusate does not cause significant hemolysis.

In many cases, rapid volume expansion is critical. Circulatory volume is decreased, and peripheral vascular resistance is increased. In neonates, adequate fluid resuscitation greatly decreases mortality. Adults receiving hemodynamic monitoring show improvement of cardiovascular efficiency during crystalloid administration. VF immediately after rescue is attributed to both core temperature afterdrop and vascular imbalance in patients who are moved suddenly from a horizontal supine position. The fluxing relationship between active vascular capacity and circulating fluid volume depends not only on the mechanism of cooling but also on the method of rewarming.[353]

Hypothermic patients, particularly those with frostbite, are at high risk for extremity compartment syndromes and rhabdomyolysis. Pelvic fracture belt slings should be considered only to temporarily stabilize coexistent exsanguinating major pelvic fractures.

**BOX 7-6 Rewarming Techniques**

**Passive External**
- Thermal stabilization

**Active**

***External***
- Radiant heat
- Hot-water bottles
- Plumbed garments
- Electric heating pads and blankets
- Forced circulated hot air
- Immersion in warm water
- Negative-pressure rewarming

***Core***
- Inhalation rewarming
- Heated infusions
- Gastric and colonic lavage
- Mediastinal lavage
- Thoracic lavage
- Peritoneal lavage
- Diathermy
- Hemodialysis
- Venovenous extracorporeal blood rewarming
- Arteriovenous extracorporeal blood rewarming
- Cardiopulmonary bypass

## REWARMING OPTIONS

Hypothermia is an extremely heterogeneous condition, and definitive evidence-based treatment guidelines do not exist. Therefore, rigid treatment protocols are ill advised.[274,280,356] A versatile approach to rewarming can be developed after careful consideration of the observations from animal experiments, human experiments on mild hypothermia, and various clinical reports (Box 7-6).[113,114,260] Treatment should be predicated on the presenting pathophysiology and the available resources and expertise. The initial key treatment decision is whether to use passive or active rewarming (Box 7-7).

### PASSIVE EXTERNAL REWARMING

Noninvasive passive external rewarming (PER) is ideal for most previously healthy patients with mild hypothermia. The patient is covered with dry insulating materials in a warm environment

**BOX 7-7 Indications for Active Rewarming**

- Cardiovascular instability
- Moderate or severe hypothermia (<32.2°C [90°F]) (poikilothermia)
- Inadequate rate or failure to rewarm
- Endocrinologic insufficiency
- Traumatic or toxicologic peripheral vasodilation
- Secondary hypothermia impairing thermoregulation
- Identification of predisposing factors (see Box 7-2)

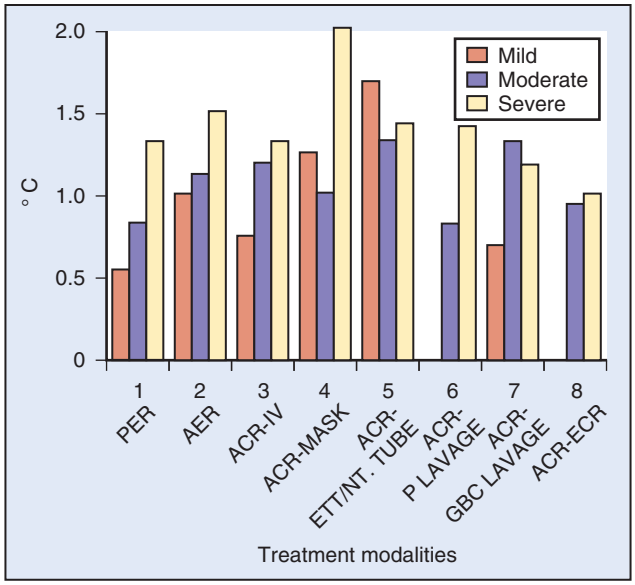



**FIGURE 7-8** First-hour rewarming rates from a large multicenter survey. *ACR,* Active core rewarming; *AER,* active external rewarming; *ECR,* extracorporeal rewarming; *ETT,* endotracheal tube; *GBC,* gastric-bladder-colon; *IV,* intravenous; *NT,* nasotracheal tube; *P,* peritoneal; *PER,* passive external rewarming. *(Data from Danzl DF, Pozos RS, Auerbach PS, et al: Multicenter hypothermia survey,* Ann Emerg Med *16:1042, 1987.)*



to minimize the normal mechanisms of heat loss. When the wind is blocked, less heat escapes through radiation, convection, and conduction. Conditions with higher ambient humidity slightly limit respiratory heat loss.

Aluminized body covers also reduce heat loss.[83] Nevertheless, endogenous thermogenesis must generate an acceptable rate of rewarming for PER to be effective.[239] Humans are functionally poikilothermic below 30°C (86°F), and metabolic heat production is less than 50% of normal below 28°C (82.4°F). Shivering thermogenesis is also extinguished below 32°C (89.6°F). This thermoregulatory neuromuscular response to cold normally increases heat production from 250 to 1000 kcal/hr unless glycogen is depleted before or during cooling.

Older adult patients in whom mild hypothermia develops gradually are less acceptable candidates for PER. When rewarming times are markedly prolonged (more than 12 hours), complications tend to increase.

Patients who are centrally hypovolemic, glycogen depleted, and without normal cardiovascular responses should be stabilized and rewarmed at a conservative rate. In a multicenter survey, the rewarming rates for older adults in the first (0.75°C [1.35°F]), second (1.17°C [2.11°F]), and third (1.26°C [2.27°F]) hours far exceeded 0.5°C (0.9°F) per hour, with no increase in mortality rate (Figure 7-8).[62]

## ACTIVE REWARMING

Active rewarming, which is the direct transfer of exogenous heat to a patient, is usually required with temperatures below 32°C (89.6°F).[185] Rapid identification of any impediment to normal thermoregulation, such as cardiovascular instability or endocrinologic insufficiency, is essential.[186] Intrinsic thermogenesis may also be insufficient after traumatic spinal cord transection or pharmacologically induced peripheral vasodilation. Some patient populations generally require active rewarming.[66] For example, aggressive rewarming of infants minimizes energy expenditure and decreases mortality. In these circumstances, vigorous monitoring for respiratory, hematologic, metabolic, and infectious complications is essential.[329]

When active rewarming is needed, heat can be delivered externally or to the core. Active external rewarming (AER) techniques deliver heat directly to the skin. Examples include forced-air rewarming, immersion, arteriovenous anastomosis (AVA) rewarming, plumbed garments, hot-water bottles, heating pads and blankets, and radiant heat sources.[69,328]

During rewarming of hypothermic patients, there are metabolic pH and inflammatory interleukin fluxes.[216,321] Cytokine production may be activated by accidental hypothermia.[2]

## ACTIVE EXTERNAL REWARMING

The interpretation of survival rates with AER is affected by various risk factors and patient selection criteria.[296] Some experimental and clinical reports link AER with peripheral vasodilation, hypotension, and core temperature afterdrop, but previously healthy, young, and acutely hypothermic patients are usually safe candidates for AER.[31] Heat application confined to the thorax may mitigate many of the physiologic concerns pertaining to the depressed cardiovascular and metabolic systems, which are unable to meet accelerated peripheral demands.[318] Combining truncal AER with active core rewarming may further avert many potential side effects.[74]

### Forced-Air Surface Rewarming

Forced-air surface warming systems efficiently transfer heat.[11,99,176] Hot air is circulated through a blanket. The air exits apertures on the patient side of the cover, permitting the convective transfer of heat.[215] In one study that rewarmed accidental hypothermia patients in the ED, rewarming shock and core temperature afterdrop were not noted[299] with the use of heated inhalation and warmed IV fluids. A group also treated with a convective cover inflated at 43°C (109.4°F) rewarmed 1°C (1.8°F) per hour faster than a group covered with a cotton blanket (1.4°C [2.5°F] per hour). Experimentally, resistive external heating is more effective than passive metallic-foil insulation.[115]

A study of full-body forced-air warming compared a commercially available convective blanket with simple air delivery beneath bedsheets.[163] Directed 38°C (100.4°F) warm air under the sheets warmed standardized thermal bodies containing water very efficiently. Commercially available convective air rewarming devices are also effective. Another option is conductive warming with a warm-water–filled heat exchange blanket.

The use of forced-air surface warming systems is most practical in the ED.[174,189] Although these devices decrease shivering thermogenesis, afterdrop is minimized and heat transfer can be significant. Thermal injury to poorly perfused, vasoconstricted skin using some of the other external heat application techniques is a hazard in both adults and children.[118] In particular, avoid resistance-heat electric blankets on which a patient lies, because vasoconstricted capillaries are compressed and burns occur easily.

Another AER option is a thermoregulatory system that circulates warm water through energy transfer pads placed on the chest and lower limbs.[48] The core temperature measured via probe is fed back to the control module.

### Immersion

Immersion in a 40°C (104°F) circulating bath presents difficulties in monitoring, resuscitation, treatment of injuries, and maintenance of extremity vasoconstriction to prevent core temperature afterdrop. In normothermic men with coronary artery disease, the cardiovascular stress and arrhythmogenic response to immersion in a hot tub are mild, less than those induced by exercise. In contrast, placing the hands and feet in warm water theoretically opens arteriovenous shunts and accelerates rewarming in acute hypothermia. Scandinavian palmar heat packs may capitalize on this physiology.

### Arteriovenous Anastomosis Rewarming

The original description of this noninvasive AER technique is by Vangaard.[324] Exogenous heat is provided by immersion of the distal extremities (hands, forearms, feet, calves) in 44° to 45°C (111.2° to 113°F) water. The heat opens arteriovenous anastomoses (AVAs). These structures are 1 mm (0.04 inch) below the epidermal surface in the digits.[16,220] Countercurrent heat loss is

minimized because the superficial veins are not close to the arterial tree.

To be efficacious, the cutaneous heat exchange area must include the lower legs and forearms, and the water must be 44° to 45°C (111.2° to 113°F). Advantages with AVA rewarming include patient comfort and decreased afterdrop after cooling.[296]

A permutation of AVA rewarming is negative-pressure rewarming. Under hypothermic conditions, the AVAs remain closed during peripheral vasoconstriction. In combination with localized heat application, application of subatmospheric pressure theoretically distends the venous rete and increases flow through the AVAs.

To initiate negative-pressure rewarming, the forearm is inserted through an acrylic tubing sleeve device fitted with a neoprene collar. After a vacuum pressure of −40 mm Hg is created, heat is applied over the dilated AVAs. The thermal load can be provided by an exothermic chemical reaction or a heated perfusion blanket.

The clinical efficacy of AVA rewarming in accidental hypothermia is unclear.[39,56] The potential for superficial burns of anesthetic, vasoconstricted skin is a consideration. Another caveat is hypotension precipitated in hypovolemic patients who remain semiupright with this technique. In one study, the rate of core rewarming increased dramatically,[109] but another study comparing negative-pressure rewarming with forced-air warming failed to replicate these results.[308]

### Active Core Rewarming

Various techniques that can effectively deliver heat to the core include heated inhalation, heated infusion, diathermy, lavage (gastric, colonic, mediastinal, thoracic, peritoneal), and extracorporeal rewarming. Figure 7-8 lists average first-hour rewarming rates reported with some of these techniques in one multicenter study. Although hemodynamic instability impacts the rewarming strategy, noninvasive techniques often succeed unless significant comorbidities exist.[269,323]

### Airway Rewarming

The effectiveness of the respiratory tract as a heat exchanger varies with technique and ambient conditions.[218] Dry air has low thermal conductivity, and complete humidification coupled with an inhalant temperature of 40° to 45°C (104° to 113°F) is required.[267] The main benefit of airway rewarming is prevention of respiratory heat loss. Heat yield can represent 10% to 30% of the hypothermic patient's heat production when respiratory minute volume is adequate.[27]

The rate of rewarming is greater using an endotracheal tube (ETT) than by mask. In one series, the reported rewarming rate with a 40°C (104°F) aerosol was 0.74°C (1.33°F) per hour by mask and 1.22°C (2.2°F) per hour by ETT.[222] In a multicenter survey,[62] the average first- and second-hour rewarming rates in severe cases were 1.5° to 2°C (2.7° to 3.6°F) per hour. The decremental efficiency at higher temperatures slows the rate (10 kcal/hr) in mild cases.[62]

Thermal countercurrent exchange in the cerebrovascular bed of humans[67] affects the efficiency and influence of heated-mask ventilation during hypothermia. Known as the rete mirabile, this system could preferentially rewarm the brainstem. Heated inhalation by face mask continuous positive airway pressure (CPAP) may correct the ventilation-perfusion mismatch.[40] Heated humidified oxygen by face mask is not feasible in some patients with coexistent midface trauma.

Heat liberated during airway rewarming is produced mainly from condensation of water vapor. The latent heat of vaporization of water in the lungs is slightly lower than 540 kcal/g $H_2O$. This is multiplied by the liters per minute (L/min) ventilation to calculate the quantity of heat transfer. When core temperature is 28°C (82.4°F), the rate of rewarming with heated ventilation at 42°C (107.6°F) equals endogenous heat production. Although the effect on overall thermal balance can be minimal, there may be preferential rewarming of thermoregulatory control centers.[58]

Heated humidified inhalation ensures adequate oxygenation, stimulates pulmonary cilia, and reduces the amount and viscosity of cold-induced bronchorrhea. Although preexisting premature ventricular contractions (PVCs) may reappear during rewarming, there is no evidence that inhalation rewarming precipitates new, clinically significant ventricular arrhythmias. Vapor absorption does not increase pulmonary congestion or wash out surfactant. When the pulmonary vasculature is heated, warmed oxygenated blood that returns to the myocardium could attenuate intermittent temperature gradients. The amplitude of shivering is also lowered, an advantage in more severe cases. This suppression could decrease heat production in mild hypothermia, although experimentally the core temperature continues to rise.[56]

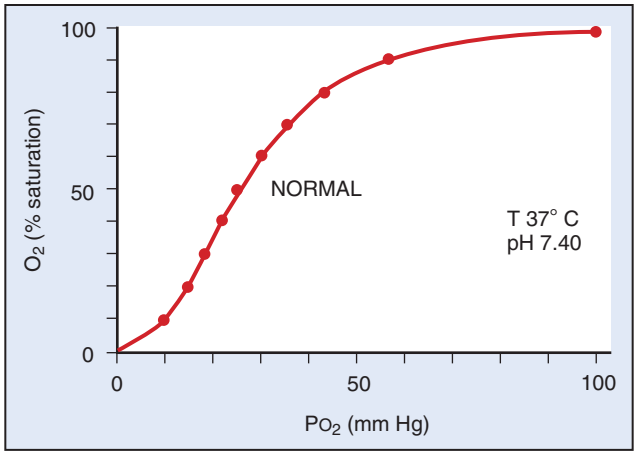



**FIGURE 7-9** Oxyhemoglobin dissociation curve at 37°C (98.6°F). At colder temperatures, the curve shifts to the left.

There are numerous oxygenation considerations in hypothermia (see Box 7-1). The "functional" value of hemoglobin at 28°C (82.4°F) is 4.2 g/10 g in patients on CPB. The oxyhemoglobin dissociation curve also shifts to the left (Figure 7-9). This impairs release of oxygen from hemoglobin into the tissues. Although some patients can self-adjust their respiratory minute volume (RMV) for current $CO_2$ production, this may not be possible if there are additional toxins or metabolic depressants.[58]

Most humidifiers are manufactured in accordance with International Standards Organization (ISO) regulations. The humidifier will not exceed 41°C (105.8°F) close to the patient outlet with a 6-foot (180-cm) tubing length.[331] If the decision is made to alter equipment, carefully monitor the temperature and do not exceed 45°C (113°F). The only report of thermal airway injury was in a patient ventilated by ETT for 11 hours with 80°C (176°F) inhalant.

Strategies to circumvent the 41°C ceiling include reduction of tubing length, adding additional heat sources, disabling the humidifier safety system, and placing the temperature probe outside the patient circuit.[331] Label all modified equipment to avoid routine use. A volume ventilator with a heated cascade humidifier can also deliver CPAP or positive end-expiratory pressure (PEEP) if needed during rewarming. The airway rewarming rates clinically range from 1° to 2.5°C (1.8° to 4.5°F) per hour.[58] In stable patients, circumventing the 41°C ceiling may not be worth the effort because the clinical benefit is modest.[162]

Heat and moisture exchangers function as artificial nares by trapping exhaled moisture and then returning it. The exchangers provide inadequate humidification to treat accidental hypothermia. With prolonged use, ETT occlusion and atelectasis are both problems.[49]

Airway rewarming is indicated in the ED when core temperature is lower than 32.2°C (90°F) on arrival. Although airway rewarming provides less heat than other forms of active core warming, it prevents normal respiratory heat and moisture loss and is safe, fairly noninvasive, and practical in all settings.

### Heated Infusions

Cold-fluid resuscitation of hypovolemic patients can induce hypothermia. In one series of previously normothermic patients with major abdominal vascular trauma, the average temperature after resuscitation was 31.2°C (88.2°F) in those with refractory

coagulopathies. IV fluids are heated to 40° to 42°C (104° to 107.6°F), although higher temperatures may be safe. The amount of heat provided by solutions becomes significant during massive volume resuscitations.[26,291] One liter of fluid at 42°C (107.6°F) provides 14 kcal to a 70-kg (154-lb) patient at 28°C (82.4°F), elevating the core temperature almost 0.33°C (0.6°F).

Significant conductive heat loss occurs through IV tubing, so long lengths of IV tubing increase heat loss, especially at slow flow rates.[84] IV tubing insulators are available. There are various methods to achieve and maintain ideal delivery temperature of IV and lavage fluids in hypothermia, but there is no standardized approach.[119,277]

Blood preheated to 38°C (100.4°F) in a standard warmer is useful, but clotting and shortened RBC life are hazards with blood-warming packs. Local microwave overheating hemolyzes blood. An alternative is to dilute packed RBCs with warm, calcium-free crystalloid. Portable and other commercial fluid warmers heat cold crystalloid and blood through a heat exchanger at flow rates of up to 500 mL/min.

Microwave heating of IV fluids in flexible plastic bags is another option when more standardized heaters are unavailable. The plasticizer in the polyvinyl chloride containers is stable to microwave heating. Heating times should average 2 minutes at high power for a 1-L bag of crystalloid. The fluid should be thoroughly mixed before administration to eliminate hot spots.

Rapid administration of fluid into the right atrium at a temperature significantly different from that of circulating blood may produce myocardial thermal gradients. In one study, heated IV fluid, up to 550 mL/min, was administered through the internal jugular vein without complication. In an experimental canine model with adequate cardiac output, central infusion of extremely hot (65°C [149°F]) IV fluids accelerates rewarming without hemolysis.[90,288]

Using amino acid infusions may accelerate energy metabolism.[285] Fever is common in patients receiving hyperalimentation. In patients recovering from elective surgery, however, amino acids have no significant thermogenic effect.[133] The results might differ in energy-depleted patients with chronically induced accidental hypothermia.

In summary, IV solutions and blood should be routinely heated during hypothermia resuscitations. Various blood warmers are available commercially, but countercurrent in-line warmers are the most efficient.[148] A mathematic model indicates that infusion heating devices are essential in trauma patients with high fluid requirements.[26]

## HEATED LAVAGE

### Gastrointestinal Lavage

Heat transfer from irrigation fluids is usually limited by the available surface area. The irrigant should not exceed 45°C (113°F). Direct GI irrigation is less desirable than irrigation via intragastric or intracolonic balloons because of induced fluid and electrolyte fluxes. Exceeding 200- to 300-mL aliquots may force fluid into the duodenum; therefore frequent fluid removal by gravity drainage minimizes "lost" fluid. A log of input and output is essential. This facilitates estimation of fluid balance during resuscitation and helps determine if irrigation should be abandoned in anticipation of dilutional electrolyte disturbances.

To avoid these limitations, a double-lumen esophageal tube is available, as are other modified tubes. Patients should be tracheally intubated before gastric lavage. Because of the proximity of an irritable heart, overly vigorous placement of a large gastric tube is not advised. In a multicenter survey, gastric, bladder, and colon lavage rewarmed severely hypothermic patients at 1° to 1.5°C (1.8° to 2.7°F) for the first hour and 1.5° to 2°C (2.7° to 3.6°F) for the second hour.[62]

Commercially available kits designed for gastric decontamination are convenient (Figure 7-10). The use of a Y connector and clamp simplifies the exchanges. Ideal dwell times for thermal exchange depend on flow rates and may average several minutes. In direct gastric lavage, warmed electrolyte solutions, such as normal saline or Ringer's lactate, are administered via nasogastric tube.[191] After 15 minutes the solution is aspirated and replaced with warm fluids. Disadvantages include the small surface area available for heat exchange and the large amount of fluid escaping into the duodenum.[38] Regurgitation is common, and the technique must be terminated during CPR. Esophageal and bladder heat exchange are also very limited.[336,337] Aesthetic obstacles aside, heat transfer through colonic irrigation is negligible.

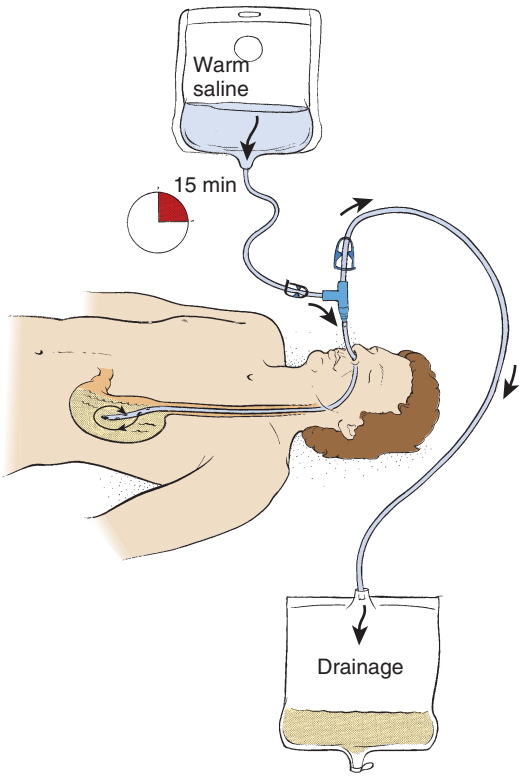



FIGURE 7-10 Gastric lavage.

### Mediastinal Lavage

Mediastinal irrigation and direct myocardial lavage are alternatives in patients lacking spontaneous perfusion. A standard left thoracotomy is performed while CPR is continued. Opening the pericardium is unnecessary unless an effusion or tamponade is present. The physician bathes the heart for several minutes in 1 to 2 L of an isotonic electrolyte solution heated to 40°C (104°F), then suctions and replaces warm fluids.[36]

The physician may attempt internal defibrillation after myocardial temperature reaches 26° to 28°C (78.8° to 82.4°F). Unless a perfusing rhythm is achieved, lavage and all available heating techniques are continued until myocardial temperature exceeds 32° to 33°C (89.6° to 91.4°F). A standard post-thoracotomy tube in the left side of the chest could provide an avenue for continued rewarming via thoracic irrigation.

A median sternotomy also allows ventricular decompression and direct defibrillation.[190] One potential disadvantage of both these techniques is that open cardiac massage of a cold, rigid, and contracted heart may not generate flow.[5,57] Unless immediate CPB is an option, mediastinal irrigation and direct myocardial lavage are indicated only if cardiac arrest has occurred. In this circumstance, personnel skilled in the technique should also initiate all other available rewarming modalities.

### Thoracic Lavage

Irrigation of the hemithoraces is a valuable rewarming adjunct.[37,171,317] An important semantic issue is that closed thoracic lavage via two thoracostomy tubes differs from open mediastinal and direct myocardial lavage. With the latter, closed-chest CPR is not possible. Two large-bore thoracostomy tubes (36 French [36F] to 40F in adults; 14F to 24F, ages 1 to 3; 20F to 32F, ages 4 to 7) are inserted in one or both of the hemithoraces. One is placed anteriorly in the second to third intercostal space at the

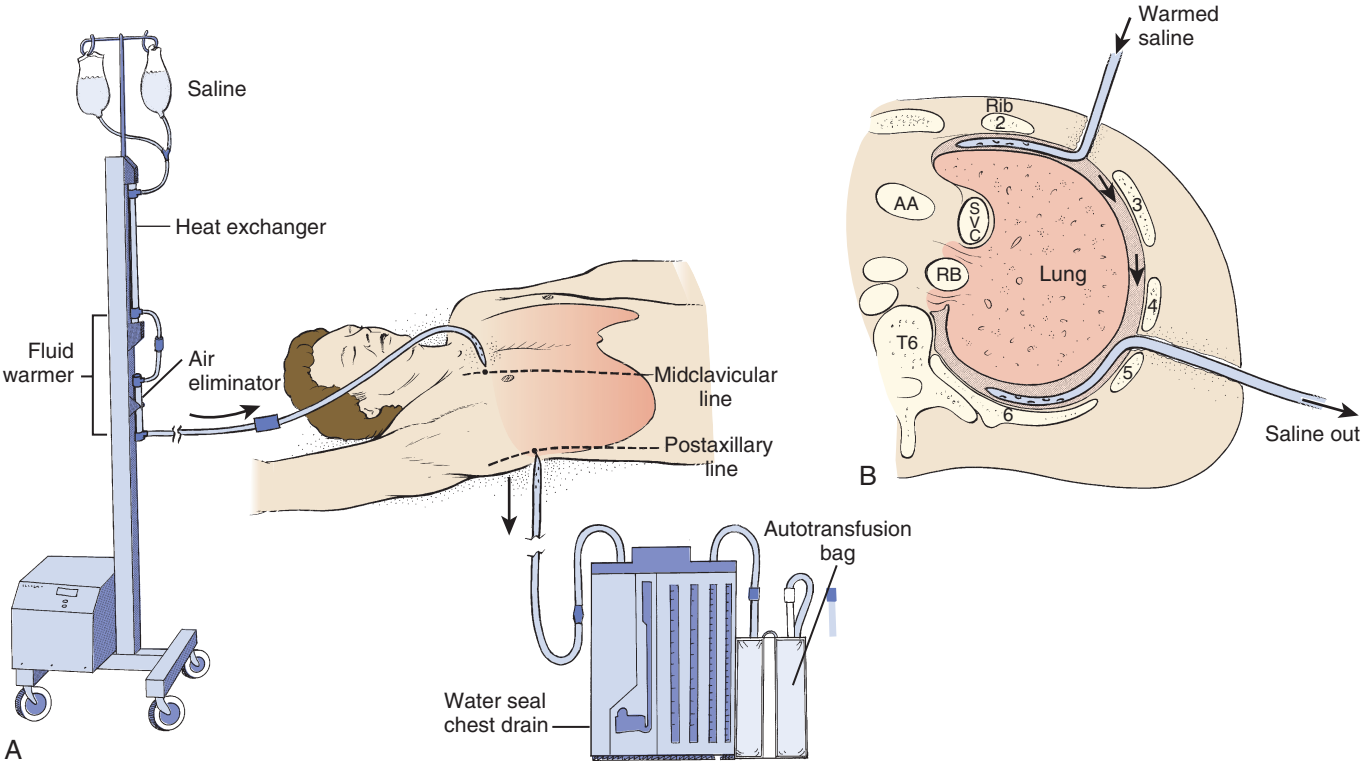



**FIGURE 7-11** Thoracic lavage. **A,** Cycle. **B,** Cross section. *AA,* ascending aorta; *RB,* right bronchus; *SVC,* superior vena cava; *T6,* sixth thoracic vertebra.

midclavicular line, and the other in the posterior axillary line at the fourth to fifth intercostal space. Normal saline heated to 40° to 42° C (104° to 107.6° F) is then infused via a nonrecycled sterile system (Figure 7-11A).[169]

A high-flow countercurrent fluid infuser heats to 40° C (104° F) and delivers normal saline in 1-L or preferably 3-L bags into the afferent chest tube.[260] Ideally, connect into the tubing with standard 0.19-inch internal-diameter suction connection tubing and a sterilized plastic graduated two-way connector, because this facilitates adaptation to any size of chest tube (Figure 7-11A). The effluent is then collected in a thoracostomy drainage set. The reservoir must be emptied frequently. Alternatively, when a single chest tube is used, 200- to 300-mL aliquots are used for irrigation, and suctioning is achieved through a Y connector. The Y connector is also useful for irrigating both hemithoraces with a single fluid warmer (Figure 7-11B).

Fluid can be infused into the anterior higher chest tube (afferent limb) and suctioned or gravity drained out the lower posterior tube (efferent limb) into a water-seal chest drain.[117] Infusion inferoposteriorly with suction anteriorly can increase dwell times.[148] The efficiency of thermal transfer varies with flow rates and dwell times. Once the patient is successfully rewarmed, the upper tube should be removed and the lower tube left in place to allow residual drainage.

Closed sterile thoracic lavage is a natural choice in the ED during potentially salvageable cardiac arrest resuscitations.[346] Thoracic lavage is an option either as a bridge to CPB or when CPB is initially unavailable. In patients who are perfusing, this technique should be considered hazardous unless extracorporeal rewarming capability is immediately available. Many hypothermic trauma patients are irrigated successfully during surgery.

The clinically reported infusion rates range from 180 to 550 mL/min. The overall rate of rewarming should easily equal or exceed that achievable with peritoneal lavage and is often 3° to 6° C (5.4° to 10.8° F) per hour. The surface area of the pleural space is well perfused. An added benefit is preferential mediastinal rewarming. In addition, closed-chest compressions during cardiac arrest can maintain perfusion. Open cardiac massage of a rigid, contracted heart may not be possible in severe cases before bypass, which is a problem with mediastinal irrigation.[5,57,61]

Various complications should be considered. Left-sided thoracostomy tube insertion into patients who are perfusing could easily induce VF. Patients with pleural adhesions or a history of pleurodesis have poor infusion rates, and subcutaneous edema may develop. If the fluids are infused under pressure without adequate drainage, intrathoracic hypertension or even a tension hydrothorax can develop and cause expected adverse cardiovascular effects.[157,256]

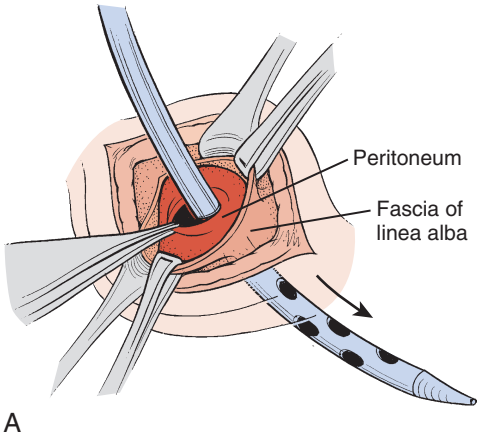
## Peritoneal Lavage

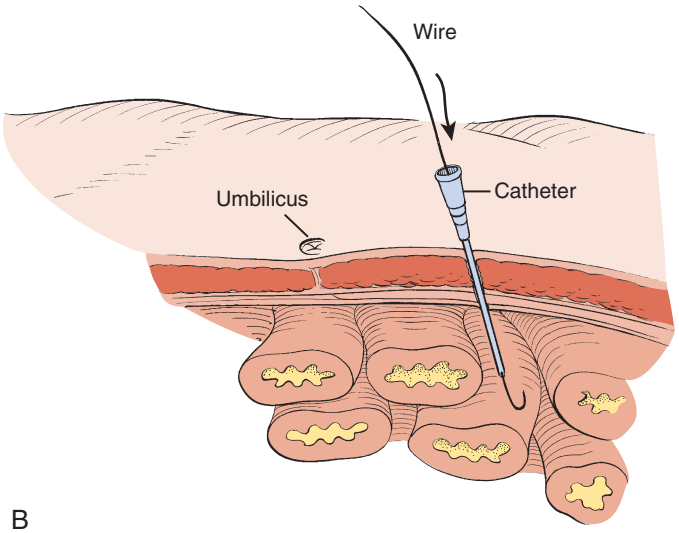
Heated peritoneal lavage is a technique available in most facilities (Figure 7-12). Heat is conducted intraperitoneally via isotonic dialysate delivered at 40° to 45° C (104° to 113° F).[327]

Before lavage is initiated, imaging should be obtained because subsequent films may reveal subdiaphragmatic air introduced during the procedure. The bladder and stomach must be emptied before insertion of the catheter. The two common techniques for introducing fluid into the peritoneal cavity are the mini-laparotomy and the percutaneous puncture.

The "minilap" requires an infraumbilical incision through the linea alba. A supraumbilical approach is necessary if previous surgical scars, a gravid uterus, or pelvic trauma is identified. The peritoneum is punctured under direct visualization and dialysis catheter(s) inserted. A much simpler and more rapid technique is the guidewire, or Seldinger, variation of the percutaneous puncture. The site is infiltrated if necessary with lidocaine, and a small stab incision is made. An 18- to 20-gauge needle penetrates the peritoneum, and a guidewire is introduced. Entry into the peritoneum is usually recognizable by a distinct "pop." Disposable kits are available. The 8F lavage catheter is inserted over the wire and advanced into one of the pelvic gutters. Double-catheter systems with outflow suction speed rewarming.

Normal saline, lactated Ringer's solution, or standard 1.5% dextrose dialysate solution with optional potassium supplementation can be used. Isotonic dialysate is heated to 40° to 45° C (104°



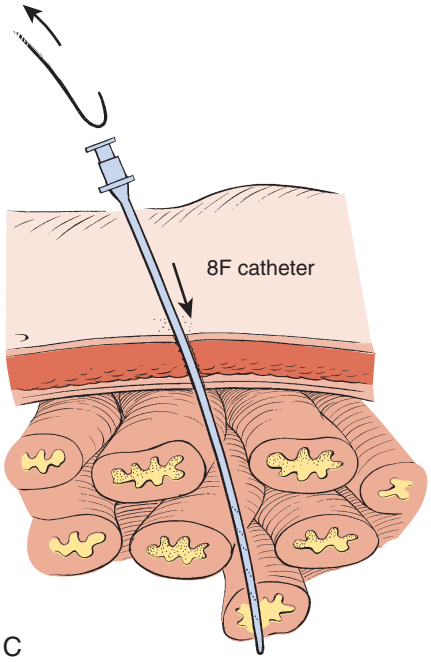




**FIGURE 7-12** Peritoneal lavage. **A,** Mini-laparotomy for peritoneal lavage. **B,** The catheter in place with the needle removed and the wire introduced. **C,** An 8F catheter is introduced over the wire, and the wire is then removed.

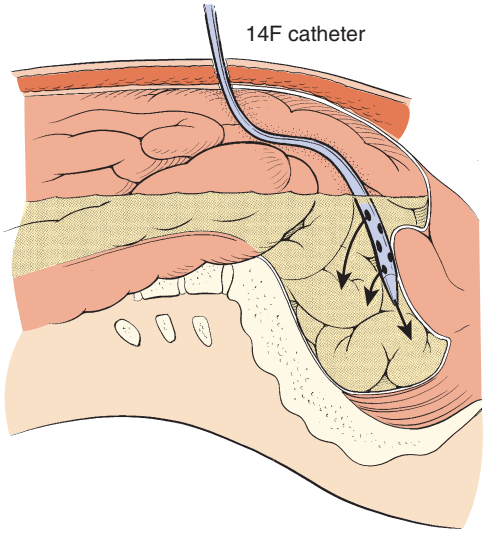



**FIGURE 7-13** Peritoneal lavage. A 14F catheter is of a caliber that can infuse fluids rapidly.

to 113°F). Up to 2 L is then infused (10 to 20 mL/kg), retained for 20 to 30 minutes, and aspirated. The usual clinical exchange rate is 6 L/hr, which yields rewarming rates of 1° to 3°C (1.8° to 5.4°F) per hour. An alternative for severe cases is a larger catheter, as found in cavity drainage kits (Figure 7-13). The catheter can be placed with the Seldinger technique. The higher drainage capability greatly increases exchange rates and minimizes the dwell times necessary for maximal thermal transfer. The flow rate via gravity through regular tubing is approximately 500 mL/min, which can be tripled under infusion pressure.

A unique advantage of peritoneal dialysis is drug overdose and rhabdomyolysis detoxification when hemodialysis is unavailable. In addition, direct hepatic rewarming reactivates detoxification and conversion enzymes. Peritoneal dialysis worsens preexisting hypokalemia. Vigilant electrolyte monitoring is essential before empirical modification of the dialysate. The presence of adhesions from previous abdominal surgery increases the complication rate and minimizes heat exchange.

Peritoneal dialysis during standard mechanical CPR is as effective as partial cardiac bypass in resuscitating severely hypothermic dogs.[341] In contrast to AER, peritoneal lavage rewarming did not require significantly greater quantities of crystalloids and bicarbonate. This exchange rate is rarely possible in humans. Bowel infarction may be a concern when using prolonged warm peritoneal dialysis in patients with severe hypothermia with inadequate visceral perfusion during CPR.

Peritoneal lavage is invasive and should not be routinely used in treating stable, mildly hypothermic patients. This technique is indicated in combination with all available rewarming techniques in cardiac arrest patients.

## ENDOVASCULAR WARMING

Another active rewarming option is endovascular warming with commercially available temperature control devices. They are used in EDs for therapeutic cooling of resuscitated comatose cardiac arrest patients.[344]

Less invasive and technically easier than extracorporeal rewarming, endovascular systems that involve femoral vein catheterization may prove to be a promising alternative. The closed-loop catheter has a temperature control element at the tip. Available models have a fail-safe feature on the console that must be circumvented to allow rewarming if the core temperature is below 30°C (86°F).[181]

## EXTRACORPOREAL BLOOD REWARMING

Table 7-4 summarizes the techniques for extracorporeal blood rewarming.

**TABLE 7-4** Techniques for Extracorporeal Blood Rewarming

| Technique | Comments |
|---|---|
| Cardiopulmonary bypass | Full circulatory support<br>Perfusate temperature gradient: consider 5°-10° C (9°-18° F)<br>Flow rates of 2-7 L/min (average, 3-5 L/min)<br>Rate of rewarming, up to 9.5° C (17.1° F) per hour<br>Consider if K <10 mmol/L, pH > 6.5, at least 10°-12° C (50°-53.6° F) |
| Continuous arteriovenous warming | Percutaneous Seldinger technique to insert catheters<br>Requires blood pressure of ≥ 60 mm Hg<br>No need for perfusionist/pump/anticoagulation<br>Average flow rates of 225-375 mL/min<br>Rate of rewarming, 3°-4° C (5.4°-7.2° F) per hour<br>Consider for trauma |
| Venovenous rewarming | Circuit not complex<br>Efficient nonbypass modality<br>Volume infusion to augment cardiac output<br>Flow rates of 150-400 mL/min<br>Rate of rewarming, 2°-3° C (3.6°-5.4° F) per hour |
| Hemodialysis | Widely available<br>Portable and efficient<br>Single or dual catheter<br>Exchange cycle volumes, 200-500 mL/min<br>Rate of rewarming, 2°-3° C (3.6°-5.4° F) per hour<br>Consider if there are electrolyte/toxicologic derangements |

Modified from Danzl DF: Hypothermia, *Semin Resp Crit Care Med* 23:57, 2002.

## Hemodialysis

Standard hemodialysis is widely available, practical, portable, and efficient and should be strongly considered in perfusing patients with significant electrolyte abnormalities, renal failure, or intoxication with a dialyzable substance.[140,233,247] Two-way flow catheters allow the option of cannulation of a single vessel.[183,307] A Drake-Willock single-needle dialysis catheter can be used with a portable hemodialysis machine and an external warmer. After central venous cannulation, exchange cycle volumes of 200 to 250 mL/min are possible.

Although heat exchange is less than with standard two-vessel hemodialysis, the ease of percutaneous subclavian vein placement is a major advantage. Hemodialysis via two separate single-lumen catheters placed in the femoral vein can achieve continuous blood flow at 450 to 500 mL/min.[130,131] In-line hemodialysis also simplifies correction of electrolyte abnormalities. Local vascular complications, including thrombosis of vessels and hemorrhage secondary to anticoagulation, may occur.

## Continuous Venovenous Rewarming

In extracorporeal venovenous rewarming, blood is removed, usually from a central venous catheter, heated to 40° C (104° F), and returned via a second central or large peripheral venous catheter. Flow rates average 150 to 400 mL/min.[111,125,298,315]

The circuit is not complex and is more efficient than many other nonbypass modalities. There is no oxygenator, and because the method does not provide full circulatory support, volume infusion is the only option to augment inadequate cardiac output. Although the use of CAVR is limited by profound hypotension, high-flow venovenous rewarming may prove to be an alternative.[150]

In another variation of the extracorporeal venovenous circuit, blood is removed from the femoral vein, heparinized, and sent through a blood rewarmer via an infusion pump accelerator. It is neutralized with protamine before reinjection into the subclavian or internal jugular vein, which would preferentially rewarm the heart. Another option is to insert a femoral vein dual-lumen dialysis catheter.

## Continuous Arteriovenous Rewarming

The CAVR technique involves the use of percutaneously inserted femoral arterial and contralateral femoral venous catheters.[93,94] This technique requires a blood pressure of at least 60 mm Hg. The Seldinger technique is used to insert 8.5F catheters. Heparin-bonded tubing circuits obviate the need for systemic anticoagulation. CAVR has principally been performed on traumatized patients (Figure 7-14).

The blood pressure of spontaneously perfusing traumatized hypothermic patients creates a functional arteriovenous fistula by diverting part of the cardiac output out of the femoral artery through a countercurrent heat exchanger. The heated blood is then returned with admixed heated crystalloids via the femoral vein. The additional fluids are titrated and infused by piggyback until hypotension is corrected.[230]

The rate of rewarming exceeds that of hemodialysis. CAVR does not require the specialized equipment and perfusionist necessary for CPB. The average flow rates are 225 to 375 mL/min, resulting in a rate of rewarming of 3° to 4° C (5.4° to 7.2° F) per hour. Because the catheters are 8.5F, the patient must weigh at least 40 kg (88 lb). Coagulation begins to appear in the heparinized circuits at around 3 hours.

## Cardiopulmonary Bypass

Partial or complete CPB or extracorporeal membrane oxygenation (ECMO) should be considered in unstable, severely hypothermic patients.[14,33,211,270,348] Favorable considerations include absence of severe head injury or asphyxia.[292] Some centers initiate CPB or ECMO only if the presenting arterial pH is above 6.5, serum potassium is below 10 mmol/L, and core temperature is above 10° to 12° C (50° to 54° F).[135,332]

Fischer's considerations for CPB include a potassium level under 10 mmol/L in adults or under 12 mmol/L in children, coupled with a core temperature below 30° C (86° F). Patients are not resuscitated if extreme hyperkalemia is identified in a patient with a temperature over 30° C (86° F).[91]

A major advantage of CPB is preservation of oxygenated flow if mechanical cardiac activity is lost during rewarming.[73,144] CPB is three to four times faster at rewarming than other active core

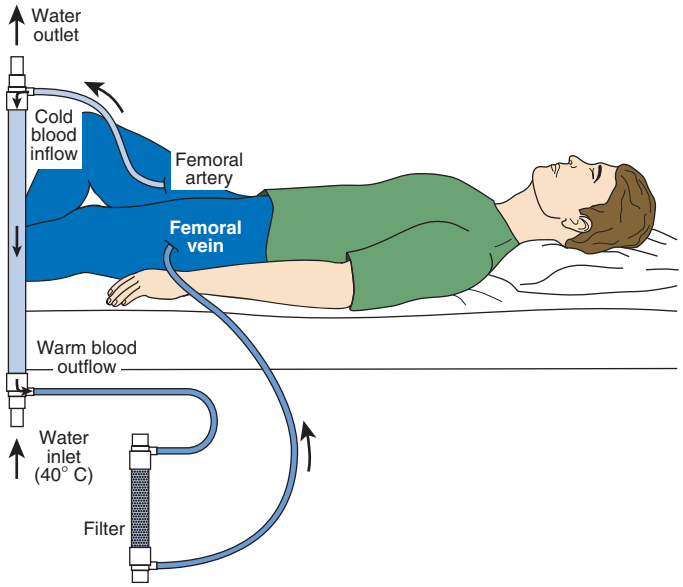



**FIGURE 7-14** Schematic of continuous arteriovenous rewarming.

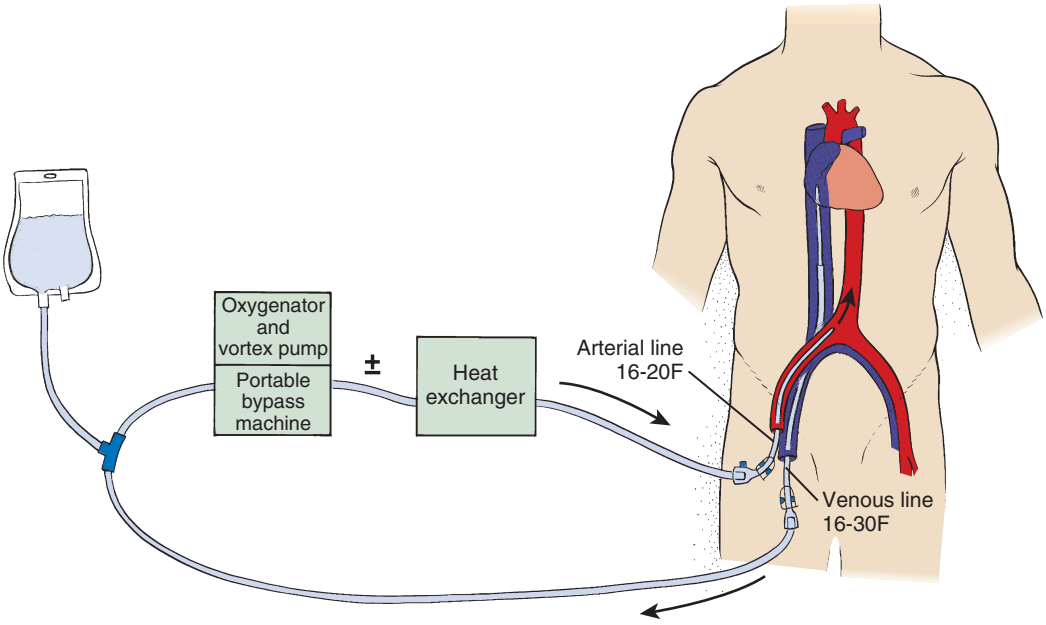



**FIGURE 7-15** Femoral-femoral bypass.



rewarming (ACR) techniques, and it reduces the high blood viscosity associated with severe cases. CPB should also be considered when severe cases do not respond to less invasive rewarming techniques, in patients with completely frozen extremities, and when extensive rhabdomyolysis is accompanied by major electrolyte disturbances.[154]

Various extracorporeal rewarming techniques can be lifesaving in select profound cases of hypothermia.[122] A 65-year-old woman survived sequela free after 520 minutes of cardiac arrest treated with CPR and CPB.[221] Complete recovery was also reported in three severely hypothermic tourists after prolonged periods of cardiac arrest and CPR.[5] In a review of 17 cases, there were 13 survivors.[297,332] In another series rewarming 32 patients with CPB, 15 are long-term survivors. The average age was 25.2 years. Their mean presenting esophageal temperature was 21.8°C (71.2°F), and the mean interval between discovery and CPB was 141 minutes.

The standard femoral-femoral circuit includes arterial and venous catheters, mechanical pump, membrane or bubble oxygenator, and heat exchanger (Figure 7-15). A 16F to 30F venous cannula is inserted via the femoral vein to the junction of the right atrium and the inferior vena cava. The tip of the shorter 16F to 20F arterial cannula is inserted 5 cm (2 inches) or proximal to the aortic bifurcation. Consider use of 32F venous and 28F arterial cannulae with the open surgical technique, and 21F venous and 19F arterial cannulae if inserted percutaneously.[8] Closed-chest compressions can be maintained during percutaneous or open surgical technique insertion and may help decompress the dilated, nonbeating heart. Transesophageal echocardiography can help evaluate ventricular load and valve function.

Heated, oxygenated blood is returned via the femoral artery.[19] Femoral flow rates of 2 to 3 L/min can elevate core temperature 1° to 2°C (1.8° to 3.6°F) every 3 to 5 minutes. In one review, the mean CPB temperature increase was 9.5°C (17.1°F) per hour. Most pumps can generate full flow rates up to 7 L/min.[297] Consider the use of vasodilator therapy with IV nitroglycerin to facilitate perfusion.[199,200] Initiate bypass flow rates at about 2 L/min and gradually increase to 4 to 5 L/min. Vasoactive agents may be needed to maintain the cardiac index at 30 L/min/$m^2$ or more and a (low) systemic vascular resistance of 1000 dynes/sec × $cm^{-5}$ or less.[207]

The optimal temperature gradient and bypass rewarming rates are unknown. One study of rewarming via CPB in a swine model cooled to 23°C (73.4°F) addresses this concern. An excessive temperature gradient between brain tissue and circulant adversely affected electroencephalographic (EEG) regeneration. The other theoretical concern is the possibility of increased bubbling if high perfusate temperature gradients are used. Most investigators use 5°C (9°F) gradients[21]or 10°C (18°F) gradients.[22] Neuromonitoring during rewarming is advised. In severe cases, evoked cerebral responses before EEG regeneration could help assess the recovering brain.[284]

A variety of techniques decrease the need for IV anticoagulation with heparin, which previously limited clinical applicability.[168] Heparin-coated perfusion equipment can be considered without systemic heparinization in patients with hypothermic cardiac arrest and intracranial trauma. The use of nonthrombogenic pumps, coupled with enhanced physiologic fibrinolysis seen in the first hour of CPB, should be considered. ECMO requires lower levels of anticoagulation in addition to the possibility of prolonged extracorporeal-assisted resuscitation; these factors may explain the published mortality reduction compared with CPB.[33]

Complications with the standard technique include vessel damage, air embolism, hemolysis, DIC, and pulmonary edema (Box 7-8). ECMO appears to decrease the incidence of severe pulmonary edema in some patients.[33] Endothelial leakage increases compartment pressures and exacerbates frostbite. If adequate flow rates of 3 to 4 L/min (50 to 60 mL/kg/min) cannot

**BOX 7-8 Extracorporeal Rewarming: Complications and Contraindications**

**Complications**
- Vascular injury
- Air embolism
- Pulmonary edema
- Coagulopathies (hemolysis, disseminated intravascular coagulation)
- Frostbite tissue damage
- Extremity compartment syndromes

**Contraindications**
- Futile resuscitations
- Lack of venous return
- Intravascular clots or slush
- Complete heparinization would be hazardous*
- Cardiopulmonary resuscitation is contraindicated (see Box 7-9)

*Unless with athrombogenic tubing or adequate physiologic fibrinolysis.

**BOX 7-9 Contraindications to Initiating Cardiopulmonary Resuscitation in Accidental Hypothermia**

- Do-not-resuscitate status is documented and verified.
- Obviously lethal injuries are present.
- Chest wall depression is impossible.
- Any sign of life is present.
- Rescuers are endangered by evacuation delays or altered triage conditions.

Data from Zafren K, Giesbrecht GG, Danzl DF, et al. Wilderness Medical Society practice guidelines for the out-of-hospital evaluation and treatment of accidental hypothermia. 2014 update. Wilderness & Environmental Medicine 2014;25:425–445.

be maintained, thoracotomy or a venous catheter with side holes, augmenting intravascular volume, should be considered.

With all four of these techniques, there is no proof that rapid acceleration of the rate of rewarming improves survival rates in perfused patients. The value of the maintenance of some degree of mild hypothermia after hypothermic cardiac arrest and extracorporeal rewarming is speculative. With accidental hypothermia, patients may have had neuroprotection before cardiac arrest from hypothermia. Potential complications of uncontrolled rapid rewarming in severe hypothermia include DIC, pulmonary edema, hemolysis, and acute tubular necrosis. As an alternative, a conservative core-rewarming approach can be highly effective for patients with severe hypothermia, despite hemodynamic instability.[271]

In hypothermic cardiac arrest, rewarming should be attempted via CPB and hemodialysis when CPR is not contraindicated (Box 7-9), unless frozen intravascular contents prevent flow. Clotted atrial blood or failure to obtain venous return indicates that these techniques will be futile. If experienced personnel and necessary equipment are unavailable, all other rewarming techniques should be used in combination.[21,329,347]

### Diathermy

Diathermy, the transmission of heat by conversion of energy, is a potential rewarming adjunct in accidental hypothermia.[197] Large amounts of heat can be delivered to deep tissues with ultrasonic (0.8 to 1 MHz) and low-frequency (915 to 2450 MHz) microwave radiation. Short-wave (13.56 to 40.68 MHz) modalities are high frequency and do not penetrate deeply. Contraindications include frostbite, burns, significant edema, and all types of metallic implants and pacemakers.

Under ideal conditions in a laboratory study, radio-wave frequency (13.56 MHz) electromagnetic regional heating of hypothermic dogs after immersion does not damage tissue at 4 to 6 watts/kg and rapidly elevates core temperature.[342] In one study, 16 piglets were rewarmed with microwave irradiation "until they squealed and suckled."[357] Subsequently, 20 of 28 human infants rewarmed with microwave irradiation at 90 to 100 watts survived. The temperature rose an average 1° C (1.8° F) after 6 to 7 minutes, and the average infant required 45 minutes to achieve a rectal temperature of 36° C (96.8° F). In an experimental study of men cooled to 35° C (95° F), warm-water immersion rewarming is more rapid than radio-wave rewarming with 2.5 watts/kg.[160]

Both ultrasonic and low-frequency microwave diathermy can deliver large quantities of heat below the skin. Potential complications and ideal application sites for this experimental technique deserve further study in the hospital. In the field setting, potential problems with power supply and electronic and navigational interference compound the physiologic problems.

## CARDIOPULMONARY RESUSCITATION

Basic and advanced life support recommendations in hypothermia continue to evolve* (Figure 7-16). Cardiac output generated with closed-chest compressions maintains viability in select

*References 187, 227, 242, 248, 295, 353.

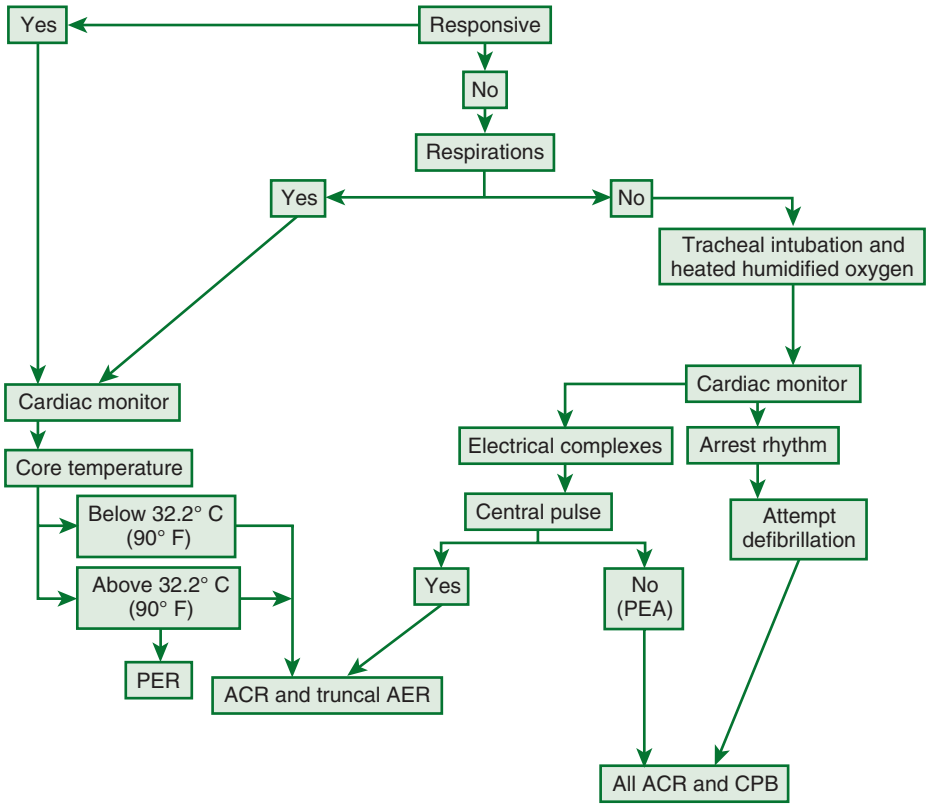



**FIGURE 7-16** Emergency department algorithm. *ACR,* Active core rewarming; *AER,* active external rewarming; *CPB,* cardiopulmonary bypass; *PEA,* pulseless electrical activity; *PER,* passive external rewarming.

patients with hypothermia.[303] The optimal rate and technique remain unclear. Definitive prehospital determination of cardiac activity requires a cardiac monitor or portable ultrasound, because misdiagnosis of cardiac arrest is a hazard. Peripheral pulses are difficult to palpate when extreme bradycardia is present with peripheral vasoconstriction.[124,249,343]

Asystole may be as common a presenting rhythm as VF. In the field, differentiating VF from asystole may be impossible. Possible causes of VF include acid-base fluxes, hypoxia, and coronary vasoconstriction with increased blood viscosity. Chest compressions and various therapeutic interventions are also implicated.[116,245] The role of acid-base fluxes is not clear. Mild alkalosis appears somewhat protective against VF during controlled, induced hypothermia.[179]

## RESPIRATORY CONSIDERATIONS

When cardiopulmonary arrest develops during resuscitation, noncardiac causes are often pulmonary emboli or progressive respiratory insufficiency. Provision of adequate oxygen supply is essential during rapid rewarming. For each 1°C (1.8°F) rise in temperature, oxygen consumption increases up to three times (see Box 7-1). Eventually, regional cerebral oxygen saturation monitoring may help differentiate shockable VF and ventricular tachycardia (VT).[1]

Endotracheal intubation and ventilation decrease atelectasis and ventilation-perfusion mismatch. Complete airway protection averts aspiration, which is otherwise common with depressed airway reflexes, bronchorrhea, and ileus. $CO_2$ production also drops by one-half with an 8°C (14.4°F) fall in the temperature. During induced hypothermia, carbogen (1% to 5% $CO_2$ added to oxygen) facilitates acid-base management by allowing adjustment of the fractional inspired carbon dioxide concentration ($FiCO_2$) while adjusting the ventilation.

Past controversy regarding the hazards of endotracheal intubation reflected coincidental episodes and a mis-citation regarding a series of hypothermic overdoses.[87,188] In a multicenter survey, endotracheal intubation was performed on 117 patients by multiple operators in various settings.[62] No induced arrhythmias were recognized, which is consistent with several reports.[186,222] Potential arrhythmogenic factors include hypoxia, mechanical jostling, and acid-base or electrolyte fluctuations.

The indications for endotracheal intubation in hypothermia are identical to those in normothermia.[103] Ciliary activity is depressed in hypothermia, frothy sputum produces chest congestion, and bronchorrhea resembles pulmonary edema. Fiberoptic or blind nasotracheal intubation may be preferable to cricothyroidotomy when cold-induced trismus or potential cervical spine trauma is present. Oral rather than nasal intubation is advisable in patients with coagulopathy, to avoid major epistaxis.

Rapid-sequence intubation may be impossible when severe cold-induced trismus is present and the mandible will not move. In the milder cases, hypothermia prolongs the duration of neuromuscular blockade. Drug metabolism is also prolonged with vecuronium and atracurium. As a result, neuromuscular blockade should be avoided.[162] Efficacy, metabolism, and clearance are very unpredictable, and assessment of sedation adequacy is difficult.

## BLOOD FLOW DURING CHEST COMPRESSIONS

During normothermic conditions, blood flow partially results from phasic alterations in intrathoracic pressure and not just from direct cardiac compression. Antegrade flow occurs without left ventricular compression in a normothermic canine model.[240] Closed-chest compressions increase intrathoracic pressure.[206] When thoracic inlet venous valves are competent, the resultant pressure gradient between arterial and venous compartments generates supradiaphragmatic antegrade flow.

The "cardiac pump" model is predicated on closure of the mitral valve and opening of the aortic valve during chest compression. This allows a forward stroke volume. During release of compression, transmitral flow can fill the left ventricle. Optimal cardiac output is thus generated by achieving the maximal compression rate that allows maximal left ventricular end-diastolic filling. Interestingly, transesophageal echocardiography in a canine model demonstrates mitral valve closure during chest compression except during low-impulse (downstroke momentum) compressions. Compression of a cold, stiff chest wall may be equivalent to low impulse.[57]

In hypothermia, the role of a "thoracic pump" with the heart as a passive conduit is an attractive hypothesis. The phasic alterations in intrathoracic pressure generated by compressions are equally applied to all the cardiac chambers and thoracic vessels. The mitral valve remains open during compression, and blood continues to circulate through the left side of the heart.

Myocardial compliance can be severely reduced in hypothermia. Althaus and colleagues[5] noted at thoracotomy in one of three survivors of hypothermia that "the heart was found to be hard as stone and it is hardly conceivable how effective external cardiac massage could have been." Open cardiac massage can be combined with mediastinal irrigation when immediate CPB is an option.[36,37,38]

Chest wall elasticity is also decreased with cold, as is pulmonary compliance. If the abdominal muscles are not kneadable, the clinician should anticipate that the stiff chest wall will prevent adequate ventilation. Lastly, more force is needed to depress the chest wall sufficiently to generate intrathoracic vascular compartment pressure gradients.

Despite these potential physiologic explanations, a large number of neurologically intact survivors are reported after prolonged closed-chest compressions. The explanation lies in measuring intrathoracic pressures during hypothermic closed-chest compressions.[23]

Perfusion enhancement maneuvers remain largely unstudied in hypothermia. Ancillary abdominal binding might favorably inhibit paradoxical diaphragmatic motion.[57,240] Simultaneous compression and ventilation can increase flow in the heart's left side. Ventilation with the proper carbogen concentration also allows high ventilatory rates while maintaining uncorrected $PaCO_2$ at 40 mm Hg. Placement of a counterpulsation intraaortic balloon is another option.

Mechanical thoracic compression devices should be considered during prolonged resuscitations with limited availability of personnel. In addition, an automatic mechanical chest compression device may serve as a bridge while establishing the capability for CPB.[343]

During hypothermic cardiac arrest in swine, cardiac output, cerebral blood flow, and myocardial blood flow averaged 50%, 55%, and 31%, respectively, of those achieved during normothermic closed-chest compressions. Blood flow to these areas did not decrease with time, unlike in the normothermic group. Hypothermic rheologic changes, including increased viscosity, also affect flow. Peripheral vascular resistance is expected to increase during vasoconstriction, but in the swine there was no difference in systemic and organ vascular resistance between normothermic and hypothermic CPR.[209]

In a multicenter survey of 428 cases, 9 of the 27 patients receiving CPR initiated in the field survived, as did 6 of 14 patients with ED-initiated CPR[62] (see Box 7-9).

Cardiac output is the product of heart rate and stroke volume; therefore, the optimal closed-chest compression rate should be the fastest rate allowing optimal ventricular filling. Many patients have recovered neurologically with slow compression rates. One recovered after 220 minutes at half the normal compression rate.[243] A patient at 16.9°C (62.4°F) recovered neurologically after 307 minutes of intermittent CPR. At 3-month follow-up, she showed a good physical and neurologic recovery.[23] The optimal rate probably has a direct linear relationship with the degree of hypothermia.

Tissue decomposition, apparent rigor mortis, dependent lividity, and fixed, dilated pupils are not reliable criteria for withholding CPR. In addition, intermittent flow may provide adequate support during evacuation. CPR should not be withheld only because continuous chest compressions cannot be ensured.[44,78] Intermittent flow may be preferable to no flow. The lowest temperature documented in an infant survivor of accidental hypothermia is 15.2°C (59.4°F); in an adult, 13.7°C (56.7°F); and in

induced hypothermia, 9°C (48.2°F).[102,237,244] One patient recovered after 6.5 hours of closed-chest compressions.[193] In Saskatchewan in 1994, a 2-year-old child reportedly recovered from a core temperature of 13.9°C (57°F). Remarkably, a physician who authored the report was successfully resuscitated from 13.7°C (57°F) after she received 165 minutes of CPR and then CPB.[102]

## CEREBRAL RESUSCITATION

The ability to reestablish cerebral blow flow (CBF) with CPR and improve neurologic outcome is inversely proportional to the duration of cardiac arrest. Significant delay can greatly elevate the cerebral perfusion pressure (CPP) required to establish CBF.[18]

It appears that thermal stabilization rather than aggressive field rewarming should be the focus, except for severely hypothermic patients or those in cardiac arrest. Mild hypothermia may be therapeutic and improve neurologic outcome after global cerebral ischemia. Hypothermia decreases glutamate release, metabolic demand, free radical formation, and release of inflammatory cytokines.

In the prehospital setting, addressing disproportionate hypotension, hypoperfusion, and hypoxia is paramount. Once the airway is secured, elevating the head 5 to 10 degrees can attenuate intracerebral hypertension induced by global cerebral ischemia. Normally, CBF is independent of CPP over a range of pressures. After cerebral autoregulation is extinguished, CBF passively depends on the arterial blood pressure. When venous access is difficult, medications may be administered intratracheally or via the intraosseous route. Of interest, large internal jugular catheters may partially obstruct cerebral venous outflow.[353]

The goal is normoxia. The prolonged use of 100% oxygen after the return of spontaneous circulation may increase oxidative brain injury by generating reactive oxygen species, including superoxide and hydrogen peroxide. The rescuer should avoid PEEP unless it is essential to maintain normoxia, because it decreases cerebral venous outflow.

Cerebral vasculature autoregulation may be lost after global brain ischemia, and yet hypocarbia-induced vasoconstrictive mechanisms remain intact. Therefore, avoid protracted hyperventilation except in the rare case of a cranially traumatized hypothermic patient with impending uncal herniation. In the field, attempt to ventilate the patient at a rate that would maintain the uncorrected partial pressure of carbon dioxide ($P_{CO_2}$) between 35 and 40 mm Hg.[210]

Postischemic hyperglycemia is potentially detrimental, because glucose levels over 250 mg/dL are associated with lactate generation and exacerbation of metabolic acidosis.

Cerebral resuscitation strategies in hypothermia reflect complex neurophysiology. The brain, although making up only 2% of total body weight, requires 15% of the cardiac output and consumes 20% of the available oxygen at 37°C. CBF depends on the CPP, which equals the mean arterial pressure minus the intracranial pressure. When the CPP drops below 50 to 60 mm Hg, CBF drops. Once CBF is below 20%, a cascade is initiated that includes the failure to maintain ionic gradients in neurons, cellular depolarization, and acidosis. Even when cold, neurons are more susceptible to hypoxic insult than are glial or endothelial cells.[139]

When reperfusion is reestablished, the initial transient hyperemic period is characterized by increased CBF with low oxygen consumption. This lasts for minutes and is followed by the "no reflow" phase, which lasts for hours. Reperfusion is also characterized by both cytotoxic edema during ischemia, and vasogenic edema caused by blood-brain barrier injury. Intraluminal vascular damage is caused by nitric oxide (NO) and reactive oxygen species (ROS), and proteases inflict abluminal injury.[47]

The decrease in CBF decreases mitochondrial ATP generation. Ionic gradients collapse across the neuronal membrane, as a result of failure of the sodium-potassium (Na-K) pump. Sodium influx results in depolarization, which causes axonal release of the excitatory neurotransmitter glutamate. Glutamate is the ultimate trigger of neuronal injury caused by *N*-methyl-D-aspartate receptor activation, because it allows cellular calcium influx.

Second messengers in the cascade are signals during ischemia from trigger events that activate other second messengers or perpetrators of damage. Intracellular overload of calcium inhibits mitochondrial respiration. In addition, nitric oxide synthase generates NO and ROS, both of which damage DNA and increase cytokine levels. In the field, emphasis should be placed on avoidance of factors known to exacerbate adverse neuronal responses to cerebral ischemia: disproportionate hypotension, hypoperfusion, hyperglycemia, hypoxia, and hyperoxia.

## RESUSCITATION PHARMACOLOGY

The pharmacologic effects of medications are temperature dependent; the lower the temperature, the greater the degree of protein binding. Enterohepatic circulation and renal excretion are also altered, so abnormal physiologic drug responses should be anticipated. The usual clinical scenario consists of substandard therapeutic activity while the patient is severely hypothermic, progressing to toxicity after rewarming.[182] Medications are not given orally because of decreased GI function, and intramuscular medications are avoided because they may be erratically absorbed from vasoconstricted sites.

The pharmacologic manipulation of respiratory drive, pulse, and blood pressure is generally not indicated except in profound cases. When a relative tachycardia is not consistent with temperature depression, the possibility of hypovolemia, hypoglycemia, or a toxic ingestion should be considered. Vasopressors are potentially arrhythmogenic, might lower VF threshold, and cannot increase peripheral vascular resistance if the vasculature is already maximally constricted.[186]

If intraarterial pressure is not consistent with the degree of hypothermia, judicious use of inotropic agents may be necessary.[246] Dopamine can be a successful adjunctive treatment.[281] Dopamine reverses cardiovascular depression under hypothermic conditions, equivalent to up to 5°C (9°F) rewarming. Shock requiring vasoactive drugs is a risk factor for mortality.[37]

In severe cases, the target mean arterial pressure is about 60 mm Hg. Epinephrine and vasoconstrictors should probably be avoided.[175,178] Balancing the need for flow versus pressure, one might suggest therapy with labetalol, IV nitroglycerin, and 2 to 4 mcg/kg of dopamine.[354]

Epinephrine is not recommended for hypothermic cardiac arrest below 30°C (86°F). In porcine models, there is no evidence that repeated or high-dose epinephrine during hypothermic CPR improves outcome.[175,178] In the same model, a single 0.4-unit/kg dose of vasopressin below 30°C (86°F) improved defibrillation success.[283]

There is conflicting evidence regarding cardiovascular function after rewarming. In some studies, there is complete reversal of cold-induced changes, whereas in another, the physiologic response to norepinephrine is paradoxical.[338]

Patients with profound hypothermia after ethanol ingestion have been resuscitated with low-dose dopamine support. In frostbite victims, however, the use of catecholamines may jeopardize the extremities.[199,200] Catecholamines also exacerbate preexisting occult hypokalemia.

The effect of temperature depression on the autonomic nervous system is complex. In primates, cooling produces a biphasic response in plasma catecholamine concentrations. After an initial increase, the autonomic nervous system switches off at 29°C (84.2°F),[43] suggesting that catecholamine support might be useful below that temperature. The initial rise in catecholamine levels could also be caused by acute respiratory acidosis, which stimulates the sympathetic nervous system.[30] Low-dose dopamine (1 to 5 mcg/kg/min) or other catecholamine infusions are generally reserved for disproportionately severe hypotensive patients who do not respond to crystalloid resuscitation and rewarming.

### THYROID

The most dramatic Rip Van Winkle–type rude awakening from hypothermic myxedema coma was Dr. Richard Asher's patient in the 1950s. He was successfully metabolically aroused from a

7-year, 30°C (86°F) slumber. Ironically, so was a quiescent oat cell carcinoma.

Cold induces stimulation of the hypothalamic-pituitary-thyroid axis. Unless myxedema is suspected, empirical therapy is not recommended. A history of neck irradiation, radioactive iodine, Hashimoto's thyroiditis, or surgical treatment of hyperthyroidism should heighten the clinician's suspicion of myxedema. Failure to rewarm despite an appropriate course of therapy is a further clue.[204]

Myxedema coma is usually precipitated in older adult patients with chronic hypothyroidism who are stressed by trauma, infection, anesthesia, or medication ingestion. Typical nonspecific laboratory abnormalities include hyponatremia, anemia, and liver function tests and lipid elevations. If myxedema coma is suspected, thyroid function studies, including serum thyroxine ($T_4$) by radioimmunoassay, triiodothyronine ($T_3$) resin uptake, and thyroid-stimulating hormone level, should be obtained and serum cortisol level measured.

Considering the previous discussion, administer 250 to 500 mcg of levothyroxine ($T_4$) intravenously over several minutes, without waiting for confirmatory laboratory results. Daily injections of 100 mcg are required for 5 to 7 days. The clinician should consider adding at least 100 to 250 mg of hydrocortisone to the first 3 L of IV fluid. Absorption of $T_4$ is erratic if the drug is given orally or intramuscularly. The onset of action of $T_3$ is more rapid, which jeopardizes cardiovascular stability; therefore $T_3$ is avoided in acute replacement therapy. The onset of action of $T_4$ is 6 to 12 hours, evidenced by continuous improvement of the vital signs during rewarming. Up to one-half the $T_4$ is eventually converted by the peripheral tissues into $T_3$.

### CORTICOSTEROIDS

Acute cold stress and many coexisting disease processes stimulate cortisol secretion. The free active fraction of cortisol decreases as the temperature drops because of increased protein binding, and cortisol utilization is similarly decreased. The increase in adrenocorticotropic hormone (ACTH) and adrenal steroid secretion may also be a neurogenic or an emotional response in the conscious person to an unpleasant environment.

Cold exposure also induces adrenal unresponsiveness to ACTH. As a result, false diagnosis of decreased adrenal reserve is possible and does not represent functional adrenal insufficiency, because ACTH levels return to normal after rewarming. Serum cortisol levels are usually elevated. Secondary adrenal insufficiency resulting from panhypopituitarism may also coexist with myxedema. Empirical administration of corticosteroids is indicated if hypoadrenocorticism is suspected on the basis of a previous history of corticosteroid dependence, suggestive physical findings, or an inexplicable failure to rewarm.

The use of narcotic antagonists in hypothermia is reported. Naloxone may reduce the severity of hypothermia in drug overdoses and in spinal shock and appears to have activity at the μ-opioid receptor sites.[58]

## RESUSCITATION COMPLICATIONS

### ATRIAL ARRHYTHMIAS

All atrial arrhythmias, including atrial fibrillation (AF), should have a slow ventricular response during temperature depression. AF is typically noted below 32°C (89.6°F). AF usually converts spontaneously during rewarming, and digitalization or other pharmacologic intervention is not warranted. Electrophysiologic studies show that the interval prolongation present on His bundle electrocardiography is unresponsive to atropine. Mesenteric embolization and embolic stroke are potential hazards when the rhythm converts back to sinus rhythm. Hypothermia renders the negative inotropic effects of calcium channel blockers redundant.[58]

In summary, all new atrial arrhythmias usually convert spontaneously during rewarming and should be considered innocent. Attention is directed toward correcting acid-base, fluid, and electrolyte imbalances and avoiding administration of atrial antiarrhythmics.

### VENTRICULAR ARRHYTHMIAS

Preexisting chronic ventricular ectopy may be suppressed in a cold heart. Ectopy developing during rewarming is problematic. The history from the hypothermic patient may be unproductive, and the past cardiac history is often unavailable.

Transient ventricular arrhythmias should generally be left untreated. In one study of 22 continuously monitored patients with hypothermia, supraventricular arrhythmias were common (nine cases) and benign.[266] Ventricular extrasystoles developed in 10 patients, but none experienced VT or VF during rewarming. The terminal rhythm in the eight patients who died while being monitored was asystole and not VF. The energetics of the fibrillating hypothermic ventricle suggest that asystole may consume less energy and may be more protective.

Pharmacologic options are limited because hypothermia induces complex physiologic changes that result in abnormal responses.[349] Drug metabolism and excretion are both progressively decreased. In normothermia, class IA ventricular antiarrhythmics have negative inotropic and indirect anticholinergic effects and moderately decrease conduction velocity (Box 7-10). Procainamide increases the incidence of VF during hypothermia. Quinidine has been useful during induced profound hypothermia, preventing VF during cardiac manipulation at 25° to 30°C (77° to 86°F). The efficacy and safety of disopyramide are unknown.

The role of the class IB agent lidocaine for prophylaxis or treatment is unresolved. In animal studies, lidocaine and propranolol have minimal hemodynamic effects in hypothermia. If normothermic effects persist during hypothermia, the class IB agents would appear attractive because they minimally slow conduction while shortening the action-potential duration (APD).

The class III agent bretylium tosylate is effective in several animal studies and ineffective in others.[80,304] It is not commercially available. This class of agents seems most ideal pharmacologically because it possesses direct antifibrillatory properties. The ability to prolong the APD is temperature dependent. Ideally, a drug would lengthen the APD only in warmer regions of the myocardium to reduce dispersion (Box 7-11). Two cases of chemical ventricular defibrillation after infusion of bretylium (10 mg/kg) in accidental hypothermia are reported.[58,173]

**BOX 7-10 Antiarrhythmic Agents**

**Class I. Sodium Channel Blockers**

IA. Conduction and depolarization moderately slowed, and action potential duration (APD) and repolarization prolonged
- Disopyramide
- Procainamide
- Quinidine

IB. Conduction and depolarization minimally slowed, and APD and repolarization shortened
- Lidocaine
- Mexiletine
- Moricizine
- Phenytoin
- Tocainide

IC. Conduction and depolarization markedly slowed, and APD and repolarization prolonged
- Encainide
- Flecainide

**Class II. β-Adrenergic Blockers**

**Class III. Antifibrillatory Properties (APD Prolonged)**
- Amiodarone
- Bretylium
- D-sotalol

**Class IV. Calcium Channel Blockers**
- Diltiazem
- Verapamil

**Unclassified**
- Adenosine
- Magnesium sulfate

**BOX 7-11 Antiarrhythmic Characteristics**

The ideal ventricular antiarrhythmic would do the following:
- Cause no further decrease in conduction velocity
- Shorten the action potential duration (APD)
- Lengthen the APD only in warmer regions of the myocardium to reduce dispersion
- Possess direct antifibrillatory properties

In a study to evaluate the effects of bretylium administered after induction of hypothermia, only 1 of 11 dogs given bretylium (mean, 40.5 mg/kg) before five invasive maneuvers developed VF.[231] No dog, including control animals, fibrillated during endotracheal intubation. Of note in discussions regarding prophylaxis, 3 of the 11 dogs converted to VF during the drug infusion. Because catecholamine levels increase during cooling, the demonstrated protection appears to result from alteration of electrophysiologic properties of the cardiac tissues.

Amiodarone is another class III drug that possesses direct antifibrillatory activity.[164] In a canine model of severe hypothermic VF, neither bretylium nor amiodarone improved resuscitation.[304] The safety of the class III antiarrhythmic agent D-sotalol is problematic.[20] It has temperature-dependent effectiveness and lengthens prolonged action potentials more efficiently at long pacing cycle lengths. Also of note, magnesium sulfate at a dose of 100 mg/kg intravenously can spontaneously defibrillate most patients on CPB at 30°C (86°F) with induced hypothermia.

Emergency transvenous intracardiac pacing of bradyarrhythmias is extremely risky with cold hearts because it frequently precipitates VF. New arrhythmias that develop after rewarming may, on rare occasions, require pacing. Transcutaneous pacing (TCP) with low-resistance electrodes seems far preferable before stabilization.[136] In a canine model, TCP restored and maintained hemodynamic stability and rewarmed hypothermic animals twice as rapidly as it did the controls.[72]

In summary, there are no commercially available ventricular antiarrhythmics proven safe and effective in accidental hypothermia.

## SEPSIS

In hypothermia, the classic signs of infection, including erythema and fever, are absent.[192] Rigors and shakes resemble shivering. The initial history, physical examination, and laboratory data are often unreliable, so repeated evaluations and comprehensive culturing are mandatory. The 10% subset of patients with sepsis syndrome who present with a hypothermic response have a significantly increased frequency of shock and death, and this secondary hypothermia does not appear to be protective.

Hypothermia compromises host defenses and results in serious bacterial infections. These significant infections can be accompanied by minimal inflammatory response. Some common causative organisms include gram-negative bacteria, gram-positive cocci, oral anaerobes, and Enterobacteriaceae.[192]

The core endotoxin components of gram-negative bacteria normally signal macrophages. At a normal or elevated temperature, active cytokine triggers include tumor necrosis factor, interleukin-1, and interleukin-6. Bone marrow release and circulation of neutrophils are compromised for up to 12 hours. In addition, human and porcine neutrophils are susceptible to hypothermia. In vitro, neutrophil migration and bacterial phagocytosis are reduced at 29°C (84.2°F). Neutrophilic extermination of various bacteria, including *Staphylococcus aureus* and *Streptococcus faecalis,* is also impaired.

Acquired neutrophil dysfunction occurs. In addition, hypothermia is associated with decreased neutrophil levels in near-drowned children. As a clinical demonstration of the importance of these factors, therapeutic maintenance of hypothermia to control cerebral edema in near drowning is abandoned because of the substantial incidence of infectious complications.

The incidence of infection varies dramatically with the patient's age and the clinical series reported.[192,340] In one large group of infants, more than half were septic. Although there were no reliable indicators of infection, some suggestive clues emerged. Serum glucose and leukocyte abnormalities, anemia, uremia, and bradycardia were often identified. In addition to *Staphylococcus* and *Streptococcus,* the predominant organisms were *Haemophilus* and Enterobacteriaceae.

Lung infections are reported in many hypothermic infants. Evaluation of the gastric aspirate is a diagnostic predictor of sepsis in the majority of infected infants. In several studies, sepsis is found in a large percentage of hypothermic infants, and empirical broad-spectrum antibiotics are warranted.

In adults, the incidence of infection ranges from less than 1% to more than 40%, depending on patient selection criteria.[61] Serious soft tissue or pulmonary infections may be common.[192] Occult bacteremia is uncommon, as is meningitis.[340] In other studies of hypothermic older adult patients admitted to hospitals, most have had evidence of probable or definite infections.[63]

In summary, unlike children and older adults, most previously healthy young adults do not need empirical antibiotic prophylaxis. Nevertheless, treatment indications should be liberalized from normothermia. They should include failure to rewarm, and any suspicion or evidence of aspiration, myositis, chest film infiltrate, bacteriuria, or persistent altered mental status. In choosing broad-spectrum coverage, the physician should consider altered drug interactions, volumes of distribution, protein binding, hepatic metabolism, and renal excretion.

# FORENSIC PATHOLOGY

Macromorphologic and micromorphologic lesions are variable and nonspecific in hypothermia, and there is no single pathognomonic finding at autopsy.[194,261,262] Establishing hypothermia as the primary cause of death requires an adequate history of exposure and the absence of other lethal findings at necropsy.[149] Unnatural deaths in nursing home patients, for example, may be significantly underreported for these reasons.[53]

Macroscopic skin changes can suggest the diagnosis. Hyperemia of the dorsa of the hands and knees is often found. Nonpathognomonic pancreatic findings include fat necrosis, aseptic pancreatitis, and hemorrhage. Pulmonary changes consist of intraalveolar, interstitial, and intrabronchial hemorrhages.

An eye that has been directly exposed to the environment can be a chemical indicator of both the environmental and victims' temperatures at the time of death. Vitreous humor chemistry profiles at autopsy can reveal that glucose concentration and total $CO_2$ content vary inversely with temperature, with values significantly higher in the winter. An elevated vitreous glucose in a nondiabetic patient should suggest hypothermia.

The total urinary catecholamine, particularly epinephrine, content was high in one group of casualties known to be hypothermic. Erosions of the gastric mucosa, termed Wischnewsky spots, are also frequently found.[316] In addition, exposure to extreme cold should be suspected when unusual intravascular hemolysis, which is seen after freezing of blood, is observed in a corpse. Fatty degeneration in renal tubule epithelia may help confirm the diagnosis.[261]

## PREVENTION

To function optimally "as the water stiffens" requires an understanding of the principles of heat conservation and loss. Well-trained and educated urban adults can participate in prolonged Arctic maneuvers safely.[289,290,311]

To maintain core temperature in the narrow band necessary for peak functioning in cold environments, appropriate adaptive behavioral responses are essential.[137] Autonomic and endocrinologic mechanisms are only supplemental.

Studies of human cold adaptation reach highly variable conclusions. Explanations for these discrepancies include changes in core and shell temperatures and in metabolic rates before and after cold adaptation. Hypothermic, insulative, isometabolic cold adaptation may be associated with local cold adaptation of the extremities.

Excellent physical conditioning with adequate rest and nutrition is paramount. Hikers and skiers must be accompanied by a partner and should wear effective thermal insulation. Wet inner garments must be changed promptly. Persons who exert themselves, including long-distance skiers, should switch garments depending on current exertional heat production.[139] Dehydration must be avoided, and drinking from a cold stream is preferable to snow ingestion. Significant energy is needed to convert ice at 0°C (32°F) into water.

All areas with a large surface area–to–volume ratio should be well insulated. Excellent synthetic insulating materials include Gore-Tex, Flectalon, Thinsulate, and taslanized nylon.

Under certain circumstances, insidious hypothermia may develop during exposure to cold water because of the effects of increased insulation on compensatory physiologic events.[12] The U.S. Army mnemonic COLD, in reference to insulation with clothing, means *clean, open* during exercise to avoid sweating, *loose* layers to retain heat, and *dry* to limit conductive heat losses.

Prevention of urban accidental hypothermia requires continuous public education. For example, the optimal safe indoor temperature recommendation for older adults has risen to 21.1°C (70°F). Energy assistance and temporary sheltering are effective measures, and selective heating of sleeping quarters and use of electric blankets are economic suggestions. Prewarming the bed and bedroom at night may be the best overall advice to older adults.

## OUTCOMES

Partially in reaction to the dramatic reports of reanimations, the historical standard of care has been that "no one is dead until they are warm and dead." Clearly, some victims are indeed "cold and dead," and it would be useful to identify them safely.[10,275]

Survival is difficult to predict because human physiologic responses to temperature depression vary so widely.[214,217,255,333] The type and severity of the underlying or precipitating disease process are two determinants.[325] Age extremes, although not statistically correlated with survival, are often associated with severe illnesses. In a multicenter survey, however, there were no significant age differences in mortality.[62]

Gender, trauma, infection, and toxin ingestions affected survival differently in multiple, uncontrolled clinical studies.[134,279] There were no clinically significant differences in male versus female profiles in the multicenter survey.[62] From a large hypothermia database, a hypothermia outcome score could enable multiple observers at different sites to assess treatment modalities and outcome predictors.[271] Prehospital cardiac arrest, low or absent blood pressure reading, elevated BUN, and the need for either endotracheal or nasogastric intubation in the ED were significant predictors of outcome after multivariate analysis.[59,161] Reporting unusual cases to a hypothermia registry could stimulate advances in treatment.[143,221]

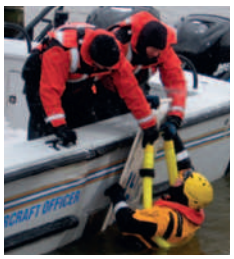
In a multiple regression analysis of 234 cases in Swiss clinics,[198] the most common negative survival factors were asphyxia, slow rate of cooling, invasive rewarming, asystole, and development of pulmonary edema or adult respiratory distress syndrome. The largest single-hospital series of adult hypothermic cardiac arrest patients rewarmed with CPB is reported from Finland. Patients with cold exposure or immersion without suffocation or asphyxia tolerated prolonged CPR before CPB.[292] Positive predictors of survival include rapid cooling rate, presence of VF during cardiac arrest, and narcotic or ethanol intoxication. In a study of 29 patients below 30°C (86°F), mode of cooling was the only independent risk factor.[255]

In a study of CPB survivors, 15 of the 32 patients are long-term survivors.[332] Their neuropsychological functioning after prolonged prehospital circulatory arrest is encouraging. These patients were not asphyxiated before becoming hypothermic. A literature review on the outcomes of 68 patients resuscitated with CPB notes the survival rate was 60%, and the coldest survivor was 15°C (59°F).[330] In a series of 26 patients given extracorporeal rewarming, those with nonasphyxiated deep accidental hypothermia had a reasonable prognosis.[86]

A valid triage marker of death is needed because vital organ damage is difficult to predict.[249,250] In one retrospective analysis of primarily avalanche burial victims, extreme hyperkalemia was noted on initial examination, and resuscitation proved fruitless.[276] A serum potassium below 7 mmol/L may be a valuable indicator for survival.[25] In the Mt Hood tragedy, the nonsurvivors were also hyperkalemic (serum potassium level >10 mmol/L).[122] Although a serum potassium level of 10 mmol/L appears to be a reasonable ceiling for viability, a child at 14.2°C (57.6°F) with a potassium level of 11.8 mmol/L did well.[34,73] In both these reports, asphyxia and compression injury may have been contributory. Do not attempt resuscitation if an avalanche victim is buried longer than 35 minutes with a snow-obstructed airway.[353] Other indicators of a grave prognosis include a core temperature below 12°C (53.6°F), arterial pH below 6.5, or evidence of intravascular thrombosis (direct visualization; fibrinogen <50 mg/dL).

## REFERENCES

***Complete references used in this text are available online at expertconsult.inkling.com.***



# CHAPTER 8
# Immersion into Cold Water

GORDON G. GIESBRECHT AND ALAN M. STEINMAN

The authors of this chapter hail from two different countries that view and measure temperature differently. The United States uses °F (Fahrenheit), whereas the country up north uses °C. (Some people think that the letter *C* stands for "Celsius," but it actually means "Canadian.") The author from up north has provided a conversion chart to allow neighbors from either side of the border to get on the same thermal wavelength (Box 8-1).

Immersion in cold water is a hazard for anyone who participates in recreational, commercial, or military activities in the oceans, lakes, and streams of all but the tropical regions of the

## REFERENCES


1. Ahn A, Nasir A, Malik H, et al. A pilot study examining the role of regional cerebral oxygen saturation monitoring as a marker of return of spontaneous circulation in shockable (VF/VT) and non-shockable (PEA/asystole) causes of cardiac arrest. Resuscitation 2013;84:1713–16.
2. Aibiki M, Maekawa S, Nishiyama T, et al. Activated cytokine production in patients with accidental hypothermia. Resuscitation 1999;41: 263.
3. Ainslie PN, Reilly T. Physiology of accidental hypothermia in the mountains: A forgotten story. Br J Sports Med 2003;37:548.
4. Aizawa Y, et al. Osborn wave in accidental hypothermia. Intern Med 2006;45:333.
5. Althaus U, Aeberhard P, Schupbach P. Management of profound accidental hypothermia with cardiorespiratory arrest. Ann Surg 1982; 195:492.
6. Ambach E, Tributsch W, Henn R. Fatal accidents on glaciers: Forensic, criminological, and glaciological conclusions. J Forensic Sci 1991; 36:1469.
7. American Heart Association Guidelines for CPR and Emergency Cardiovascular Care. Hypothermia. Circ: 2010; Part 12.9(122):S829–61.
8. Antretter H, Bonatti J, Dapunt OE. Accidental hypothermia. N Engl J Med 1995;332:1033.
9. Aslam AF, Aslam AK, Vasavada BC, Khan IA. Hypothermia: evaluation, electrocardiographic manifestations, and management. Am J Med 2006;119:297.
10. Auerbach PS. Some people are dead when they're cold and dead. JAMA 1990;264:1856.
11. Avidan MS, Jones N, Ing R, et al. Convection warmers: Not just hot air. Anaesthesia 1997;52:1073.
12. Bagian JP, Kaufman JW. Effectiveness of the space shuttle anti-exposure system in a cold water environment. Aviat Space Environ Med 1990;61:753.
13. Baraka AS, Baroody MA, Haroun ST, et al. Effect of alpha-stat versus pH-stat strategy on oxyhemoglobin dissociation and whole body oxygen consumption during hypothermia cardiopulmonary bypass. Anesth Analg 1992;74:32.
14. Baumgartner FJ, Janusz MT, Jamieson WR, et al. Cardiopulmonary bypass for resuscitation of patients with accidental hypothermia and cardiac arrest. Can J Surg 1992;35:184.
15. Beilman GJ, Blondet JJ, Nelson TR, et al. Early hypothermia in severely injured trauma patients is a significant risk factor for multiple organ dysfunction syndrome but not mortality. Ann Surg 2009;249(5):845–85.
16. Bergersen TK, Eriksen M, Walloe L. Effect of local warming on hand and finger artery blood velocities. Am J Physiol 1995;269:R325.
17. Berko J, Ingram DD, Saha S, Parker JD. Deaths attributed to heat, cold, and other weather events in the United States, 2006-2010. Natl Health Stat Rep 2014;76:1–15, National Center for Health Statistics.
18. Bernard SAF, Gray TWF, Buist MDF, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557.
19. Binnemer R, van der Wal A, Visser C, et al. Treatment of accidental hypothermia with cardiopulmonary bypass: A case report. Perfusion 2008;23:193.
20. Bjornstad H, Tande PM, Refsum H. Class III antiarrhythmic action of D-sotalol during hypothermia. Am Heart J 1999;121:1429.
21. Bolgiano E, Sykes L, Barish RA. Accidental hypothermia with cardiac arrest: Recovery following rewarming by cardiopulmonary bypass. J Emerg Med 1992;10:427.
22. Bolte RG, Black PG, Bowers RS, et al. The use of extracorporeal rewarming in a child submerged for 66 minutes. JAMA 1988;260: 377.
23. Boue Y, Lavolaine J, Bouzat P, et al. Neurologic recovery from profound accidental hypothermia after 5 hours of cardiopulmonary resuscitation. Crit Care Med 2014;42(2):e167–70.
24. Bowman W. Outdoor emergency care: Comprehensive first aid for non-urban settings. Lakewood, Colo: National Ski Patrol System; 1988.
25. Boyd J, Brugger H, Shuster M. Prognostic factors in avalanche resuscitation: A systematic review. Resuscitation 2010;81(6):645–52.
26. Brandon Bravo LJ. Thermodynamic modeling of hypothermia. Eur J Emerg Med 1999;6:123.
27. Brandson RD, Chatburn RL. Humidification of inspired gases during mechanical ventilation. Respir Care 1993;38:461.
28. Breitkreutz R, Walcher F, Seegar FH. Focused echocardiographic evaluation in resuscitation management: Concept of an advanced life support–conformed algorithm. Crit Care Med 2007;35(5):150.
29. Brevik A, Farver D. Atypical antipsychotic induced mild hypothermia. SD J Med 2003;56:67.
30. Brimioulle S. Sympathetic nervous system activity during hypothermia. Crit Care Med 1984;12:924.
31. Bristow GK, Sessler DI, Giesbrecht GG. Leg temperature and heat content in humans during immersion hypothermia and rewarming. Aviat Space Environ Med 1994;65:220.
32. Britt LD, Dascombe WH, Rodriguez A. New horizons in management of hypothermiaand frostbite injury. Surg Clin North Am 1991;71:345.
33. Brown DJ, Brugger H, Boyd J, Paal P. Accidental hypothermia. N Engl J Med 2012;367(20):1930–8.
34. Brugger H, Durrer B, Elsensohn F, et al. Resuscitation of avalanche victims: Evidence-based guidelines of the International Commission for Mountain Emergency Medicine (ICAR MEDCOM): Intended for physicians and other advanced life support personnel. Resuscitation 2013;84(5):539–46.
35. Reference deleted in proofs.
36. Brunette DD, Biros M, Mlinek EJ, et al. Internal cardiac massage and mediastinal irrigation in hypothermic cardiac arrest. Am J Emerg Med 1992;10:32.
37. Brunette DD, McVaney K. Hypothermic cardiac arrest: An 11 year review of ED management and outcome. Am J Emerg Med 2000; 18:418.
38. Brunette DD, Sterner S, Robinson EP, et al. Comparison of gastric and closed thoracic cavity lavage in the treatment of severe hypothermia in dogs. Am J Emerg Med 1987;16:1222.
39. Cahill CJ, Balmi PJ, Tipton MJ. An evaluation of hand immersion for rewarming individuals cooled by immersion in cold water. Aviat Space Environ Med 1995;66:418.
40. Canivet JL, Larbuisson R, Lamy M. Influence of face mask–CPAP in one case of severe accidental hypothermia. Acta Anaesthesiol Belg 1989;40:281.
41. Cattermole TJ. The epidemiology of cold injury in Antarctica. Aviat Space Environ Med 1999;70:135.
42. Cauchy E, Leal S, Magnan MA, Nespoulet H. Portable hyperbaric chamber and management of hypothermia and frostbite: An evident utilization. High Alt Med Biol 2014;15(1):95–6.
43. Chernow B, Lake CR, Zaritsky A. Sympathetic nervous system "switch-off" with severe hypothermia. Crit Care Med 1983;11:677.
44. Chernow B, Lake CR, Zaritsky A. Recovery of a 62-year-old male from prolonged cold water immersion. Ann Emerg Med 1998;31:127.
45. Chhabra L, Devadoss R, Liti B, Spodick DH. Electrocardiographic changes in hypothermia: A review. Ther Hypothermia Temp Manag 2013;3(2):54–62.
46. Clayton DG, Webb RK, Ralston AC, et al. A comparison of the performance of 20 pulse oximeters under conditions of poor perfusion. Anaesthesia 1991;46:3.
47. Clifton GLF, Miller ERE, Choi SCF, et al. Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med 2001;344:556.
48. Cocchi MN, Griberson B, Domino MW. Rapid rewarming of hypothermic patient using arctic sun device. J Intensive Care Med 2012;27: 128–30.
49. Cohen IL, Weinberg PF, Fein IA, et al. Endotracheal tube occlusion associated with the use of heat and moisture exchangers in the intensive care unit. Crit Care Med 1988;16:277.
50. Cohen JA, Blackshear RH, Gravenstein N, et al. Increased pulmonary artery perforating potential of pulmonary artery catheters during hypothermia. J CardiothoracVasc Anesth 1991;5:235.
51. Collins AM, Danzl DF. Hypothermia with profound anemia and pancreatitis. Wilderness Environ Med 2006;17:31.
52. Conover K. The charcoal vest: A hypothermia treatment device for search and rescue teams. Wilderness Med Newslett 1998;9:1.
53. Corey TS, Weakley-Jones B, Nichols GR. Unnatural deaths in nursing home patients. J Forensic Sci 1992;37:222.
54. Corneli HM. Accidental hypothermia. Pediatr Emerg Care 2012;28(5): 475–80, quiz 481–2.
55. Cosgriff N, Moore EE, Sauaia A, et al. Predicting life-threatening coagulopathy in the massively transfused trauma patient: Hypothermia and acidoses revisited. J Trauma 1997;42:857.
56. Daanen HA, Van De Linde FJ. Comparison of four noninvasive rewarming methods for mild hypothermia. Aviat Space Environ Med 1992;63:1070.
57. Danzl DF. Blood flow during closed chest compressions in hypothermic humans. Wilderness Med 1991;7:12.
58. Danzl DF, Lloyd E. Treatment of accidental hypothermia. In: Pandolf KB, Burr RE, Wenger CB, Pozos RS, editors. Medical aspects of harsh environments, vol. 1. In: Zajtchuk R, Bellamy RF, editors. Textbook of military medicine. Washington, DC: Department of the Army, Office of the Surgeon General, and Borden Institute; 2001. p. 491–529.
59. Danzl DF, Hedges JR, Pozos RS. Hypothermia outcome score: Development and implications. Crit Care Med 1989;17:227.
60. Danzl DF, O'Brien DJ. The ECG computer program: Mort de froid. J Wilderness Med 1992;3:328.
61. Danzl DF, Pozos RS. Accidental hypothermia. N Engl J Med 1994; 331:1756.
62. Danzl DF, Pozos RS, Auerbach PS, et al. Multicenter hypothermia survey. Ann Emerg Med 1987;16:1042–55.

63. Darowski A, Najim Z, Weinberg JR, et al. Hypothermia and infection in elderly patients admitted to hospital. Age Ageing 1991;20:100.
64. DaVee TS, Reineberg EJ. Extreme hypothermia and ventricular fibrillation. Ann Emerg Med 1980;9:100.
65. Davis PR, Byers M. Accidental hypothermia. J R Army Med Corps 2006;152:223.
66. De Caen A. Management of profound hypothermia in children without the use of extracorporeal life support therapy. Lancet 2002; 360:1394.
67. Deklunder G, Dauzat M, Lecroart JL, et al. Influence of ventilation of the face on thermoregulation in man during hyper- and hypothermia. Eur J Appl Physiol 1991;62:342.
68. Delaney KA, Howland MA, Vassallo S, et al. Assessment of acid-base disturbances and their physiologic consequences. Ann Emerg Med 1989;18:72.
69. Delaney KA, et al. Rewarming rates in urban patients with hypothermia: Prediction of underlying infection. Acad Emerg Med 2006;13: 913.
70. Reference deleted in proofs.
71. De Souza D, Riera AR, Bombig MT, et al. Electrocardiographic changes by accidental hypothermia in an urban and a tropical region. J Electrocardiol 2007;40(1):47.
72. Dixon RG, Dougherty JM, White LJ, et al. Transcutaneous pacing in a hypothermic dog model. Ann Emerg Med 1997;9:602.
73. Dobson JAR, Burgess JJ. Resuscitation of severe hypothermia by extracorporeal rewarming in a child. J Trauma 1996;40:483.
74. Ducharme MB, Tikuisis P. Role of blood as heat source or sink in human limbs during local cooling and heating. J Appl Physiol 1994; 76:2084.
75. Ducharme MB, Giesbrecht GG, Frim J, et al. Forced-air rewarming in −20 degrees C simulated field conditions. Ann N Y Acad Sci 1997; 813:676.
76. Duebener LF, Hagino I, Sakamoto T, et al. Effects of pH management during deep hypothermic bypass on cerebral microcirculation: Alpha-stat versus pH-stat. Circulation 2002;106:103.
77. Duguid H, Simpson RG, Stowers JM. Accidental hypothermia. Lancet 1961;2:1213.
78. Durrer B, Brugger H, Syme D, International Commission for Mountain Emergency Medicine. The medical on-site treatment of hypothermia: ICAR-MEDCOM recommendation. High Alt Med Biol 2003; 4:99.
79. Eddy VA, Morris JA Jr, Cullinane DC. Hypothermia, coagulopathy, and acidosis. Surg Clin North Am 2000;80:845.
80. Elenbaas RM, Mattson K, Cole H, et al. Bretylium in hypothermia-induced ventricular fibrillation in dogs. Ann Emerg Med 1984;13: 994.
81. Epstein E, Anna K. Accidental hypothermia. BMJ 2006;332:706.
82. Ereth MH, Lennon RL, Sessler DL. Limited heat transfer between thermal compartments during rewarming in vasoconstricted patients. Aviat Space Environ Med 1992;63:1065.
83. Erickson RS, Yount ST. Effect of aluminzed covers on body temperature in patients having abdominal surgery. Heart Lung 1991; 20:255.
84. Faries G, Johnston C, Pruitt KM, et al. Temperature relationship to distance and flow rate of warmed IV fluids. Ann Emerg Med 1991; 20:1198.
85. Farnell S, Maxwell L, Tan S, et al. Temperature measurement: Comparison of non-invasive methods used in adult critical care. J Clin Nurs 2005;14(5):632.
86. Farstad M, Andersen KS, Koller ME, et al. Rewarming from accidental hypothermia by extracorporeal circulation: A retrospective study. Eur J Cardiothorac Surg 2001;20:58.
87. Fell RH, Gunning AJ, Bardhan KD, et al. Severe hypothermia as a result of barbiturate overdose complicated by cardiac arrest. Lancet 1968;1:392.
88. Ferrara A, MacArthur JD, Wright HK, et al. Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. Am J Surg 1990;160:515.
89. Ferraro FJ Jr, Spillert CR, Swan KG, et al. Cold-induced hypercoagulability in vitro: A trauma connection. Am Surg 1992;58:355.
90. Fildes J, Sheaff C, Barrett J. Very hot intravenous fluid in the treatment of hypothermia. J Trauma 1993;35:683.
91. Fischer A. Cardiopulmonary bypass. Presented at Immersion Hypothermia Task Force, World Congress on Drowning. Amsterdam, June 26–28, 2002.
92. Gallaher MM, Fleming DW, Berger LR, et al. Pedestrian and hypothermia deaths among Native Americans in New Mexico: Between bar and home. JAMA 1992;267:1345.
93. Gentilello LM, Cobean RA, Offner PJ, et al. Continuous arteriovenous rewarming: Rapid reversal of hypothermia in critically ill patients. J Trauma 1992;32:316.
94. Gentilello LM. Practical approaches to hypothermia. Adv Trauma Crit Care 1994;9:39.
95. Gentilello LM, Jurkovich GJ, Stark MS, et al. Is hypothermia in the victim of major trauma protective or harmful? A randomized, prospective study. Ann Surg 1997;226:439.
96. Giesbrecht GG. The respiratory system in a cold environment. Aviat Space Environ Med 1995;66:890.
97. Giesbrecht GG. Cold stress, near drowning and accidental hypothermia: A review. Aviat Space Environ Med 2000;71:733.
98. Giesbrecht GG. Emergency treatment of hypothermia. Emerg Med (Fremantle) 2001;13:9.
99. Giesbrecht GG, Bristow GK. Recent advances in hypothermia research. Ann NY Acad Sci 1997;813:676.
100. Giesbrecht GG, Johnston CE, Bristow GK. The convective afterdrop component during hypothermic exercise decreased with delayed exercise onset. Aviat Space Environ Med 1998;69:17.
101. Giesbrecht GG, Pachu P, Xu X. Design and evaluation of a portable rigid forced-air warming cover for prehospital transport of cold patients. Aviat Space Environ Med 1998;69:1200.
102. Gilbert M, Busund R, Skagseth A, et al. Resuscitation from accidental hypothermia of 13.7 degrees C with circulatory arrest. Lancet 2000; 355:375.
103. Gillen JP, Vogel MF, Holterman RK, et al. Ventricular fibrillation during orotracheal intubation of hypothermic dogs. Ann Emerg Med 1986;15:41.
104. Ginsberg MD, Globus MY, Dietrich WD, et al. Temperature modulation of ischemic brain injury: A synthesis of recent advances. Prog Brain Res 1993;96:13.
105. Glusman A, Hasan K, Roguin N. Contraindication to thrombolytic therapy in accidental hypothermia. Int J Cardiol 1990;28: 269.
106. Goheen MS, Ducharme MB, Kenny GP, et al. Efficacy of forced-air and inhalation rewarming using a human model for severe hypothermia. J Appl Physiol 1997;83:1635.
107. Gordon L, Ellerton JA, Paal P, et al. Severe accidental hypothermia. BMJ 2014;348:g1675.
108. Graham CA, McNaughton GW, Wyatt JP. The electrocardiogram in hypothermia. Wilderness Environ Med 2001;12:232.
109. Grahn D, Brock-Utne JG, Watenpaugh DE, et al. Recovery from mild hypothermia can be accelerated by mechanically distending blood vessels in the hand. J Appl Physiol 1998;85:1643.
110. Granberg PO. Human physiology under cold exposure. Arctic Med Res 1991;50:23.
111. Gregory JS, Bergstein JM, Aprahamian C, et al. Comparison of three methods of rewarming from hypothermia: Advances of extracorporeal blood rewarming. J Trauma 1991;31:1247.
112. Gregory JS, Flancbaum L, Townsend MC, et al. Incidence and timing of hypothermia in trauma patients undergoing operations. J Trauma 1991;31:795.
113. Gregory RT. Accidental hypothermia: An Alaskan problem. Alaska Med 2001;43:73.
114. Gregory RT, Doolittle WH. Accidental hypothermia. II. Clinical implications of experimental studies. Alaska Med 1973;15:48.
115. Greif R, Rajek A, Laciny S, et al. Resistive heating is more effective than metallic-foil insulation in an experimental model of accidental hypothermia: A randomized controlled trial. Ann Emerg Med 2000;35: 337.
116. Grueskin J, Tanen DA, Harvey P, et al. A pilot study of mechanical stimulation and cardiac dysrhythmia in a porcine model of induced hypothermia. Wilderness Environ Med 2007;18:133.
117. Hall KN, Syverud SA. Closed thoracic cavity lavage in the treatment of severe hypothermia in human beings. Ann Emerg Med 1990;19: 204.
118. Hamilton RS, Paton BC. The diagnosis and treatment of hypothermia by mountain rescue teams: A survey. Wilderness Environ Med 1996;7:37.
119. Handrigan MT, Wright RO, Becker BM, et al. Factors and methodology in achieving ideal delivery temperatures for intravenous and lavage fluid in hypothermia. Am J Emerg Med 1997;15:350.
120. Harnett RM, Pruitt JR, Sias FR. A review of the literature concerning resuscitation from hypothermia. II. Selected rewarming protocols. Aviat Space Environ Med 1983;54:487.
121. Hauge A, Kofstad J. Acid-base regulation during hypothermia: A brief review. Arctic Med Res 1995;54:76.
122. Hauty MG, Esrig BC, Hill JG, et al. Prognostic factors in severe accidental hypothermia: Experience from the Mt. Hood tragedy. J Trauma 1987;27:1107.
123. Hayward JS, Eckerson JD, Kemna D. Thermal and cardiovascular changes during three methods of resuscitation from mild hypothermia. Resuscitation 1984;11:21.
124. Headdon WG, Wilson PM, Dalton HR. The management of accidental hypothermia. BMJ 2009;338:b2085.
125. Heise D, Rathgeber J, Burchardi H. Severe, accidental hypothermia: Active rewarmingwith a simple extracorporeal veno-venous warming-circuit. Anaesthesist 1996;45:1093.

126. Helm M, Lampl L, Hauke J, et al. [Accidental hypothermia in trauma patients: Is it relevant to preclinical emergency treatment?] Anaesthesist 1995;44:101–7.
127. Henriksson O, Lundgren P, Kuklane K, et al. Protection against cold in prehospital care: Thermal insulation properties of blankets and rescue bags in different wind conditions. Prehosp Disaster Med 2009;24(5):408–15.
128. Henriksson O, Lundgren P, Kuklane K, et al. Protection against cold in prehospital care: Evaporative heat loss reduction by wet clothing removal or the addition of a vapor barrier—A thermal manikin study. Prehosp Disaster Med 2012;27(1):53–8.
129. Hering JP, Schroder T, Singer D, et al. Influence of pH management on hemodynamics and metabolism in moderate hypothermia. J Thorac Cardiovasc Surg 1992;104:1388.
130. Hernandez E, Praga M, Alcazar JM. Accidental hypothermia. N Engl J Med 1995;332:1034.
131. Hernandez E, Praga M, Alcazar JM, et al. Hemodialysis for treatment of accidental hypothermia. Nephron 1993;63:214.
132. Herschman Z. Hypothermia: In the operating room and beyond. Respir Care 2004;49:158.
133. Hersio K, Takala J, Kari A, et al. Changes in whole body and tissue oxygen consumption during recovery from hypothermia: Effect of amino acid infusion. Crit Care Med 1991;19:503.
134. Hildebrand F, Giannoudis PV, van Griensven M, et al. Pathophysiologic changes and effects of hypothermia on outcome in elective surgery and trauma patients. Am J Surg 2004;187:363.
135. Hill JG, Bruhn PS, Cohen SE, et al. Emergency applications of cardiopulmonary support: A multi-institutional experience. Ann Thorac Surg 1992;54:699.
136. Ho JD, Heegaard WG, Brunette DD. Successful transcutaneous pacing in 2 severely hypothermic patients. Ann Emerg Med 2007; 49(5):678.
137. Hodgdon JA, Hesslink RL, Hackney AC, et al. Norwegian military field exercises in the Arctic: Cognitive and physical performance. Arctic Med Res 1991;50:132.
138. Holmer I. Prediction of responses to cold. Arctic Med Res 1995;54:48.
139. Holzer M. Hypothermia after Cardiac Arrest Study Group: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:1756.
140. Hughes A, Riou P, Day C. Full neurological recovery from profound (18.0 C) acute accidental hypothermia: successful resuscitation using active invasive rewarming techniques. Emerg Med J 2007;24:511.
141. Imon H, Amakawa K, Kadoya F, et al. Optimal pH and $PaCO_2$ during moderate hypothermia. Masui Jpn J Anesthesiol 1992;41:603.
142. Incagnoli P, Bourgeois B, Teboul A, Laborie JM. Resuscitation from accidental hypothermia of 22 degrees C with circulatory arrest: Importance of prehospital management. Ann Fr Anesth Reanim 2006;25:535.
143. International Hypothermia Registry. IHR Project. <https://www.hypothermia-registry.org/>, [accessed 09.05.14].
144. Ireland AJ, Pathi VL, Crawford R, et al. Back from the dead: Extracorporeal rewarming of severe accidental hypothermia victims in accident and emergency. J Accid Emerg Med 1997;14:255.
145. Irwin BR. A case report of hypothermia in the wilderness. Wilderness Environ Med 2002;13:125.
146. Reference deleted in proofs.
147. Ittner KP, Bachfischer M, Zimmermann M, Taeger K. Convective air warming is more effective than resistive heating in an experimental model with a water dummy. Eur J Emerg Med 2004;11:151.
148. Iversen RJ, Atkin SH, Jaker MA, et al. Successful CPR in a severely hypothermic patient using continuous thoracostomy lavage. Ann Emerg Med 1990;19:1335.
149. Reference deleted in proofs.
150. Janczyk RJ, Park DY, Howells GA, et al. High-flow venovenous rewarming for the correction of hypothermia in a canine model of hypovolemic shock. J Trauma 2002;53:639.
151. Johannsson BW. The hibernator heart: Nature's model of resistance to ventricular fibrillation. Arctic Med Res 1991;50:58.
152. Johnston CE, Elias DA, Ready AE, et al. Hypercapnia lowers the shivering threshold and increased core cooling rate in humans. Aviat Space Environ Med 1996;67:438.
153. Johnston CE, White MD, Wu M, et al. Eucapnic hypoxia lowers human cold thermoregulatory response thresholds and accelerates core cooling. J Appl Physiol 1996;80:422.
154. Jones AI, Swann IJ. Prolonged resuscitation in accidental hypothermia: Use of mechanical cardio-pulmonary resuscitation and partial cardio-pulmonary bypass. Eur J Emerg Med 1994;1:34.
155. Jurkovich GJ. Environmental cold-induced injury. Surg Clin North Am 2007;87:247.
156. Kallenbach J, Bagg P, Feldman C, et al. Experience with acute poisoning in an intensive care unit: A review of 103 cases. S Afr Med J 1981;59:587.
157. Kangas E, Niemela H, Kojo N. Treatment of hypothermic circulatory arrest with thoracotomy and pleural lavage. Ann Chir Gynaecol 1994;83:258.
158. Kanna B, Wani S. Giant J wave on 12-lead electrocardiogram in hypothermia. Ann Noninvasive Electrocardiol 2003;8:262.
159. Karlsen AM, Thomassen O, Vikenes BH, Brattebø G. Equipment to prevent, diagnose, and treat hypothermia: A survey of Norwegian pre-hospital services. Scand J Trauma Resusc Emerg Med 2013;21:63.
160. Kaufman JW, Hamilton R, Dejneka KY, et al. Comparative effectiveness of hypothermia rewarming techniques: Radio frequency energy versus warm water. Resuscitation 1995;29:203.
161. Keatinge WR. Hypothermia: Dead or alive? BMJ 1991;302:3.
162. Kempainen RR, Brunette DD. The evaluation and management of accidental hypothermia. Respir Care 2004;49:192.
163. Kempen PM. Full body forced air warming: Commercial blanket versus air delivery beneath bed sheets. Can J Anaesth 1996;43:1168.
164. Khan JN, Prasad N, Glancy J. Amiodarone use in therapeutic hypothermia following cardiac arrest due to ventricular tachycardia and ventricular fibrillation. Europace 2009;11(11):1566–7.
165. Kibayashi K, Shojo H. Accidental fatal hypothermia in elderly people with Alzheimer's disease. Med Sci Law 2003;43:127.
166. Kimberger O, Thell R, Schuh M, et al. Accuracy and precision of a novel non-invasive core thermometer. Br J Anaesth 2009;103(2): 226–31.
167. Kinzinger R, Risse M, Puschel K. Irrational behavior in exposure to cold: Paradoxical undressing in hypothermia. Arch Kriminol 1991; 187:47.
168. Kirkpatrick AW, Garraway N, Brown DR, et al. Use of a centrifugal vortex blood pump and heparin-bonded circuit for extracorporeal rewarming of severe hypothermia in acutely injured and coagulopathic patients. J Trauma 2003;55:407.
169. Kjaergaard B, Bach P. Warming of patients with accidental hypothermia using warm water pleural lavage. Resuscitation 2006;68:203.
170. Kjaergaard B, Yoshida K, Christensen T, Tosato M. Ordinary surface ECG electrodes accurately reflect cardiac electric activity at hypothermia. Eur J Emerg Med 2008;15:258.
171. Knottenbelt JD. Pleural lavage in post-traumatic hypothermia causing severe haemorrhage. Injury 1994;25:397.
172. Kober A, Scheck T, Lieba F, et al. The influence of active warming on signal quality of pulse oximetry in prehospital trauma care. Anesth Analg 2002;95:961.
173. Kobrin VI. Spontaneous ventricular defibrillation in hypothermia. Kardiologiia 1991;31:19.
174. Koller R, Schnider TW, Neidhart P. Deep accidental hypothermia and cardiac arrest rewarming with forced air. Acta Anaesthesiol Scand 1997;41:1359.
175. Kornberger E, Lindner KH, Mayr VD, et al. Effects of epinephrine in a pig model of hypothermic cardiac arrest and closed-chest cardiopulmonary resuscitation combined with active rewarming. Resuscitation 2001;50:301.
176. Kornberger E, Schwarz B, Lindner KH, et al. Forced air surface rewarming in patients with severe accidental hypothermia. Resuscitation 1999;41:105.
177. Krantz MJ, Lowery CM. Giant Osborn waves in hypothermia. N Engl J Med 2005;352:184.
178. Krismer AC, Lindner KH, Kornberger R, et al. Cardiopulmonary resuscitation during severe hypothermia in pigs: Does epinephrine or vasopressin increase coronary perfusion pressure? Anesth Analg 2000;90:69.
179. Kroncke GM, Nichols RD, Mendenhall JT, et al. Ectothermic philosophy of acid-base balance to prevent fibrillation during hypothermia. Arch Surg 1986;121:303.
180. Kurisu S, Inoue I. Prominent J wave in accidental hypothermia. Mayo Clin Proc 2007;82(12):1449.
181. Laniewicz M, Lyn-Kew K, Silbergleit R. Rapid endovascular warming for profound hypothermia. Ann Emerg Med 2008;51:160.
182. Larach MG. Accidental hypothermia. Lancet 1995;345:493.
183. Laub GW, Banaszak D, Kupferschmid J, et al. Percutaneous cardiopulmonary bypass for the treatment of hypothermic circulatory collapse. Ann Thorac Surg 1989;47:608.
184. Lauri T, Leskinen M, Timisjarvi J, et al. Cardiac function in hypothermia. Arctic Med Res 1991;50:63.
185. Lazar HL. The treatment of hypothermia. N Engl J Med 1997;337:1545.
186. Ledingham IM, Mone JG. Treatment of accidental hypothermia: A prospective clinical study. Br Med J 1980;280:1102.
187. Lee CH, Van Gelder C, Burns K, Cone DC. Advanced cardiac life support and defibrillation in severe hypothermic cardiac arrest. Prehosp Emerg Care 2009;13(1):85–9.
188. Lee HA, Ames AC. Hemodialysis in severe barbiturate poisoning. BMJ 1965;1:1217.
189. Lennon RL, Hosking MP, Conover MA, et al. Evaluation of a forced air system for warming hypothermic postoperative patients. Anesth Analg 1990;70:424.

190. Letsou GV, Kopf GS. Is cardiopulmonary bypass effective for treatment of hypothermic arrest due to drowning or exposure? Arch Surg 1992;127:525.
191. Levitt MA, Kane V, Henderson J, et al. A comparative rewarming trial of gastric versus peritoneal lavage in a hypothermic model. Am J Emerg Med 1990;8:285.
192. Lewin S, Brettman LR, Holzman RS. Infections in hypothermic patients. Arch Intern Med 1981;141:920.
193. Lexow K. Severe accidental hypothermia: Survival after 6 hours 30 minutes of cardiopulmonary resuscitation. Arctic Med Res 1991;50: 112.
194. Lifschultz BD, Donoghue ER. Forensic pathology of heat- and cold-related injuries. Clin Lab Med 1998;18:77.
195. Lloyd EL. Equipment for airway warming in the treatment of accidental hypothermia. J Wilderness Med 1991;2:330.
196. Lloyd EL. Accidental hypothermia. Resuscitation 1996;32:111.
197. Lloyd JR, Olsen RG. Radio frequency energy for rewarming of cold extremities. Undersea Biomed Res 1992;19:199.
198. Locher T, Walpoth B, Pfluger D, et al. Accidental hypothermia in Switzerland (1980-1987): Case reports and prognostic factors. Schweiz Med Wochenschr 1991;121:1020.
199. Long WB: Cardiopulmonary bypass for rewarming profound hypothermia patients: Critical decisions in hypothermia. Annual International Forum, Portland, Ore, Feb 28, 1992.
200. Long WB III, Edlich RF, Winters KL, Britt LD. Cold injuries. J Long Term Eff Med Implants 2005;15:67.
201. Lundgren P, Henriksson O, Naredi P, Bjornstig U. The effect of active warming in prehospital trauma care during road and air ambulance transportation: A clinical randomized trial. Scand J Trauma Resusc Emerg Med 2011;19:59.
202. Lundgren JP, Henriksson O, Pretorius T, et al. Field torso-warming modalities: A comparative study using a human model. Prehosp Emerg Care 2009;13(3):371–8.
203. Maaravi AY, Weiss AT. The effect of prolonged hypothermia on cardiac function in a young patient with accidental hypothermia. Chest 1990;98:1019.
204. Maclean D, Emslie-Smith D. Accidental hypothermia. Philadelphia: JB Lippincott; 1977.
205. Macleod DB, et al. The desaturation response time of finger pulse oximeters during mild hypothermia. Anaesthesia 2005;60:65.
206. Mair P, Kornberger E, Schwarz B, et al. Forward blood flow during cardiopulmonary resuscitation in patients with severe accidental hypothermia: An echocardiographic study. Acta Anaesth Scand 1998;42:113.
207. Maisch S, Ntalakoura K, Boettcher H, et al. Severe accidental hypothermia with cardiac arrest and extracorporeal rewarming. Anaesthesist 2007;56(2):25.
208. Mallet ML. Pathophysiology of accidental hypothermia. Q J Med 2002;95:775.
209. Maningas PA, DeGuzman LR, Hollenbach SJ. Regional blood flow during hypothermic arrest. Ann Emerg Med 1986;15:390.
210. Marion DW, Leonov Y, Ginsberg M, et al. Resuscitative hypothermia. Crit Care Med 1996;24:S81.
211. Mark E, Jacobsen O, Kjerstad A, et al. Hypothermic cardiac arrest far away from the center providing rewarming with extracorporeal circulation. Int J Emerg Med 2012;5:7.
212. Marsigny B, Lecoq-Jammes F, Cauchy E. Medical mountain rescue in the Mont-Blancmassif. Wilderness Environ Med 1999;10:152.
213. Mattu A, Brady WJ, Perron AD. Electrocardiographic manifestations of hypothermia. Am J Emerg Med 2002;20:314.
214. Mayor Pleines AF, Guyot E, Yersin B. Accidental hypothermia: An extreme case of successful resuscitation. Ann Emerg Med 2006; 95(27–28):1075.
215. McGuire JP, Giesbrecht GG. A comparison of three forced-air patient warming systems. Anesth Analg 1993;76:S256.
216. McInerney JJ, Breakell A, Madira W, et al. Accidental hypothermia and active rewarming: The metabolic and inflammatory changes observed above and below 32 degrees C. Emerg Med J 2002;19:219.
217. Megarbane B, Axler O, Chary I, et al. Hypothermia with indoor occurrence is associated with a worse outcome. Intensive Care Med 2000;26:1843.
218. Mekjavic IB, Eiken O. Inhalation rewarming from hypothermia: An evaluation inminus 20°C simulated field conditions. Aviat Space Environ Med 1995;66:424.
219. Menard MR, Hahn G. Acute and chronic hypothermia in a man with spinal cord injury: Environmental and pharmacologic causes. Arch Phys Med Rehabil 1991;72:421.
220. Mercer JB. Enhancing tolerance to cold exposure: How successful have we been? Arctic Med Res 1995;54:70.
221. Meyer M, Pelurson N, Khabiri E, et al. Sequela-free long-term survival of a 65-year-old woman after 8 hours and 40 minutes of cardiac arrest from deep accidental hypothermia. J Thorac Cardiovasc Surg 2014;147(1):e1–2.
222. Miller JW, Danzl DF, Thomas DM. Urban accidental hypothermia: 135 cases. Ann Emerg Med 1980;9:456.
223. Mills WJ Jr. Field care of the hypothermic patient. Int J Sports Med 1992;13(Suppl. 1):S199.
224. Mills WJ Jr. Accidental hypothermia: Management approach: 1980. Alaska Med 1993;35:54.
225. Mitra B, Tullio F, Cameron PA, Fitzgerald M. Trauma patients with the "triad of death." Emerg Med J 2012;29(8):622–5.
226. Moran DS, Heled Y, Shani Y, et al. Hypothermia and local cold injuries in combat and non-combat situations: The Israeli experience. Aviat Space Environ Med 2003;74:281.
227. Morrison LJ, Deakin CD, Morley PT, et al. Part 8: Advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Circulation 2010;122(16 Suppl. 2):S345–421.
228. Moss J. Accidental severe hypothermia. Surg Gynecol Obstet 1986; 162:501.
229. Mulcahy AR, Watts MR. Accidental hypothermia: an evidence-based approach. EBMedicine.net 2009;11(1).
230. Mulpur AK, Mirsadraee S, Hassan TB, et al. Refractory ventricular fibrillation in accidental hypothermia: Salvage with cardiopulmonary bypass. Perfusion 2004;19:311.
231. Murphy K, Nowak RM, Tomlanovich MC. Use of bretylium tosylate as prophylaxis and treatment in hypothermic ventricular fibrillation in the canine model. Ann Emerg Med 1986;15:1160.
232. Murray BJ. Severe lactic acidosis and hypothermia. West J Med 1981;134:162.
233. Murray PT, Fellner SK. Accidental hypothermia. N Engl J Med 1995;332:1034.
234. Mustafa S, Shaikh N, Gowda RM, Khan IA. Electrocardiographic features of hypothermia. Cardiology 2005;103(3):118.
235. Muszkat M, Durst RM, Ben-Yehuda A. Factors associated with mortality among elderly patients with hypothermia. Am J Med 2002;113: 234.
236. Nayha S. Environmental temperature and mortality. Int J Circumpolar Health 2005;64:451.
237. Niazi SA, Lewis FJ. Profound hypothermia in man: Report of a case. Ann Surg 1958;147:264.
238. Nicholson RW, Iserson KV. Core temperature measurement in hypovolemic resuscitation. Ann Emerg Med 1991;20:62.
239. Nielsen HK, Toft P, Koch J, et al. Hypothermic patients admitted to an intensive care unit: A fifteen year survey. Dan Med Bull 1992;39:190.
240. Niemann JT, Rosborough JP. Petikan P: Hemodynamic determinants of subdiaphragmatic venous return during closed chest CPR in a canine cardiac arrest model. Ann Emerg Med 1990;19: 1232.
241. Nolan J, Soar J. Images in resuscitation: the ECG in hypothermia. Resuscitation 2005;64:133.
242. Nordberg P, Ivert T, Dalén M, et al. Surviving two hours of ventricular fibrillation in accidental hypothermia. Prehosp Emerg Care 2014; 18(3):446–9.
243. Nordrehaug JE. Sustained ventricular fibrillation in deep accidental hypothermia. BrMed J 1982;284:867.
244. Nozaki R, Ishibashi K, Adachi N, et al. Accidental profound hypothermia [letter]. N Engl J Med 1986;315:1680.
245. Oberhamer R, Beikircher W, Hormann C, et al. Full recovery of an avalanche victim with profound hypothermia and prolonged cardiac arrest treated by extracorporeal rewarming. Resuscitation 2008; 76(3):317.
246. Oung CM, English M, Chiu RC, et al. Effects of hypothermia on hemodynamic responses to dopamine and dobutamine. J Trauma 1992;33:671.
247. Owda A, Osama S. Hemodialysis in management of hypothermia. Am J Kidney Dis 2001;38:E8.
248. Paal P, Brown D. Cardiac arrest from accidental hypothermia, a rare condition with potentially excellent neurological outcome, if you treat it right. Resuscitation 2014;85(6):707–8.
249. Paal P, Milani M, Brown D, et al. Termination of cardiopulmonary resuscitation in mountain rescue. High Alt Med Biol 2012;13(3): 200–8.
250. Paal P, Strapazzon G, Braun P, et al. Factors affecting survival from avalanche burial: A randomised prospective porcine pilot study. Resuscitation 2013;84(2):239–43.
251. Parke TR. Resuscitation from hypothermia. J Accid Emerg Med 1998; 15:69.
252. Pasquier M, Zurron N, Weith B, et al. Deep accidental hypothermia with core temperature below 24°C presenting with vital signs. High Alt Med Biol 2014;15(1):58–63.
253. Paton BC. Accidental hypothermia. Pharmacol Ther 1983;22:331.
254. Pedley DK, Paterson B, Morrison W. Hypothermia in elderly patients presenting to accident and emergency during the onset of winter. Scott Med J 2002;47:10.

255. Pillgram-Larsen J, Svennevig JL, Abdelnoor M, et al. Accidental hypothermia: Risk factors in 29 patients with body temperature of 30°C and below. Tidsskr norLaegeforen 1991;111:180.
256. Plaisier BR. Thoracic lavage in accidental hypothermia with cardiac arrest: Report of a case review of the literature. Resuscitation 2005; 66:99.
257. Platts-Mills TF, Stendell E, Lewin MR, et al. An experimental study of warming intravenous fluid in a cold environment. Wilderness Environ Med 2007;18(3):177.
258. Poulos ND, Mollitt DL. The nature and reversibility of hypothermia-induced alterations of blood viscosity. J Trauma 1991;31:996.
259. Pozos RS, Wittmers LE. The nature and treatment of hypothermia. Minneapolis: University of Minnesota Press; 1983.
260. Prendergast HM, Erickson TB. Procedures pertaining to hypothermia and hyperthermia. In: Roberts JR, editor. Roberts and Hedges' clinical procedures in emergency medicine. 6th ed. Philadelphia: Elsevier; 2014. p. 1235.
261. Preuss J, Dettmeyer R, Lignitz E, et al. Fatty degeneration in renal tubule epithelium in accidental hypothermia victims. Forensic Sci Int 2004;141:131.
262. Preuss J, Dettmeyer R, Lignitz E, Madfea B. Fatty degeneration of myocardial cells as a sign of death due to hypothermia versus degenerative deposition of lipofuscin. Forens Sci Int 2006;159:1.
263. Quinn R, Williams J, Bennett B, et al. Wilderness Medical Society Practice Guidelines for Spine Immobilization in the Austere Environment. Wilderness Environ Med 2013;24(3):241–52.
264. Rahn H. Body temperature and acid-base regulation. Pneumonologie 1974;151:87.
265. Ranhoff AH. Accidental hypothermia in the elderly. Int J Circumpolar Health 2000;59:255.
266. Rankin AC, Rae AP. Cardiac arrhythmias during rewarming of patients with accidental hypothermia. Br Med J (Clin Res Ed) 1984; 289:874.
267. Rathgeber J, Weyland W, Bettka T, et al. Is reduction of intraoperative heat loss and management of hypothermic patients with anesthetic gas climate control advisable? Heat and humidity exchangers vs. active humidifiers in a functional lung model. Anaesthesist 1996;45:807.
268. Ream AK, Reitz BA, Silverberg G. Temperature correction of $PaCO_2$ and pH in estimating acid-base status: An example of emperor's new clothes? Anesthesiology 1982;56:41.
269. Reed RL 2nd, Johnson TD, Hudson JD, et al. The disparity between hypothermiccoagulopathy and clotting studies. J Trauma 1992;33: 465.
270. Roeggla G, Wagner A, Roeggla M, et al. Immediate use of cardiopulmonary bypass in patients with severe accidental hypothermia in the emergency department. Eur J Emerg Med 1994;1:155.
271. Roggla M, Frossard M, Wagner A, et al. Severe accidental hypothermia with or without hemodynamic instability: Rewarming without the use of extracorporeal circulation. Wien Klin Wochenschr 2002; 114:315.
272. Rohrer MJ, Natale AM. Effect of hypothermia on the coagulation cascade. Crit Care Med 1992;20:1402.
273. Rosenthal TB. The effect of temperature on the pH of blood and plasma in vitro. J Biol Chem 1948;173:25.
274. Samuelson T. Experience with standardized protocols in hypothermia: Boom or bane? The Alaska experience. Arctic Med Res 1991;50:28.
275. Sawamoto K, Bird SB, Katayama Y, et al. Outcome from severe accidental hypothermia with cardiac arrest resuscitated with extracorporeal cardiopulmonary resuscitation. Am J Emerg Med 2014; 32(4):320–4.
276. Schaller MD, Fischer AP, Perret CH. Hyperkalemia: A prognostic factor during acute severe hypothermia. JAMA 1842;264:1990.
277. Scheck T, Kober A, Heigl P, et al. [Evaluation of a new insulating system for infusion solutions in preclinical trauma therapy: A prospective. randomized study.] Wien KlinWochenschr 2003;115:259.
278. Schissel DJ, Barney DL, Keller R. Cold weather injuries in an arctic environment. Mil Med 1998;163:568.
279. Schober A, Sterz F, Handler C, et al. Cardiac arrest due to accidental hypothermia: A 20-year review of a rare condition in an urban area. Resuscitation 2014;85(6):749–56.
280. Schrijver G, van der Maten J. Severe accidental hypothermia: Pathophysiology and therapeutic options for hospitals without cardiopulmonary bypass equipment. Neth J Med 1996;49:167.
281. Schroder T, Hering JP, Heidelmeyer CF, et al. Dopamine dependent diastolic dysfunction in moderate hypothermia. J Cardiovasc Pharm 1994;23:689.
282. Schulman H, Laufer L, Berginer J, et al. CT findings in neonatal hypothermia. Pediatr Radiol 1998;28:414.
283. Schwarz B, Mair P, Raedler C, et al. Vasopressin improves survival in a pig model of hypothermic cardiopulmonary resuscitation. Crit Care Med 2006;30:131.
284. Seiji M, Sadaki I, Shigeaki I, et al. The efficacy of rewarming with a portable and percutaneous cardiopulmonary bypass system in accidental deep hypothermia patients with hemodynamic instability. J Trauma 2008;65:1391.
285. Sellden E. Perioperative amino acid administration and the metabolic response to surgery. Proc Nutr Soc 2002;61:337.
286. Reference deleted in proofs.
287. Shafi S, Elliott AC, Gentilello L. Is hypothermia simply a marker of shock and injury severity or an independent risk factor for mortality in trauma patients? J Trauma 2005;59(5):1081.
288. Sheaff CM, Fildes JJ, Keogh P, et al. Safety of 65°C intravenous fluid for the treatment of hypothermia. Am J Surg 1996;172:52.
289. Shephard RJ. Some consequences of polar stress: Data from a transpolar ski-trek. Arctic Med Res 1991;50:25.
290. Shephard RJ. Asphyxial death of a young skier. J Sports Med Phys Fitness 1996;36:223.
291. Silbergleit R, Satz W, Lee DC, et al. Hypothermia from realistic fluid resuscitation in a model of hemorrhagic shock. Ann Emerg Med 1998;31:339.
292. Silfvast T, Pettila V. Outcome from severe accidental hypothermia in Southern Finland: A 10-year review. Resuscitation 2003; 59:285.
293. Sim MM, Kuo YC. Accidental hypothermia in the subtropics. Am J Emerg Med 2000;18:357.
294. Reference deleted in proofs.
295. Soar J, Perkins GD, Abbas G, et al. European Resuscitation Council Guidelines for Resuscitation 2010. Section 8. Cardiac arrest in special circumstances: Electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. Resuscitation 2010;81(10): 1400–33.
296. Soreide E, Grahn DA, Brock-Utne JG, et al. A non-invasive means to effectively restore normothermia in cold stressed individuals: A preliminary report. J Emerg Med 1999;17:725.
297. Splittgerber FH, Talbert JG, Sweezer WP, et al. Partial cardiopulmonary bypass for core rewarming in profound accidental hypothermia. Am Surg 1986;52:407.
298. Spooner K, Hassani A. Extracorporeal rewarming in a severely hypothermic patient using venovenous haemofiltration in the accident and emergency department. J Accid Emerg Med 2000;17: 422.
299. Steele MT, Nelson MJ, Sessler DI, et al. Forced air speeds rewarming in accidental hypothermia. Ann Emerg Med 1996;27:479.
300. Steinemann S, Shackford SR, Davis JW. Implications of admission hypothermia in trauma patients. J Trauma 1990;30:200.
301. Reference deleted in proofs.
302. Sterba JA. Efficacy and safety of prehospital rewarming techniques to treat accidental hypothermia. Ann Emerg Med 1991;20:896.
303. Stoneham MD, Squires SJ. Prolonged resuscitation in acute deep hypothermia. Anaesthesia 1992;47:784.
304. Stoner J, Martin G, O'Mara K, et al. Amiodarone and bretylium in the treatment of hypothermic ventricular fibrillation in a canine model. Acad Emerg Med 2003;10:187.
305. Strapazzon G, Nardin M, Zanon P, et al. Respiratory failure and spontaneous hypoglycemia during noninvasive rewarming from 24.7 degrees C (76.5 degrees F) core body temperature after prolonged avalanche burial. Ann Emerg Med 2011;60(2):193–6.
306. Strapazzon G, Procter E, Paal P, Brugger H. Pre-hospital core temperature measurement in accidental and therapeutic hypothermia. High Alt Med Biol 2014;15(2):104–11.
307. Sultan N, Theakston KD, Butler R, Suri RS. Treatment of severe accidental hypothermia with intermittent hemodialysis. CJEM 2009; 11(2):174.
308. Taguchi A, Arkilic CF, Ahluwalia A, et al. Negative pressure rewarming vs. forced air warming in hypothermic postanesthetic volunteers. Anesth Analg 2001;92:261.
309. Tanaka M, Tokudome S. Accidental hypothermia and death from cold in urban areas. Int J Biometeorol 1991;34:242.
310. Taniguchi T, Okeie K, Mizukoshi Y, et al. Acute respiratory distress syndrome associated with accidental hypothermia. Intensive Care Med 2001;27:793.
311. Taylor MS. Cold weather injuries during peace time military training. Mil Med 1992;157:602.
312. Reference deleted in proofs.
313. Thomassen O, Faerevik H, Osteras O, et al. Comparison of three different prehospital wrapping methods for preventing hypothermia: a crossover study in humans. Scand J Trauma Resusc Emerg Med 2011;19:41.
314. Thompson DA, Anderson N. Successful resuscitation of a severely hypothermic neonate. Ann Emerg Med 1994;23:1390.
315. Tiruvoipati R, Baiasubramanian SK, Khoshbin E, et al. Successful use of venovenous extracorporeal membrane oxygenation in accidental hypothermic cardiac arrest. ASAIO J 2005;51:474.

316. Tsokos M, Rothschild MA, Madea B, et al. Histochemical and immunohistochemical study of Wischnevsky spots in fatal hypothermia. Am J Forens Med Pathol 2006;27:70.
317. Turtiainen J, Halonen J, Syvaoja S, Hakala T. Rewarming a patient with accidental hypothermia and cardiac arrest using thoracic lavage. Ann Thorac Surg 2014;97(6):2165–6.
318. Tveita T. Rewarming from hypothermia: Newer aspects on the pathophysiology of rewarming shock. Int J Circumpolar Health 2000;59:260.
319. Tyndal CM Jr, Rose MW, McFalls RE, et al. Profound accidental hypothermia in the Deep South: Clinical exposure. Perfusion 1996; 11:57.
320. Udy AA, Ziegenfuss MD, Fraser JF. Deep accidental hypothermia during the Queensland summer. Crit Care Res 2007;9(4):341.
321. Vaagenes P, Gundersen Y, Opstad PK. Rapid rewarming after mild hypothermia accentuates the inflammatory response after acute volume controlled haemorrhage in spontaneously breathing rats. Resuscitation 2003;58:103.
322. Reference deleted in proofs.
323. Van der Ploeg GJ, Goslings JC, Walpoth BH, Bierens JJ. Accidental hypothermia: Rewarming treatments, complications and outcomes from one university medical centre. Resuscitation 2010;81:1550–5.
324. Vangaard L, Eyolfson D, Xu X, et al. Immersion of distal arms and legs in warm water (AVA rewarming) effectively rewarms mildly hypothermic humans. Aviat Space Environ Med 1999;70:1081.
325. Vassal T, Benoit-Gonin B, Carrat F, et al. Severe accidental hypothermia treated in an ICU: Prognosis and outcome. Chest 1998; 120:2001.
326. Vassallo SU, Delaney KA, Hoffman RS, et al. Prospective evaluation of the electrocardiographic manifestations of hypothermia. Acad Emerg Med 1999;6:1121.
327. Vella J, Farrell J, Leavey S, et al. The rapid reversal of profound hypothermia using peritoneal dialysis. Ir J Med Sci 1996;165:113.
328. Vince SC, Flint NJ, Hall AP. A novel non-invasive warming technique in severe accidental hypothermia. Resuscitation 2008;77(1):144.
329. Vionnet M, Mueller X, von Segesser LK. Unusual complications after rewarming for deep accidental hypothermia. Thorac Cardiovasc Surg 2004;52:185.
330. Vretenar DF, Urschel JD, Parrott JC, et al. Cardiopulmonary bypass resuscitation for accidental hypothermia. Ann Thorac Surg 1994; 58:895.
331. Wallace W. Does it make sense to heat gases higher than body temperature for the treatment of cold water near-drowning or hypothermia? A point of view paper. Alaska Med 1997;39:75.
332. Walpoth BH, Walpoth-Aslan BN, Mattle HP, et al. Outcome of survivors of accidental deep hypothermia and circulatory arrest treated with extracorporeal blood warming. N Engl J Med 1997;337:1500.
333. Wanscher M, Agersnap L, Ravn J, et al. Outcome of accidental hypothermia with or without circulatory arrest: Experience from the Danish Praesto Fjord boating accident. Resuscitation 2012;83: 1078–84.
334. Watts DD, Trask A, Soeken K, et al. Hypothermic coagulopathy in trauma: Effect of varying levels of hypothermia on enzyme speed, platelet function and fibrinolytic activity. J Trauma 1998;44:846.
335. Watts DD, Roche M, Tricarico R, et al. The utility of traditional prehospital interventions in maintaining thermostasis. Prehosp Emerg Care 1999;3:115.
336. Weinberg AD. Hypothermia. Ann Emerg Med 1993;22:370.
337. Weinberg AD. The role of inhalation rewarming in the early management of hypothermia. Resuscitation 1998;36:101.
338. Weiss SJ, Muniz A, Ernst AA, et al. The physiological response to norepinephrine during hypothermia and rewarming. Resuscitation 1998;39:189.
339. White FN. Reassessing acid-base balance in hypothermia: A comparative point of view. West J Med 1983;138:255.
340. White JD. Hypothermia: The Bellevue experience. Ann Emerg Med 1982;11:417.
341. White JD, Butterfield AB, Almquist TD, et al. Controlled comparison of humidified inhalation and peritoneal lavage in rewarming immersion hypothermia. Am J Emerg Med 1984;2:210.
342. White JD, Butterfield AB, Nucci RC, et al. Rewarming in accidental hypothermia: Radio wave versus inhalation therapy. Ann Emerg Med 1987;16:50.
343. Wik L, Kiil S. Use of an automatic mechanical chest compression devise (LUCAS) as a bridge to establishing cardiopulmonary bypass for a patient with hypothermic cardiac arrest. Resuscitation 2005; 66:391.
344. Willekes T, Naunheim R, Lasater M. A novel method of intravascular temperature modulation to treat severe hypothermia. Emerg Med J 2006;23:56.
345. Wilson E, Waring WS. Severe hypotension and hypothermia caused by acute ethanol toxicity. Emerg Med J 2007;24:7.
346. Winegard C. Successful treatment of severe hypothermia and prolonged cardiac arrest with closed thoracic cavity lavage. J Emerg Med 1997;15:629.
347. Wisborg T, Husby P, Engedal H. Anesthesiologist-manned helicopters and regionalized extracorporeal circulation facilities: A unique chance in deep hypothermia. Arctic Med Res 1991;50:108.
348. Wollenek G, Honarwar N, Golej J, et al. Cold water submersion and cardiac arrest in treatment of severe hypothermia with cardiopulmonary bypass. Resuscitation 2002;52:255.
349. Wong KC. Physiology and pharmacology of hypothermia. West J Med 1983;138:227.
350. Wong FW. J wave and hypothermia. Dynamics 2005;16:17.
351. Ying CL, Tsang SF, Ng KF. The potential use of desmopressin to correct hypothermia-induced impairment of primary haemostasis: an in vitro study using PFA-100. Resuscitation 2008;76(1):129.
352. Young DM. Risk factors for hypothermia in psychiatric patients. Ann Clin Psychiatry 1996;8:93.
353. Zafren K, Giesbrecht GF, Danzl DF, et al. Wilderness Medical Society Practice Guidelines for the Out-of-Hospital Evaluation and Treatment of Accidental Hypothermia. Wilderness Environ Med 2014;25(4): 425–45.
354. Zandstra D: Extracorporeal rewarming. Immersion Hypothermia Task Force, World Congress on Drowning. Amsterdam, June 26–28, 2002.
355. Zehner WJ, Terndrup TE. Ear temperatures during rewarming from hypothermia. Ann Emerg Med 1994;23:901.
356. Zell SC, Kurtz KJ. Severe exposure hypothermia: A resuscitation protocol. Ann Emerg Med 1985;14:339.
357. Zhong H, Qinyi S, Mingjlang S. Rewarming with microwave irradiation in severe cold injury syndrome. Chin Med J 1980;93:19.

**BOX 8-1 The Official Canadian Temperature Conversion Chart**

10° C (50° F)
Americans shiver uncontrollably.
Canadians plant gardens.
0° C (32° F)
American water freezes.
Canadian water gets thicker.
–18° C (0° F)
New York City landlords finally turn on the heat.
Canadians have the last cookout of the season.
–51° C (–60° F)
Mt St. Helens freezes.
Canadian Girl Guides sell cookies door to door.
–114° C (–173° F)
Ethyl alcohol freezes.
Canadians get frustrated when they can't thaw the keg.
–273° C (–460° F)
Absolute zero; all American atomic motion stops.
Canadians start saying, "Cold, eh?"
–295° C (–500° F)
Hell freezes over.
A U.S. hockey team beats Canada in the Olympic gold medal game.

world. Recreational aquatic activities include swimming, fishing, sailing, power boating, ocean kayaking, white-water rafting, canoeing, ocean surfing, windsurfing, waterskiing, diving, hunting, and using personal watercraft. In addition, winter activities such as driving on icy roads and snowmobiling can involve cold-water exposure as a result of accidental entry into lakes and streams.[1] Commercial activities that involve water include fishing, shipping, offshore oil drilling, and diving. Military operations over cold water include U.S. Coast Guard (Figure 8-1), Navy, and Marine Corps missions. U.S. Army, Air Force, and Marine Corps forces may encounter cold-water exposure during winter operations on land.

The definition of cold water is variable. The temperature of *thermally neutral water,* at which heat loss balances the heat production of a nude individual at rest (i.e., not shivering), is approximately 33° to 35° C (91.4° to 95° F).[16,18] Hypothermia eventually results from immersion in water at less than this temperature. For practical purposes, significant risk for immersion hypothermia usually begins in water colder than 25° C (77° F),[114,162,163] and it is quite significant in water colder than 15° C (59° F). Table 8-1 shows the variation in water temperature throughout the year at various sites in North America.[180] Figure 8-2 shows typical worldwide sea surface temperatures for November, with data from 2015.[126] With the use of 25° C (77° F) as the defining point for cold water, the risk of immersion hypothermia in North America is nearly universal during most of the year.

Cold-water immersion is associated with two significant medical challenges: near drowning and hypothermia. This chapter discusses the physiologic responses to and treatment of immersion hypothermia, the risk of near drowning with respect to the physiologic consequences of sudden immersion in cold water, and the problems of survival in rough seas. Controversies are also identified and discussed. Chapter 7 discusses land-based hypothermia; Chapter 69 provides a more complete discussion of drowning; and Chapter 71 discusses diving injuries.

## HISTORY AND EPIDEMIOLOGY

The history of human association with the sea and with inland waters provides abundant examples of the effects of accidental cold-water immersion. Case studies demonstrate the scope of the problem. Perhaps the most famous occurrence was the sinking of the *Titanic* in 1912. After striking an iceberg at approximately 11:40 PM on April 14, the ship sank in calm seas, but the water temperature was near 0° C (32° F). Of the 2201 people on board, only 712 were rescued, all from the ship's lifeboats. The remaining 1489 people died in the water, despite the arrival of a rescue vessel within 2 hours. Almost all these people were wearing "life preservers," yet their causes of death were officially listed as "drowning."[119] However, their deaths were more likely caused by immersion hypothermia. Survivors reported hearing victims' screams for periods long enough (>1 hour) to indicate that the individuals in the water survived for a time sufficient to result in severe hypothermia.[102,110]

### RECREATIONAL ACTIVITIES AND COLD WATER

A Canadian Red Cross Report stated that, from 1991 to 2000, there were 5900 water-related deaths in Canada. Of recreational boating drownings, 283 (21%) occurred in "extremely cold" water, which means colder than 10° C (50° F). Of the 14% of all boating drownings in which the victims were wearing personal flotation devices (PFDs), most of these occurred in cold water, and death resulted from hypothermia. Also, 232 snowmobilers drowned after breaking through the ice, and 218 individuals died after falling through the ice during other activities. Case Studies 8-1 to 8-4 illustrate problems that might occur with immersion hypothermia during recreational boating, hiking, snowmobiling and other activities.

### COMMERCIAL ACTIVITIES ON COLD WATER

Numerous examples exist of maritime occupational accidents. In 1982 the offshore mobile oil-drilling platform *Ocean Ranger* collapsed in mountainous seas near Newfoundland, Canada; the water temperature was –1° C (30.2° F) (Video 8-1). Eighty-four workers were plunged into the water, and, despite the presence of a rescue vessel, all of them died. Immersion hypothermia was a significant factor in these deaths, although the inability of the workers to combat rough seas and to maintain airway freeboard (i.e., the distance between the water surface and the mouth) were also major problems.[127]


**FIGURE 8-1** **A,** Canadian Coast Guard rescue boat in rough seas. **B,** U.S. Coast Guard helicopter rescue in rough seas. (***A*** *courtesy Canadian Coast Guard;* ***B*** *courtesy of Gordon Giesbrecht and Alan Steinman).*

**TABLE 8-1** Mean Water Temperatures in °C (°F)*

| Site | January | February | March | April | May | June | July | August | September | October | November | December |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kodiak, Alaska | 0 (32) | 0 (32) | 2 (35.6) | 4 (39.2) | 7 (44.6) | 9 (48.2) | 12 (53.6) | 12 (53.6) | 10 (50) | 7 (44.6) | 4 (39.2) | 2 (35.6) |
| Victoria, British Columbia | 7 (44.6) | 7 (44.6) | 7 (44.6) | 9 (48.2) | 10 (50) | 11 (51.8) | 11 (51.8) | 11 (51.8) | 11 (51.8) | 10 (50) | 9 (48.2) | 8 (46.4) |
| Astoria, Oregon | 4 (39.2) | 5 (41) | 7 (44.6) | 10 (50) | 13 (55.4) | 16 (60.8) | 19 (66.2) | 21 (69.8) | 17 (62.6) | 13 (55.4) | 9 (48.2) | 5 (41) |
| San Francisco | 11 (51.8) | 11 (51.8) | 12 (53.6) | 12 (53.6) | 12 (53.6) | 12 (53.6) | 13 (55.4) | 13 (55.4) | 12 (53.6) | 12 (53.6) | 11 (51.8) | 11 (51.8) |
| San Diego | 14 (57.2) | 14 (57.2) | 15 (59) | 16 (60.8) | 17 (62.6) | 18 (64.4) | 20 (68) | 20 (68) | 20 (68) | 18 (64.4) | 16 (60.8) | 15 (59) |
| Mobile, Alabama | 10 (50) | 10 (50) | 14 (57.2) | 21 (69.8) | 23 (73.4 | 28 (82.4) | 29 (84.2) | 29 (84.2) | 27 (80.6) | 23 (73.4) | 19 (66.2) | 14 (57.2) |
| Miami, Florida | 21 (69.8) | 21 (69.8) | 23 (73.4) | 25 (77) | 27 (80.6) | 29 (84.2) | 30 (86) | 30 (86) | 29 (84.2) | 27 (80.6) | 25 (77) | 23 (73.4) |
| Norfolk, Virginia | 17 (62.6) | 16 (60.8) | 15 (59) | 18 (64.4) | 20 (68) | 24 (75.2) | 26 (78.8) | 26 (78.8) | 25 (77) | 25 (77) | 21 (69.8) | 21 (69.8) |
| Cape May, New Jersey | 3 (37.4) | 3 (37.4) | 5 (41) | 10 (50) | 14 (57.2) | 19 (66.2) | 23 (73.4) | 23 4 (39.2) | 21 (69.8) | 17 (62.6) | 11 (51.8) | 6 (42.8) |
| Traverse City, Michigan | 2 (35.6) | 1 (33.8) | 1 (33.8) | 1 (33.8) | 1 (33.8) | 3 (37.4) | 5 (41) | 10 (50) | 10 (50) | 6 (42.8) | 5 (41) | 4 (39.2) |
| Puerto Rico | 26 (78.8) | 26 (78.8) | 26 (78.8) | 26 (78.8) | 26 (78.8) | 27 (80.6) | 27 (80.6) | 27 (80.6) | 28 (82.4) | 27 (80.6) | 27 (80.6) | 26 (78.8) |
| Honolulu, Hawaii | 24 (75.2) | 24 (75.2) | 24 (75.2) | 24 (75.2) | 25 (77) | 25 (77) | 26 (78.8) | 26 (78.8) | 27 (80.6) | 26 (78.8) | 25 (77) | 25 (77) |

*Temperatures of <25°C (77°F) are noted in red.

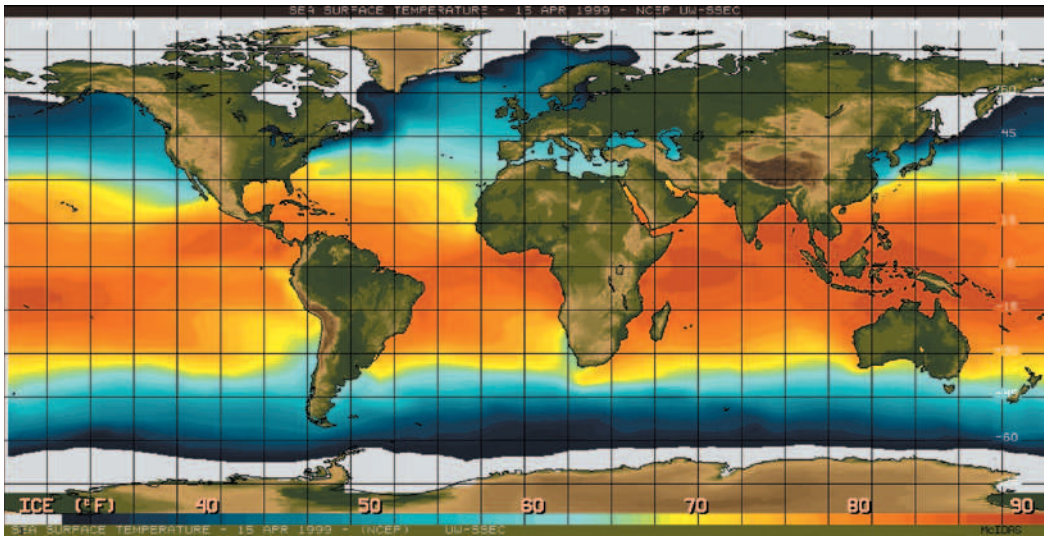



**FIGURE 8-2** Worldwide sea surface temperatures for November 2015. *(From the National Center for Environmental Prediction, Space Science and Engineering Center, University of Wisconsin–Madison. www7320.nrlssc.navy.mil/GLBhycom1-12/navo/globalsst_nowcast_anim30d.gif.)*

## Case Study 8-1 LONG-TERM IMMERSION IN MODERATELY COLD WATER

On February 28, 2009, four friends who were all former or current football players in their mid-20s set out on a fishing trip in a 6.3-m (21-foot) boat into the Gulf of Mexico west of Tampa Bay, Florida. According to the survivor's account,[148] their boat capsized in a storm before they could return to shore, and the four men were thrown into the 18° C (65° F) water. Weather conditions were 4.3-m (14-foot) seas and winds of 15 to 18 m/sec (30 to 35 knots). None of the men was wearing a PFD at the time of the capsizing. One of the survivors dove under the boat to retrieve three keyhole PFDs and one seat cushion. Despite their large size (≈190 cm [74.8 inches] tall and ranging from 98 to 120 kg [216 to 265 lb] in weight) and high level of muscle mass and physical fitness, the men all developed hypothermia as a result of the combination of a low level of body-fat insulation, cold-water temperature, effect of the wind on their wet clothing, and strenuous work to remain on the boat or to get out of the water. Two victims died after about 13 hours, a third died after 25.5 hours, and the lone survivor was rescued after 43 hours by the U.S. Coast Guard. The first casualty was the lightest (≈98 kg [216 lb]) and wore only swimming trunks and a keyhole PFD; he had discarded his T-shirt, wind pants, and jacket to try to dive under the boat for supplies. The second casualty, who died at about the same time, was the heaviest (≈120 kg [265 lb]), but had spent far more time immersed in the water than had the others. The third casualty survived another 12 hours, but perished nearly 18 hours before the lone survivor was rescued. That casualty had also taken off his wind jacket and pants, which were later lost, so that he could dive under the boat. During the first 13 hours, he struggled to help the other victims while he was in the water, and he had little insulation from the seat cushion, which he wore on his back; he later switched to the keyhole PFD that had been worn by the first casualty. These early conditions likely put him behind the survival curve of his remaining companion. The survivor (≈109 kg [240 lb]) had the double advantage of less direct water exposure (he spent more time positioned on top of the boat, often holding onto the motor) and more insulation (sweatpants, sweatshirt, water-resistant and fleece-lined hooded coat, skullcap, and gloves). He had a core temperature of 31.9° C (89.5° F) after 43 hours at sea (Figure 8-3). This case is referenced throughout this chapter.

## Case Study 8-2 PANIC IN ICE WATER

In February 1990, four teenage boys broke through the ice on Convict Lake in California. After one boy escaped and summoned help, a series of adults—including two lay and three professional rescuers—approached and also broke through the ice. It was not until a properly equipped rescue team arrived "that a safe rescue attempt could be made … on one lone adult. In just fifteen minutes, three boys and four of their five adult rescuers were dead."[48] Despite the common belief at the time, the victims did not perish as a result of hypothermia but rather from cold- and panic-induced incapacitation and drowning.

## Case Study 8-3 "SKATING" ON THIN ICE

In the winter of 1997-1998, four people died when their snowmobile broke through the thin ice of Lake Scugog, near Toronto, Ontario, Canada. The deaths occurred, ironically, during Snowmobile Safety Week in North America. The Canadian Safety Council reported that, in 1997, 101 people were killed in snowmobile mishaps, the majority of them by drowning and hypothermia after crashing through ice on frozen rivers and lakes.[1]

**FIGURE 8-3** U.S. Coast Guard vessel approaching a survivor who is sitting on top of an overturned boat. *(Courtesy U.S. Coast Guard.)*

### Case Study 8-4 PROBLEMS WITH COLD-WATER RESCUE

During winter 1988, two men died of hypothermia when their nine-man rowing scull sank during a winter storm on a small lake in western Canada. The nine rowers were immersed in 4° C (39.2° F) water. They struggled to hang on to their overturned vessel in 0.6- to 1.0-m (2- to 3.3-foot) waves and 30 km/hr (18.7 mile/hr) winds for more than 50 minutes before rescuers could reach them. One man drowned just before rescue; the others were all conscious when they were pulled from the water. However, during the 13-minute boat transport to shore, three of the thinnest victims lost consciousness, and one of these men suffered cardiopulmonary arrest. His core temperature ($T_{co}$) in the hospital 44 minutes after rescue was 23.4° C (74.1° F); subsequent resuscitation efforts were unsuccessful. The remaining seven survivors were resuscitated from $T_{co}$ as low as 25° C (77° F). This case illustrates the rapidity of onset of immersion hypothermia in lean subjects and the potentially serious consequences of cardiovascular instability, circumrescue collapse, and post-rescue $T_{co}$ afterdrop in individuals with immersion hypothermia (see Physiologic Responses to Cold-Water Immersion with the Head Above Water, later).[58]

### Case Study 8-5 DANGERS OF FISHING IN COLD WATER

In December 2004, the fishing vessel *Northern Edge* capsized near Nantucket, Massachusetts, in 4° C (39.2° F) water and 3- to 4-m (9.8- to 13.1-foot) seas. Five of the six crewmembers lost their lives.[184] In several similar cases in the same region, seven fishermen on three different vessels lost their lives during a 30-day period in the winter of 2004-2005.[181] In June 2003 the charter fishing vessel *Taki Tooo,* which was carrying 17 passengers and crew, capsized in the turbulent waters of the Tillamook River bar on the Oregon coast, with the loss of 11 lives. The water temperature was 10° C (50° F).[183] In April 2001 the fishing vessel *Arctic Rose* sank in the Bering Sea of Alaska, with a loss of 15 crewmembers.[184] The vessel sank so quickly that there was no time for either a distress call to be made or the crewmen to don survival suits.

Fishing vessel mishaps are a common cause of immersion hypothermia. Case Studies 8-5 and 8-6 illustrate the problems that face the commercial fishing industry (Figure 8-4).

Another commercial maritime disaster involving mass casualties from immersion hypothermia and drowning was the capsizing and sinking of the collier *Marine Electric* off the coast of Virginia in the early-morning hours of February 12, 1983 (Video 8-2) (www.uscg.mil/history/docs/casrep/1983marineelectric.pdf). The vessel began taking on water in gale-force winds and seas up to 11 m (35 feet) in height. Before the crew of 34 could abandon ship, the vessel capsized, throwing most of the men into the 4° C (39° F) water (air temperature was −1.7° C [29° F]). Only three of the crew survived despite the presence of PFDs; as in the *Ocean Ranger* case, the crewmembers were incapacitated by the cold water and unable to maintain airway freeboard in the heavy seas.

The *Marine Electric* disaster had one beneficial outcome. Despite the loss of 31 lives in this case, the disaster resulted in establishment of the now-famous U.S. Coast Guard (USCG) Rescue Swimmer program. USCG helicopters were on scene within about 2.5 hours of the *Marine Electric*'s capsizing, but without rescue swimmers, they could not recover possible survivors from the water because of the high seas and cold-water–induced incapacitation of the crew. USCG Rescue Swimmers have saved thousands of lives since their creation after this disaster.

### Case Study 8-6 COLD-WATER FISHING FATALITIES

A 1999 U.S. Coast Guard Fishing Vessel Casualty Task Force Report[181] found that, in just 2 months (December 1998 and January 1999), 20 commercial fishing vessels were lost at sea. During these mishaps, 21 persons on board died, mainly from exposure to cold water as a result of the vessel sinking or capsizing or from persons falling overboard. From 1994 to January 1999, U.S. Coast Guard statistics show that 396 fishermen lost their lives while fishing. Of these, 298 died from cold-water immersion as a result of falling overboard or of the vessel sinking, capsizing, or flooding. In 1998, mortality rate for fishermen was 179 per 100,000 workers; this is 16 times higher than the averaged rates for firefighters and police officers.

## MILITARY ACTIVITIES AND COLD WATER

The extensive use of combat ships and aircraft in World War II, particularly in the north Pacific and north Atlantic oceans, provided many examples of accidental immersion in cold water. Molnar[124] reviewed several hundred of these cases, including the following:

> A ship was rammed, and it sank in 3 minutes. Thirty survivors were picked up from rafts after exposure of 1.5 to 4 hours. Some drowned and others died of exposure because the water was 4° C (7.2° F) with high seas and a wind velocity of scale 7. Some of the survivors who held on to ropes couldn't let go and rescuers had to cut frozen rope to release them. It appears miraculous how the survivors could have endured such cold water. Most of those who were rescued were in an unconscious state and, when they became conscious, complained of numbness of extremities and hands.

The Falklands War in 1982 provided further examples of immersion hypothermia related to naval combat. The Argentinian cruiser *General Belgrano* sank in approximately 5° C (9° F) water, which resulted in the deaths of many sailors. Some of the deaths from cold occurred even after the sailors had managed to emerge from the water into life rafts.

Maritime military operations are not the only source of hypothermia casualties in the armed forces; land operations, either during combat or training, also have immersion hypothermia risks. In March 1995, four U.S. Army Rangers died and four others were hospitalized during a training mission in a Florida swamp. The water at the exercise site was deeper and colder than was customary for this exercise. Consequently, the Rangers were forced to spend more than 6 hours in cold and wet conditions, much of the time partially immersed in the 15° C (59° F) water. Night conditions and difficulties encountered during the medical evacuation of the accident victims contributed to the hypothermia deaths.[17,186]

In March 2001, two USCG crewmen drowned after immersion in cold water, when their four-man vessel capsized in the waves of the Niagara River bar in Lake Ontario. The water temperature was 2° C (3.6° F). All the crewmen were wearing dry suits with insulation as well as PFDs, but they were without insulated headgear. They left the boat to swim toward a buoy. Vigorous swimming caused water intrusion into two of the dry suits, as did the coxswain's use of a neck ring device before capsizing. This leakage resulted in severe immersion hypothermia and subsequent drowning.[182]

The relatively high fatality rate from accidental immersion in cold water in various military, commercial, and recreational settings has stimulated technologic advances in protective clothing and rescue devices. The current availability of commonplace items of survival equipment (e.g., wet suits, dry suits, survival suits, inflatable life rafts) is primarily a response to the needs of people who work in cold-water environments. The value of various types of protective clothing is examined later in this chapter.

## VEHICULAR ACTIVITIES ON ICE

Motor vehicle submersions account for approximately 10% of all drownings, including approximately 400 fatalities in North

**FIGURE 8-4** Fishing and merchant vessels in distress in rough seas. *(Courtesy U.S. Coast Guard.)*

America each year.[177,201] Although most of these deaths occur in open water during spring, summer, or fall, many also occur during the winter, when vehicles break through the ice while traversing either makeshift (e.g., ice fishing) or official (e.g., winter roads) transport routes. In 2005, a heavy-machine operator was maintaining an ice road when his snowplow broke through the ice, and he drowned.[91] The ice-cold-water temperature was cited as a contributing factor to his death.

In summary, numerous case histories and statistical evidence document the significance of cold-water immersion as a cause of the environmental emergencies of drowning and hypothermia. Although drowning is relatively easy to prevent (e.g., with the use of PFDs, water safety training, and restriction of alcohol use), hypothermia is not easy to prevent. Hypothermia is now more widely recognized than in the past, but the prevention of immersion hypothermia is still a difficult and often expensive proposition. Therefore, in regions with cold water (which includes most of the North American continent), cold-water safety, knowledge of cold-water risks, and the use of appropriate flotation and protective clothing are essential (Video 8-3).

## PHYSIOLOGIC RESPONSES TO COLD-WATER IMMERSION WITH THE HEAD ABOVE WATER

The effect of sudden cold-water immersion on humans is poorly understood by the general public as well as by medical and rescue personnel. Many believe that an individual who falls into ice water will die of hypothermia within minutes, even if that person is dressed in winter clothing. In a series of surveys of continuing medical education attendees,[47] 72% of respondents thought that, under these conditions, a victim would experience life-threatening hypothermia in less than 10 minutes. As discussed later, most adults can survive for 1 hour or more if they take appropriate action. The improper assumption of rapid and impending death only serves to induce panic, poor decisions, and exhaustion as a result of thrashing about, thereby causing problems for both primary victims and the persons trying to rescue them.

The primary pathophysiologic effects of hypothermia are a decrease in tissue metabolism and the gradual inhibition of neural transmission and control. However, during the initial stages of cooling of an intact and conscious victim, secondary responses to skin temperature cooling predominate. Sudden immersion in cold water results in an immediate decline in skin temperature, which in turn initiates shivering thermogenesis with increases in metabolism, ventilation, heart rate, cardiac output, and mean arterial pressure. As body temperature declines and shivering ceases, metabolism, heart rate, mean arterial pressure, and cardiac output decrease proportionally with the fall in core temperature ($T_{co}$), whereas hematocrit and total peripheral resistance increase. Renal diuresis and extravascular fluid shifts can lead to a considerable loss of intravascular volume, thus decreasing systemic perfusion. A more detailed description of the pathophysiologic effects of systemic hypothermia is provided in Chapter 7. This section pragmatically describes the effects of the pathophysiologic changes that accompany cold-water immersion and the impact of these changes on survival.

The body's responses and mechanisms of death during cold-water immersion can be divided into four phases: (1) initial immersion and the cold shock response, (2) short-term immersion and the loss of performance, (3) long-term immersion and the onset of hypothermia, and (4) circum-rescue collapse just before, during, or after rescue. Each phase is accompanied by specific survival hazards for the immersion victim that originate from or are influenced by a variety of pathophysiologic mechanisms. Deaths have occurred during all four phases of immersion.

### PHASE 1: THE COLD SHOCK RESPONSE (0 TO 2 MINUTES)

The cold shock response occurs during the first 1 to 2 minutes of cold-water immersion and depends on the extent and rate of skin cooling. The responses are generally those that affect the

respiratory system, heart, and the body's metabolism (Figure 8-5).[36,175] Rapid skin cooling initiates an immediate gasp response, an inability to hold one's breath, and hyperventilation. The gasp response may cause drowning if the head is submersed during the initial entry into cold water. The subsequent inability to hold one's breath may further potentiate drowning in high seas. Subsequent hyperventilation will normally diminish within seconds to minutes, but it could be increased and exaggerated indefinitely as a result of emotional stress and panic. Uncontrolled hyperventilation can cause numbness, muscle weakness, or fainting, which may lead to drowning. Any of these respiratory responses can lead to pulmonary aspiration of water. Panic may ensue, with subsequent drowning (Videos 8-4 and 8-5).

Skin cooling initiates peripheral vasoconstriction as well as increased cardiac output, heart rate, and arterial blood pressure. Increased workload on the heart may lead to myocardial ischemia and arrhythmias, including ventricular fibrillation (VF). Sudden death can occur either immediately or within minutes after immersion as a result of syncope or convulsions, which can lead to drowning, vagal cardiac arrest, or VF in susceptible individuals.[23,44,103,118,167]

Cold shock can occur in water colder than 20° C (68° F), with symptoms increasing as water temperature decreases to freezing. Staged entry into cold water attenuates respiratory responses because of a gradual increase in thermal stimulation. The best advice to combat this phenomenon is, when possible, to control entry into cold water by entering slowly and most importantly by keeping the head from being submersed. One should *never* dive into cold water. After cold-water immersion, it is important to focus on surviving the first minute by not panicking and by consciously getting one's breathing under control. Figure 8-6 shows that minute ventilation and breathing frequency increase dramatically with rapid immersion in cold water. These responses are blunted by more than 50% with graded immersion.

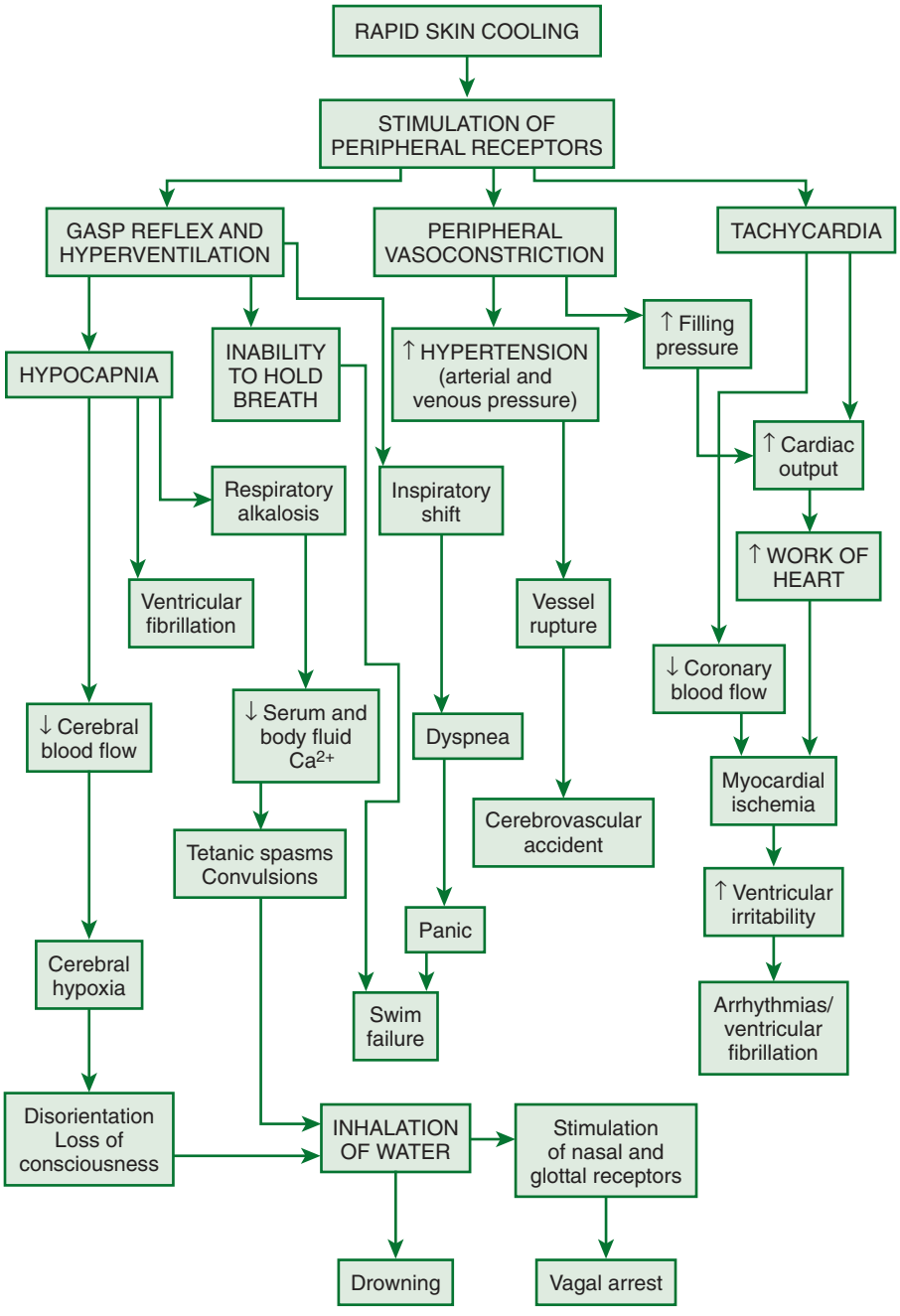



**FIGURE 8-5** Possible cold shock responses. *(From Edmonds C, Lowry C, Pennefather J: Cold and hypothermia. In* Diving and subaquatic medicine, *Oxford, UK, 1992, Butterworth-Heinemann.)*

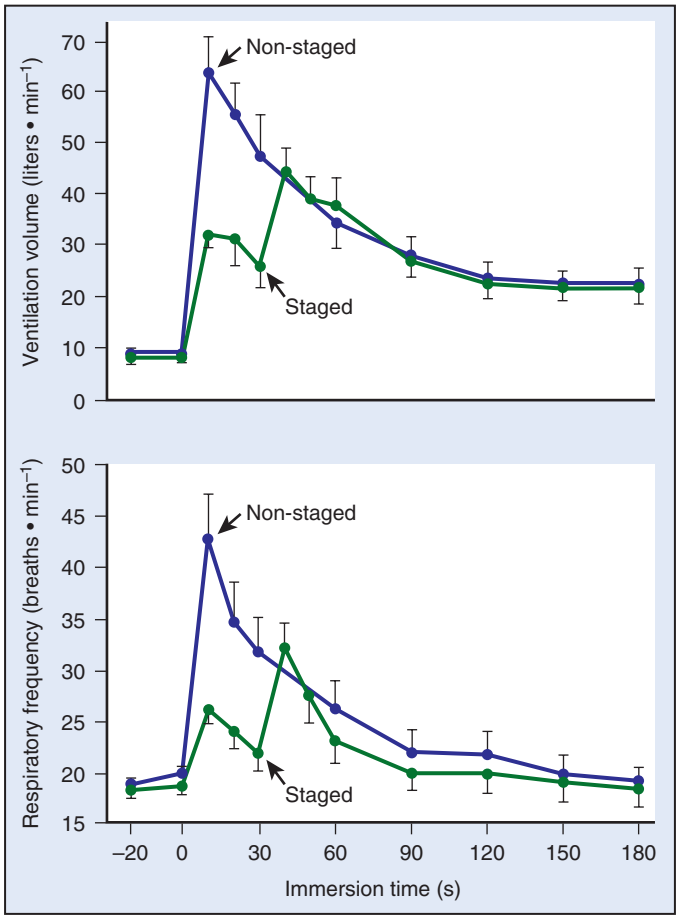



**FIGURE 8-6** Respiratory responses (minute ventilation and respiratory rates) to sudden and graded immersion into cold water. Error bars = standard deviation. *(From Hayward JS, French CD: Hyperventilation response to cold water immersion: Reduction by staged entry,* Aviat Space Environ Med *60:1163, 1989.)*

## PHASE 2: COLD INCAPACITATION (5 TO 15 MINUTES)

For persons who survive the cold shock response, significant cooling of muscle and nerve fibers—especially in the extremities—continues, with most of the effect occurring during the first 15 minutes of immersion. This cooling has a direct deleterious effect on neuromuscular activity.[186] This effect is especially significant in the hands, where blood circulation is negligible,[34] which leads to finger stiffness, poor coordination of gross and fine motor activity, loss of power,[40,51,133,134,191] and swim failure (Figure 8-7). It has been shown that this effect is primarily the result of peripheral rather than central cooling.[63] The loss of motor control makes it difficult, if not impossible, to execute survival procedures, such as grasping a rescue line or hoist. The ultimate cause of death is drowning, either through the failure to initiate or maintain survival performance (i.e., keeping afloat, swimming, or grasping onto a life raft) or excessive inhalation of water under turbulent conditions.

These phenomena have obvious survival implications. It is best to avoid cold-water exposure completely. If cold-water immersion occurs, it is best quickly to determine and execute a plan of action: (1) try to enter the water without submersing the head; (2) escape (i.e., pull oneself out of the water, inflate, and board a life raft); (3) minimize exposure (i.e., get as much of one's body as possible out of the water and onto a floating object); (4) ensure flotation if one must remain in the water (i.e., don or inflate a PFD); and (5) call for assistance (i.e., activate signaling devices). It may be difficult to execute these actions when cold shock responses predominate. However, after

**FIGURE 8-7** Swim failure test of a woman not wearing a personal flotation device (PFD) and a man wearing a PFD swimming in cold (14° C [57.2° F]) water. The man experienced difficulty early on as a result of gasping and uncontrolled breathing (i.e., cold shock response) and likely would have drowned if he was not wearing a PFD. *(Courtesy Gordon G. Giesbrecht.)*

respiratory effects are under control, immediate action should be taken. If self-rescue is not possible, actions to minimize heat loss should be initiated by remaining as still as possible in the *heat escape lessening position* (HELP), in which the arms are pressed against the chest while the legs are pressed together, or by huddling with other survivors (Figure 8-8).[86] Drawstrings should be tightened in clothing to decrease the flow of cold water within clothing layers (see Videos 8-4 and 8-5).

## PHASE 3: ONSET OF HYPOTHERMIA (IMMERSION FOR LONGER THAN 30 MINUTES)

Most cold-water deaths likely result from drowning during the first two phases of cold-water immersion, as discussed previously. In general, true hypothermia usually only becomes a significant contributor to death if immersion lasts more than 30 to 60 minutes. A survey indicates that even medical practitioners greatly underestimate the time required for a person to become hypothermic in cold water.[47] In fact, 72% of respondents believed that a properly clothed adult would become hypothermic after less than 10 minutes in ice water (0° C [32° F]) (Figure 8-9). An individual who survives the immediate and short-term phases of cold-water immersion faces the possible onset of hypothermia, because continuous heat loss from the body eventually decreases $T_{co}$. Many predictive models to determine the $T_{co}$ response to cooling are based on the relationships among body composition, thermoregulatory response (i.e., shivering

**FIGURE 8-8** Group huddle techniques for decreasing the cooling rates of survivors in cold water. *(Courtesy Gordon G. Giesbrecht.)*

**BOX 8-2 The 1-10-1 Principle**

If you fall into ice-cold water, remember that you have **1 minute—10 minutes—1 hour.***

- You have **1 minute to get your breathing under control,** so don't panic.
- You have **10 minutes of meaningful movement** to get out of the water or to attain a stable situation.
- You have up to **1 hour until you become unconscious from hypothermia** if you don't panic or struggle unnecessarily. If you are wearing a personal flotation device, you may have another hour until your heart stops beating as a result of hypothermia.

*Times are subject to individual variability and factors such as body size, water temperature, and amount of the body immersed.

**BOX 8-3 Controversy Box: Time to Hypothermia**

Most people greatly underestimate the amount of time required to become hypothermic in very cold water. This is important, because if a victim thinks that hypothermia will set in very quickly, panic is more likely. A proper understanding of the fact that cold shock is initially the greatest threat will help the victim to focus more on controlling the gasp reflex and to get control of his or her breathing.

thermogenesis), clothing and insulation, water temperature, and sea conditions[90,163,197,202,207] (see Cold-Water Survival, later).

Even in ice water, a victim may not drown when he or she becomes unconscious as a result of hypothermia (≈30°C [86°F]) if a PFD is worn or if some other factor prevents the need for vigorous exercise to prevent drowning. If the head is kept above water, the victim could still survive for another hour or more before the heart stops, as long as the sea is relatively calm and waves do not wash over the mouth. It is important for members of the public to be educated about the fact that they are not necessarily going to die if they are suddenly immersed in cold water (Box 8-2).

The relative contributions of the first three phases to death in cold water of varying temperatures are estimated schematically in Figure 8-10. In colder water, if no flotation is worn *(A),* death occurs as a result of cold shock or cold incapacitation. Only if flotation is worn *(B)* will a victim survive long enough to die as a result of hypothermia (Box 8-3).

## PHASE 4: CIRCUM-RESCUE COLLAPSE

Anecdotal cases of fatalities among immersion hypothermia victims have been noted during the immediate pre- and post-rescue periods, despite the survivor being recovered in an apparently stable and conscious condition. The hypothermic victim may experience symptoms that range from fainting to cardiac arrest. These events are often referred to as cases of "rewarming shock" or "post-rescue collapse." Golden and colleagues[73] noted that deaths can occur either shortly before rescue, during rescue, or after rescue, and they have used the term *circum-rescue collapse* to describe these events. Deaths have occurred within minutes before rescue, while climbing out of the water, while being hoisted onto a helicopter, within a few minutes of entering

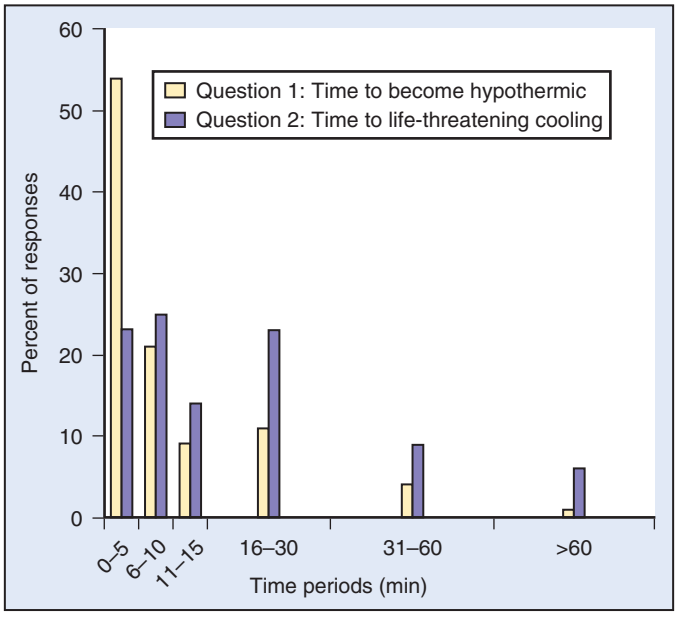



**FIGURE 8-9** Estimates of 661 respondents regarding how long it would take to become hypothermic *(yellow bars)* and to die of hypothermia *(purple bars)* in ice water when wearing winter clothing. *(From Giesbrecht G, Pretorius T: Survey of public knowledge and responses to educational slogans regarding cold water immersion,* Wilderness Med Newslett *19:261, 2008.)*

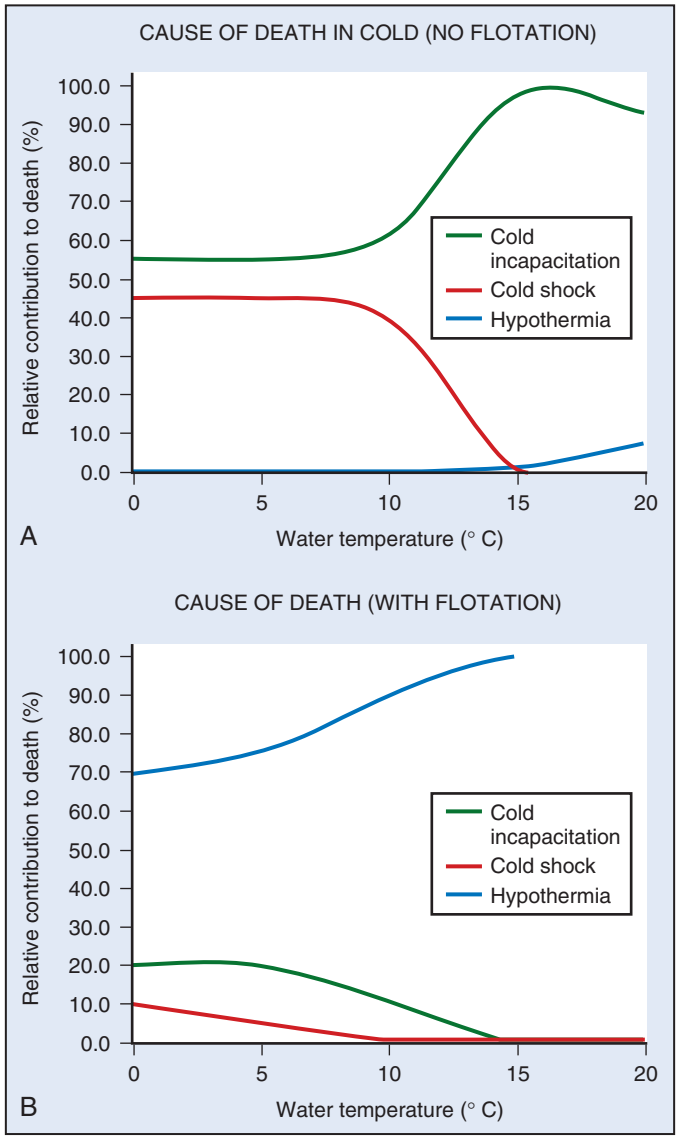



**FIGURE 8-10** Estimation of the relative contributions of cold shock, cold incapacitation, and hypothermia to death in water at different temperatures. **A,** Estimation if no flotation is available. **B,** Estimation if flotation is available.

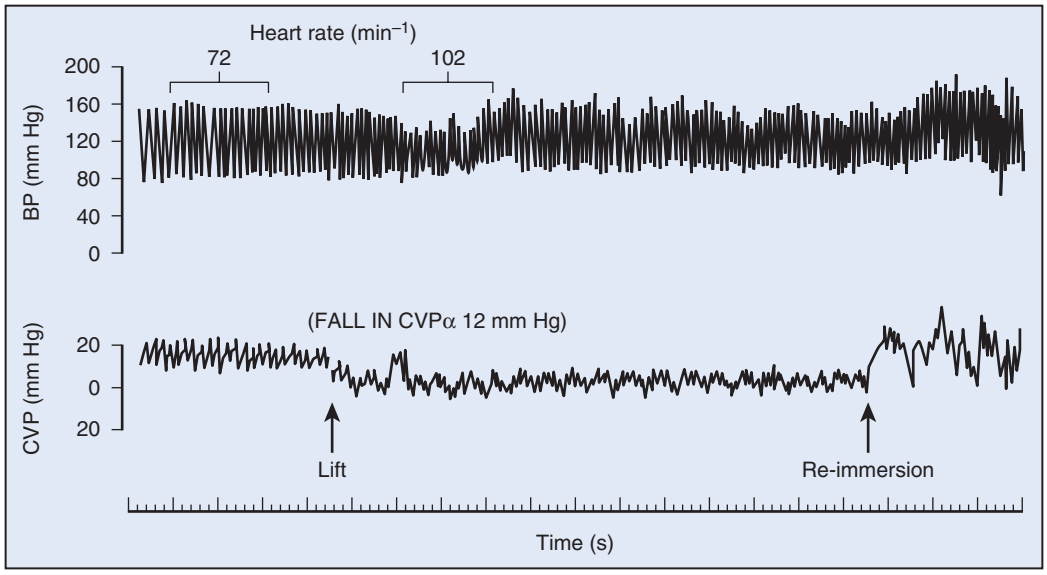



**FIGURE 8-11** Heart rate and blood pressure responses during the vertical removal of a test volunteer from cold water. *(From Golden FS, Hervey GR, Tipton MJ: Circum-rescue collapse: collapse, sometimes fatal, associated with rescue of immersion victims,* J R Navy Med Serv *77:139, 1991.)*

a warm compartment of a rescue vessel, 20 to 90 minutes after rescue, in a hospital after transport, and during the 24-hour period after rescue.[71,73,100,116]

Three causes of circum-rescue collapse have been proposed: (1) afterdrop, which is a continued drop in $T_{co}$ after recovery; (2) collapse of arterial pressure (Figure 8-11); and (3) factors that potentiate the risk of VF (e.g., hypoxia, acidosis, rapid changes in pH). These causes are discussed further later in this chapter.

When rescue is imminent, mental relaxation and the decreased output of stress hormones may result in a drop in blood pressure, which may cause fainting and drowning. The act of rescue itself may also cause sudden collapse. Pulling a victim out of the water in a vertical position removes hydrostatic squeeze around the lower limbs and may cause blood pooling in these extremities, with subsequent decreased blood pressure. Extra cardiac work or rough handling may induce reflex cardiac arrest of the cold heart.

*Afterdrop* is a well-known phenomenon that occurs after the removal of a victim from cold-water immersion. $T_{co}$ continues to decline (i.e., afterdrop) in both animate and inanimate objects, even after cold-water immersion has ended.[2,13,20,57,75,141,147,194] Afterdrop of as much as 5° to 6°C (9° to 10.8°F) has been observed in humans[6,43,161] (Figure 8-12). This afterdrop has long been

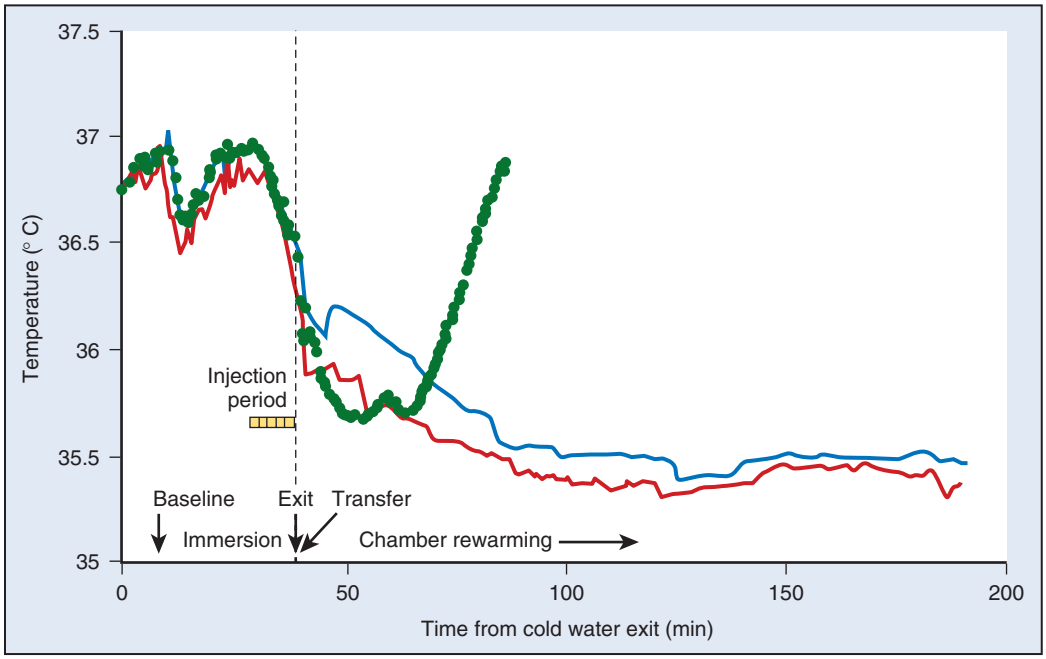



**FIGURE 8-12** Core temperature response of a nonshivering volunteer (whose response was inhibited with meperidine [in five aliquots during injection period]) during spontaneous warming *(red)*, inhalation warming *(blue)*, and forced-air warming *(green)*. Warming took place in a chamber at –20°C (–4°F). Only forced-air warming reversed the afterdrop. Temperature remained low for several hours, even with inhalation warming. *(From Giesbrecht G, Wilkerson J:* Hypothermia, frostbite and other cold injuries, *ed 2, Seattle, Wash, 2006, The Mountaineers Books.)*

proposed to be the major cause of post-rescue death, because further cooling of the heart might result in a temperature at which VF or cardiac arrest could occur.[13]

Golden and colleagues[73] discount the importance of this phenomenon and propose the collapse of arterial pressure as the cause of death during rescue. They correctly note that afterdrop occurring in victims who were hypothermic yet warm enough to climb on board a ship without assistance would be unlikely to cause enough myocardial cooling to result in cardiac arrest or VF. They also propose that removal from cold water results in a precipitous fall in blood pressure, inadequate coronary blood flow, and myocardial ischemia, which may precipitate VF. This mechanism is likely the main factor in both pre-rescue collapse and collapse that occurs during rescue. A fall in blood pressure before removal from the water may be the result of reduced sympathetic tone or catecholamine secretion when rescue is imminent. Hypotension during and shortly after rescue may be caused by a sudden decrease in hydrostatic pressure on the body (i.e., removal of the hydrostatic squeeze of water pressure that exists during immersion), hypovolemia, or impaired baroreceptor reflexes. However, this mechanism cannot fully account for all the other deaths that occur 20 minutes to 24 hours after rescue.

The importance of continued myocardial cooling cannot be discounted. Fibrillation of a cold heart can be initiated by mechanical stimuli, hypoxia, acidosis,[131] and rapid changes in pH.[101] In dogs, myocardial cooling from 30° to 22°C (86° to 71.6°F) caused a fivefold decrease in the electrical threshold for VF.[25] Also, an increase in the rate of myocardial cooling may likely stimulate fibrillation. On the basis of the large afterdrop values described previously, it is plausible that continued $T_{co}$ cooling in significantly hypothermic patients could result in VF, caused primarily by spontaneous fibrillation of the cold myocardium or secondary to a cold-induced increase in sensitivity to other fibrillation stimuli.

Death may occur within minutes to hours after rescue. A rescued victim may be severely compromised with cold alkaline or acidic blood returning from the extremities, a heart that is extremely prone to failure, a decrease in or a loss of consciousness, or low blood volume (hypovolemia). Sudden redistribution of blood to the extremities (especially the lower extremities) may cause collapse as a result of decreased blood pressure and cardiovascular instability, sudden return of metabolic byproducts to the irritable heart, or continued decrease in temperature (afterdrop) of an irritable heart. The $T_{co}$ will continue to drop, and the heart will react with profound tachycardia or fibrillation. Up to 20% of persons who are recovered alive die as a result of circumrescue complications, either before or during rescue, or within hours after rescue.

## FACTORS THAT AFFECT COOLING OF THE BODY'S CORE

Normal body core temperature fluctuates around 37°C (98.6°F). The clinical definition of hypothermia is a $T_{co}$ of 35°C (95°F) or lower; however, any exposure to cold that lowers the $T_{co}$ to less than a normal level results in the body becoming hypothermic. Although various temperatures and terms have been used to classify different levels of hypothermia, the following classifications are used here (Figure 8-13). With *mild* hypothermia ($T_{co}$ = 32° to 35°C [89.6° to 95°F]), thermoregulatory mechanisms continue to operate fully, but ataxia, dysarthria, apathy, and even amnesia are likely. With *moderate* hypothermia ($T_{co}$ = 28° to 32°C [82.4° to 89.6°F]), effectiveness of the thermoregulatory system (i.e., shivering thermogenesis) diminishes until it fails; there is a continued decrease in the level of consciousness, and cardiac dysrhythmias may occur. With *severe* hypothermia ($T_{co}$ <28°C [82.4°F]) consciousness is lost, shivering is absent, acid-base disturbances develop, and the heart is susceptible to VF or asystole. Death from hypothermia is generally a result of cardiorespiratory failure.

If a victim of cold-water immersion can avoid drowning during the initial few minutes after water entry, the prevention of hypothermia becomes an important problem. Survival time in cold water, which is based on the pathophysiologic effects of decreasing $T_{co}$, is not a precise calculation. Large individual variations among survivors with regard to body morphology and state of health and fitness, in combination with many exogenous variables that affect cooling rate (e.g., clothing, water

| Classifications | Core temperature | Patient's ability to rewarm without external heat source | Clinical presentation | |
|---|---|---|---|---|
| **Normal** | **Above 35° C (95° F)** | | **Cold sensation; shivering** | |
| **Mild** | 35-32° C (95–90° F) | Good | Physical impairment<br>• Fine motor<br>• Gross motor | Mental impairment<br>• Complex<br>• Simple |
| **Moderate** | 32-28° C (90–82° F) | Limited | **Below 30° C (86° F) shivering stops; loss of consciousness** | |
| **Severe** | Below 28° C (82° F) | Unable | Rigidity<br>Vital signs reduced or absent<br>Severe risk of mechanically stimulated (rough handling) ventricular fibrillation (VF) | |
| | **Below 25° C (77° F)** | Unable | **Spontaneous ventricular fibrillation (VF); cardiac arrest** | |

**Bold text** shows the major thresholds between stages of hypothermia.

**FIGURE 8-13** Classification of levels of hypothermia on the basis of core temperature and clinical presentation.

temperature, sea state, flotation, behavior), preclude exact predictions of survival time. However, sufficient experimental data and case history findings exist to allow for generalizations. At a $T_{co}$ of 34° C (93.2° F), there is a significant deleterious effect on manual dexterity and "useful function" in cold water.[24,132] If a survivor is trying to combat rough seas, this level of dysfunction may potentiate drowning. At a $T_{co}$ of 30° C (86° F), unconsciousness is probable. Even if a survivor is wearing a self-righting PFD that has been designed to maintain airway freeboard in an unconscious person, drowning is probable at this $T_{co}$ in any sea state where water can enter the unconscious survivor's mouth and nose. In one study on survivors wearing a type I PFD in a wave tank, even 15-cm (6-inch) waves were capable of covering a person's nose and mouth in the absence of evasive action to maintain airway freeboard, something an unconscious survivor would be unable to do. At a $T_{co}$ of less than 25° C (77° F), VF or asystole often occur spontaneously.[29] Of these three core temperatures, 30° C (86° F) is the most practical for defining the limits of survival in cold water (see Survival Modeling, p. 185).[18,29,158,159,163]

The rate of body $T_{co}$ cooling during cold-water immersion depends on the following variables: water temperature and sea state; thermal protection; body morphology; amount and surface area of the body immersed in water; behavior (e.g., excessive movement) and posture (e.g., HELP, huddle) of the body in the water; shivering thermogenesis; and other, nonthermal factors.

## WATER TEMPERATURE AND SEA STATE

Water temperature and sea state are critically important to the intensity of the cold shock response, the onset of physical and mental impairment, and the rate of $T_{co}$ cooling. Figure 8-14 graphically illustrates the inverse linear relationship between water temperature and $T_{co}$ cooling rate.[82] Water conducts heat away from the body approximately 25 times as fast as does air at the same temperature.[125]

## THERMAL PROTECTION

Many studies over the past few decades have evaluated the relationships of different types of protective clothing with heat loss and cooling rates.* Almost all these have been conducted in calm water or in laboratory settings. As illustrated by the cooling rate data in Tables 8-2 and 8-3, such studies have generally shown that, in calm water, intact "dry" and insulated garments provide better protection than do "wet" insulated garments, and that well-insulated garments provide significantly better protection than do poorly insulated garments. Figure 8-15 shows various types of cold-water protective garments.

Although calm-water studies have value in that they compare the relative degree of protection afforded by different types of protective clothing, many immersion accidents occur in rough water.[143,168,169] In this environment, a survivor's cooling rate may be affected by swimming to maintain airway freeboard, passive body movements caused by waves, flushing of cold water through "wet" suits, and leakage of cold water into "dry" suits. For example, individuals in a wave tank demonstrate higher energy expenditure and faster cooling rates than do those in calm water.[81] Several experimental studies have demonstrated significantly faster cooling rates for human volunteers wearing "wet" protective garments in rough or turbulent water[142,158,203] than for persons in calm water. Even "dry" suits have shown degradation of protection in rough water. In a study of dry immersion suits in 16° C (60.8° F) water, Ducharme and Brooks[31] found that wave heights of up to 70 cm (28 inches) resulted in a 14% decrease in total suit insulation and an average 45% decrease in thermal resistance at the head and trunk regions of the suits.

*References 5, 35, 83, 89, 98, 99, 109, 132, 150, 158, 159, 166, 170, 172, 173, 175, 198, 203.

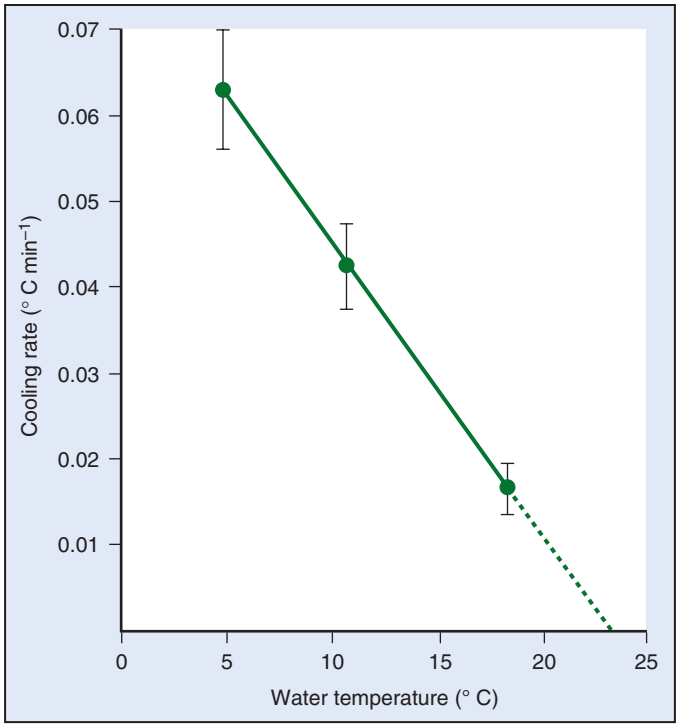



**FIGURE 8-14** Relationship between water temperature and mean rectal temperature cooling rate in lightly clothed, nonexercising males and females during immersion in seawater. Error bars = standard deviation. *(From Hayward JS: The physiology of immersion hypothermia. In Pozos RS, Wittmers LE, editors:* The nature and treatment of hypothermia, *Minneapolis, 1983, University of Minnesota Press.)*

**TABLE 8-2** Mean Linear Cooling Rates for Lean Men Dressed in Various Types of Garments in Calm Water at 10° C (50° F)

| Type of Protective Clothing | Cooling Rate Given as °C/hr ±SD (°F/hr ±SD) |
|---|---|
| Control (equivalent to ordinary street clothes) | 3.2 ±1.1 (5.8 ±2.0) |
| **"Wet" Design** | |
| Thermal float coat (loose-fitted, 5.4-mm [0.21-inch] closed-cell foam-insulated jacket) | 1.6 ±0.6 (2.9 ±1.1) |
| Short wet suit (custom-fitted, 3.2-mm [0.13-inch] closed-cell foam that covers the arms, the trunk, and the upper thighs) | 1.2 ±0.4 (2.2 ±0.7) |
| Insulated coveralls (loose-fitted, 3.2-mm [0.13-inch] closed-cell foam that covers the extremities and the trunk) | 1 ±0.4 (1.8 ±0.7) |
| Full wet suit (custom-fitted, 4.8-mm [0.19-inch] closed-cell foam that covers the extremities and the trunk) | 0.7 ±0.3 (1.3 ±0.5) |
| **"Dry" Design** | |
| Immersion suit (loose-fitted, 4.8-mm [0.19-inch] closed-cell foam with sealed openings) | 0.5 ±0.3 (0.9 ±0.5) |

From Steinman AM, Hayward JS, Nemiroff MJ, et al: Immersion hypothermia: Comparative protection of anti-exposure garments in calm versus rough seas, *Aviat Space Environ Med* 58:550, 1987.
*SD*, Standard deviation.

**TABLE 8-3** Comparison of Mean Cooling Rates for Thin Men (Mean Body Fat = 9.1%) Wearing Various Types of Protective Clothing in Calm Water at 11.8°C (53°F)

| Clothing Type | Mean Cooling Rate Given as °C/hr (°F/hr) | Ratios as Compared with Control | |
|---|---|---|---|
| | | Direct | Inverse |
| Dry, closed-cell foam insulation (4.8-mm [0.19-inch] thick) | 0.31 (0.56) | 0.14 | 7.35 |
| Wet, closed-cell foam insulation (4.8-mm [0.19-inch] thick) | 0.54 (0.97) | 0.23 | 4.26 |
| Dry and uninsulated (watertight shell over lightweight clothing) | 1.07 (1.93) | 0.47 | 2.15 |
| Control (lightweight clothing alone) | 2.3 (4.14) | 1 | 1 |

From Hayward JS: Design concepts of survival suits for cold-water immersion and their thermal protection performance. In *17th symposium of the SAFE (Survival and Flight Equipment) Association*. Van Nuys, Calif. 1979.

Figure 8-16 shows a comparison of cooling rates for lean males dressed in the various types of protective clothing shown in Figure 8-15 in both calm and rough waters at approximately 10°C (50°F).[158] The most dramatic differences occurred in the loose-fitted "wet" protective clothing (e.g., float coat, insulated coveralls), where cooling rates almost doubled in rough seas compared with those seen in calm seas. This was primarily caused by the flushing of cold water through the garments. However, even the tight-fitted full "wet" suit allowed for a 30% faster cooling rate in rough water than that seen in calm water. The "dry" suit, which did not leak, showed no significant difference between calm and rough seas.

Estimated survival times in rough seas, on the basis of experimental data, were published for thin males wearing different


**FIGURE 8-15** Antiexposure garments. **A,** Float coat. **B,** Aviation coveralls with personal flotation device. **C,** Boat-crew coveralls or snowmobile suit. **D,** Short wet suit worn as an undergarment. **E,** Full wet suit with personal flotation device. **F,** Insulated dry suit. **G,** Immersion suit. The garments in **A, B,** and **C** are loose-fitting, closed-cell, foam-insulated wet suits. The garments in **D** and **E** are tight-fitting, closed-cell, foam-insulated wet suits. The garments in **F** and **G** are closed-cell, foam-insulated dry suits.

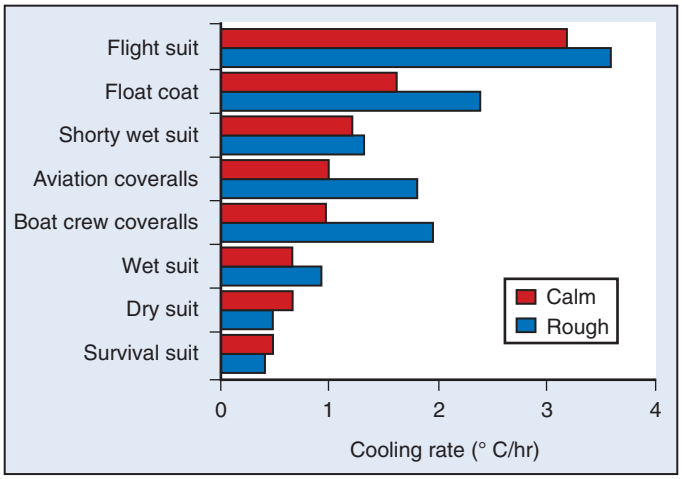



**FIGURE 8-16** A comparison of mean rectal temperature cooling rates in lean male subjects in calm versus rough seas at 10.7° C (51.3° F). The flight suit, when used as a control garment, is equivalent to lightweight clothing. *(From Steinman AM, Hayward JS, Nemiroff MJ, et al: Immersion hypothermia: Comparative protection of anti-exposure garments in calm vs rough seas,* Aviat Space Environ Med *58:550, 1987.)*

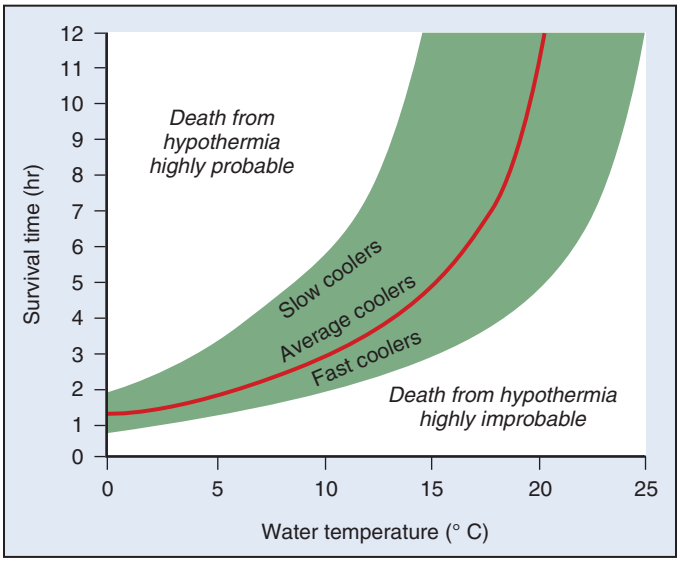



**FIGURE 8-17** Predicted calm-water survival time (defined as the time required to cool to 30° C [86° F]) in lightly clothed, nonexercising persons in cold water. The graph shows a line for the average expectancy and a broad zone that indicates the large amount of individual variability associated with different body sizes, builds, fatness levels, physical fitness levels, and states of health. The zone would include approximately 95% of the variations expected for adults and teenagers under the conditions specified. The zone would be shifted downward by physical activity (e.g., swimming) and upward slightly for heavy clothing or protective behaviors (e.g., huddling with other survivors, adopting a fetal position in the water). Specialized insulated protective clothing (e.g., a survival suit or wet suit) is capable of increasing survival time from 2 to 10 times (or more) the basic duration shown here. For the zone in which death from hypothermia is highly improbable, cold shock on initial immersion can potentiate death from drowning, particularly for those who are not wearing flotation devices. *(From the U.S. Coast Guard: Addendum to the National Search and Rescue (SAR) Manual, COMDTINST M16120.5 and M16120.6, 1995.)*

types of protective clothing in 6° C (42.8° F) water.[159] Table 8-4 shows these times for three different levels of survival. Underlying these estimations are the following assumptions:

1. Cooling rates are linear.[89,158,159,163]
2. Initial $T_{co}$ is 37.5° C (99.5° F).
3. Survivors are able to maintain airway freeboard until unconsciousness occurs at a rectal temperature of 30° C (86° F).
4. Self-righting flotation maintains airway freeboard when survivors are unconscious.

When comparing these estimated survival times with those of Figure 8-17 (i.e., calm-water survival times), the reader must recall that Figure 8-17 concerns only survival to a $T_{co}$ of 30° C (86° F). Furthermore, the zone in the graph must be adjusted downward for rough seas and for survivors wearing only lightweight clothing, and it should be adjusted upward for survivors wearing insulated clothing. For 6° C (42.8° F) water, the survival times (to a $T_{co}$ of 30° C [86° F]) correlate well between Figure 8-17 and Table 8-4. We must emphasize that the estimates in Table 8-4 pertain to lean individuals with a mean body fat level of only 11.1%. Because many populations of adults (e.g., offshore oil workers) in the 30- to 50-year-old range average 25% to 30% body fat, the estimates of "time to unconsciousness" and "time to cardiac arrest" must be considered conservative for a broader spectrum of adults.

A recent video production called *Cold Water Boot Camp* (Video 8-6) tested various flotation ensembles, including closed-cell and inflatable PFDs, heavy dry suits, and lighter extended-wear (paddling) dry suits. Figure 8-18 schematically shows that $T_{co}$ and survival time decrease as the amount of thermoprotection and flotation decreases (Box 8-4).

**TABLE 8-4** Estimated Survival Times for Lean Persons (Mean Body Fat = 11.1%) Wearing Various Types of Protective Clothing in Rough Seas

| Clothing Type | Time to Incapacity (hr) (T = 34° C [93.2° F]) | Estimated Survival Time (hr) (95% CI) | |
|---|---|---|---|
| | | Time to Unconsciousness (hr) (T = 30° C [86° F]) | Time to Cardiac Arrest (hr) (T = 25° C [77° F]) |
| Control (lightweight clothing) | 0.4-1.3 | 0.8-2.6 | 1.3-4.3 |
| Torn, non–foam-insulated, dry coveralls (50.8 mm [2-inch] tear in left shoulder) | 0.9-2.7 | 1.6-5.2 | 2.5-8.4 |
| Closed-cell foam-insulated, wet coveralls (3.2-mm [0.13-inch]–thick insulation in loose-fitted coveralls) | 1-2.9 | 1.9-6 | 3-9.9 |
| Closed-cell foam-insulated, custom-fitted wet suit (4.8-mm [0.19-inch]–thick insulation; tight-fitted) | 1.6-4.7 | 3.1-9.9 | 4.9-16.2 |
| Intact, non-foam–insulated, dry coveralls (watertight shell over thick, fiberfill, insulated underwear) | 2.9-8.8 | 5.7-18.2 | 9.1-30 |

From Steinman AM, Kubilis P: *Survival at sea,* report no CG-D-26-86, US Coast Guard. 1986, National Technical Information Service.
*CI,* Confidence interval; *T,* temperature.

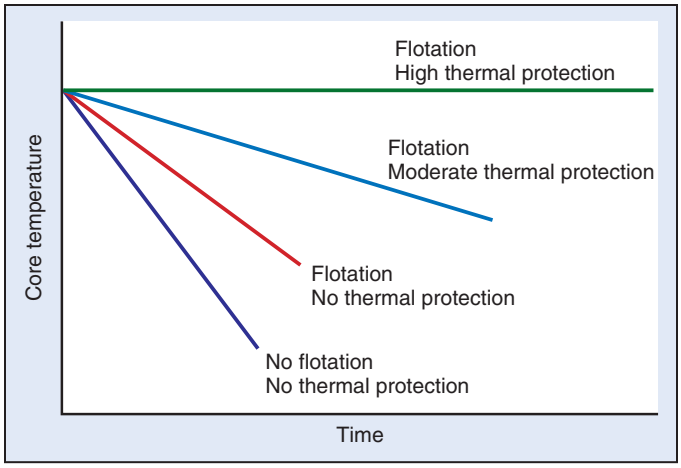



**FIGURE 8-18** Schematic estimation of core temperature and survival times with varying flotation devices and thermal protective clothing.

**BOX 8-4 Controversy Box: Flotation Clothing Impedes Escape from Submersed Vehicles**

In many winter road jurisdictions, workers are mandated to wear thermoprotective flotation jackets or overalls. Some workers resist wearing this clothing because of fears that clothing buoyancy may impede exit by forcing the occupant upward against the roof of the vehicle, and that increased bulk may impede passage through a window or hatch. Flotation jackets or overalls do not pose an exit threat and should be considered safe for ice road use. Inflatable PFDs have been considered as an option, but because they may be inflated prematurely before exit, PFDs might impede exit and are not recommended for vehicle use in any situation.[59]

## BODY MORPHOLOGY (SIZE AND COMPOSITION)

Children cool faster than adults because children have a greater surface area–to–mass ratio. The *rate* of heat loss is generally proportional to surface area, whereas the *amount* of heat that can be lost is proportional to mass. Thus, a large surface area–to–mass ratio favors cooling. Similarly, smaller adults generally cool faster than larger adults, and tall, lanky individuals cool faster than short, stout individuals. Body composition is also important. Subcutaneous fat is a very efficient insulator against heat loss, and cooling rate is inversely related to skinfold thickness. For example, persons in the 10th percentile for skinfold thickness and mass wearing light clothing in 5° C (41° F) water have nine times the core cooling rate of those in the 90th percentile for skinfold thickness and mass.[132] Figure 8-19 shows the linear relationship between change in $T_{co}$ and mean skinfold thickness.[101] Shivering, which is a primary defense against $T_{co}$ cooling, also varies with skinfold thickness. At a given skin temperature, the shivering response is less in persons with greater amounts of subcutaneous fat.[108] In moderately cold water temperatures (18° to 26° C [64.4° to 78.8° F]), $T_{co}$ cooling has been shown to proceed at the same rate in high- and low-fat individuals because of greater shivering thermogenesis in the low-fat group. However, at colder water temperatures (8° C [46.4° F]), $T_{co}$ cooling is attenuated by greater amounts of subcutaneous fat and body mass as a result of increased insulation.[53]

In general, for a survivor who is immersed in cold water, the $T_{co}$ cooling rate is fairly linear after $T_{co}$ begins to decline. This has been shown to be true for mildly hypothermic experimental participants. The only data that exist for severely hypothermic humans are those from the infamous Dachau concentration camp atrocities, in which conscious victims were inhumanely cooled to death in ice water.[2] Because these unfortunate victims were emaciated and ill, these data do not apply to healthy, cold-water immersion volunteers and should be considered atrocious.

The advantage of body fat as an insulator against cold is discussed earlier. With the use of an extrapolation of a linear cooling rate to 30° C (86° F), Figure 8-17 shows predicted calm-water survival times of lightly clothed, nonexercising individuals in cold water. The graph shows a line for the average survival expectancy. A broad zone indicates the large amount of individual variability associated with different body sizes, builds, and degrees of fatness. The zone would include approximately 95% of the variation expected for adults and teenagers under the conditions specified. For the zone in which death from hypothermia is highly improbable, cold water still potentiates death from drowning as a result of cold shock (as discussed previously) during the first few minutes of immersion, especially for those who are not wearing PFDs. Again, importantly, Figure 8-17 discusses only calm-water survival times. Because rough-water conditions decrease survival times, as discussed later, Figure 8-17 may be useful for estimating maximum survival times for an individual who is immersed in cold water. Search and rescue organizations might find such a maximum survival time helpful, because they often use the longest possible survival time to decide when to terminate a search effort.

## AMOUNT OF BODY IMMERSED

Because of the difference in thermal conductivity between air and water (as discussed previously), heat loss from body surfaces immersed in cold water is much greater than from body surfaces exposed to cold air, even considering the effect of windchill. Thus, immersed victims should attempt to get as much of their bodies out of the water as possible (Figure 8-20) (see Cold-Water Survival, later).

## HEAD IMMERSION

Exposure of the dorsal head to cold water may increase a survivor's rate of cooling and adversely affect mental performance. Survival may depend on the ability to conduct multiple tasks to avoid drowning and hypothermia. The ability to carry out these tasks involves both physical components, which are affected by local muscle and nerve temperature,[63] and mental components,

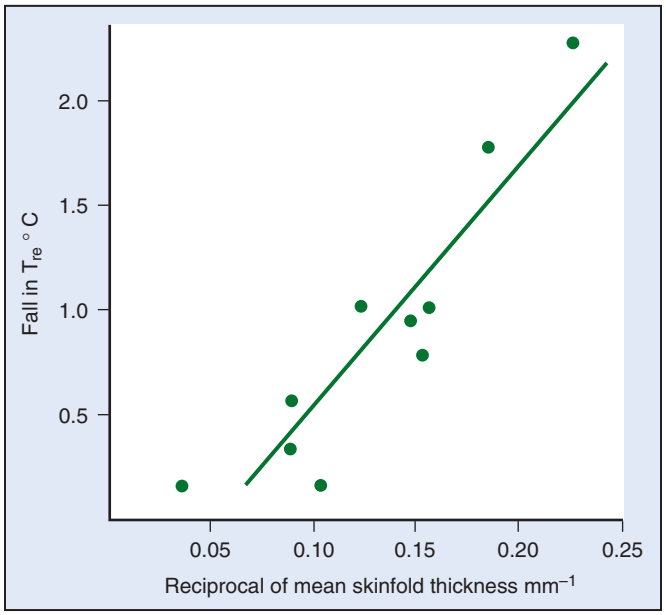



**FIGURE 8-19** Relationship between subcutaneous fat thickness in 10 men and the decline in rectal temperature during 30-minute immersions in stirred water at 15° C (59° F). Skinfold thickness is given as a mean of readings at the biceps, the abdomen, and subscapular and subcostal sites. $T_{re}$, Rectal temperature. *(From Keatinge WR:* Survival in cold water, *ed 2, Oxford, 1969, Blackwell Scientific Publications.)*

**FIGURE 8-20** Nick Schuyler sitting atop an overturned boat, awaiting rescue. He survived for 43 hours in 18°C (64°F) water, whereas his three companions perished after 13 to 25 hours. His position on top of the boat decreased his heat loss, and his bright-colored jacket and keyhole personal flotation device resulted in him being seen by U.S. Coast Guard personnel. *(Courtesy U.S. Coast Guard.)*

which are affected by brain temperature;[50] both may be adversely affected by hypothermia.

Head immersion has traditionally been of concern in survival situations.[69] In the absence of water in the airways, heat is lost through the head either through *convection* (heat loss from the blood that perfuses the scalp) or *conduction* (direct heat loss through bone and soft tissue).[206] One hypothesis predicts substantial heat loss through the head because of abundant scalp vascularity and because the scalp vasculature does not vasoconstrict in response to cold as do superficial blood vessels in other body areas.[45] Alternatively, heat loss from the back of the head might be minimal, because dorsal head and neck immersion would only involve an additional 3% to 5% of the body surface area.[107] In addition, conductive heat loss directly through the scalp and skull is likely to be minimal.[206]

A few studies have addressed the head cooling of animals in water[22] or of humans in cold air,[45,139] but only one human study has included cold-water exposure of the head. Alexander[2] reported the data regarding head cooling from studies carried out on prisoners of war in Dachau during World War II. These studies were horrific, reprehensible, and grossly unethical, and the results are considered invalid and unusable because of the emaciated condition of the prisoners as well as questions regarding the protocol and accuracy of the results.

Few experimental data are available to evaluate the effects of mild hypothermia on mental performance. A few medical studies have evaluated the impairment of memory among divers during cold-water dives.[9,190,193] Two other studies involved cognitive testing during hypothermia without direct head cooling.[19,50]

Lockhart and colleagues[111] evaluated the effects of dorsal head and neck immersion among human volunteers immersed in 10°C (50°F) water on $T_{co}$ cooling rates and mental performance. Dorsal head and neck immersion (with the body insulated) resulted in a cooling rate of 0.4° ±0.2°C/hr (0.7° ±0.4°F/hr). Body immersion with the head, neck, and upper thorax out of the water resulted in a cooling rate of 1.5° ±0.7°C/hr (2.7° ±1.3°F/hr). Immersion of both the whole body and the dorsal head and neck nearly doubled the cooling rate to 2.8° ±1.6°C/hr (5.0° ±2.9°F/hr) ($p$ <0.0002). In addition, there were significant correlations between diminished cognitive performance and decreasing $T_{co}$. The time required to complete correctly the Stroop Color-Word Test increased as $T_{co}$ decreased ($p$ <0.001). The number of correct responses decreased with $T_{co}$ for digit symbol coding ($p$ <0.02), backward digit span ($p$ <0.05), and paced auditory serial addition testing ($p$ <0.05). Figures 8-21 to 8-30 demonstrates the effects of different PFDs on the position of the head in water.

Giesbrecht and co-workers[46] repeated the head-cooling study with participants immersed in 12°C (53.6°F) water whose shivering thermogenesis had been inhibited with intravenous meperidine to model severe hypothermia.[67] When the body was insulated, there was no $T_{co}$ cooling with the head out of the water, and immersing the dorsum of the head had no further effect. However, when the body was not insulated but instead exposed to the cold water, $T_{co}$ decreased at 3.6°C/hr (6.5°F/hr). In this condition, also immersing the dorsum of the head significantly increased the rate of $T_{co}$ cooling to 5.0°C/hr (9°F/hr) (Figure 8-31).

These results did not confirm the supposition of proportionately greater heat loss from the head. The measured heat loss

**FIGURE 8-21** Effectiveness of various types of personal flotation devices for keeping the head and the upper chest out of the water. *Top left,* Type I jacket; *top right,* type 3 jacket; *bottom left,* typical keyhole inflatable jacket; *bottom right,* waist-mounted inflatable device. *(Courtesy Gordon G. Giesbrecht.)*

**FIGURE 8-22** Lead investigator testing head cooling during a submersion study to assess the relative contributions of the head and body to core-temperature decline in cold water.

**FIGURE 8-23** Lead investigator assessing participant in dorsal head and body immersion study in cold water.

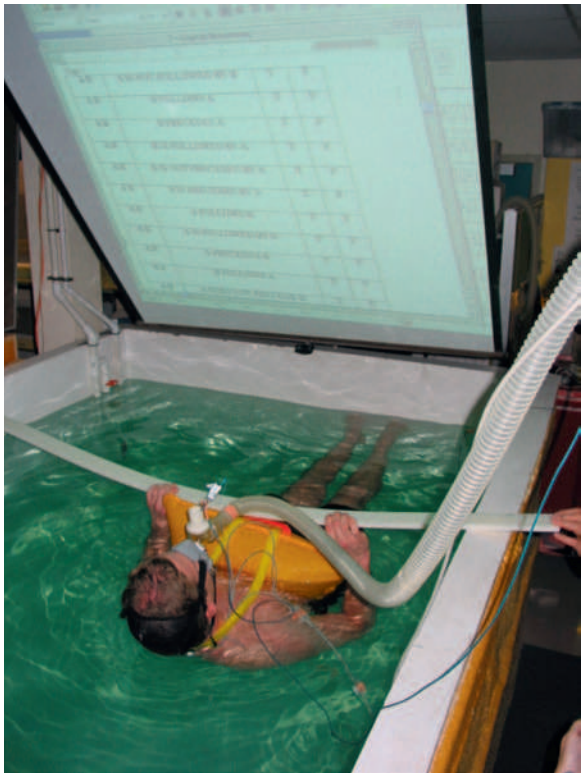


**FIGURE 8-25** Cognitive function testing in a participant wearing a prototype inflatable personal flotation device in a study to assess the relative contributions of the dorsal head and the body to core-temperature decline and cognitive function in cold-water immersion.

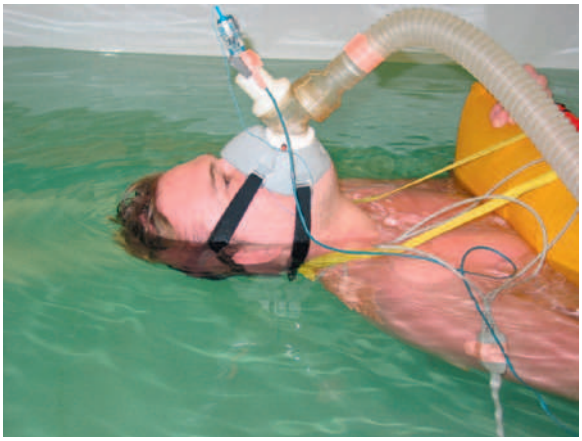


**FIGURE 8-24** Participant testing prototype inflatable personal flotation device in a study to assess the relative contributions of the dorsal head and the body to core-temperature decline and cognitive function in cold-water immersion.

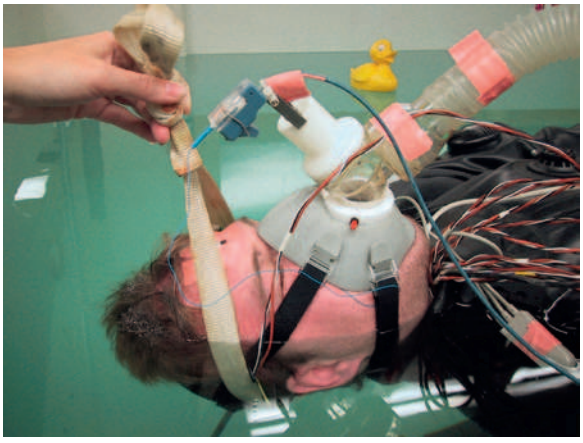


**FIGURE 8-26** Dorsal head–only immersion in a study to assess the relative contributions of the dorsal head and the body to core-temperature decline and cognitive function in cold-water immersion. The participant is wearing a full-body dry suit so that only his dorsal head is exposed to the cold water. Core temperature from the esophageal site, skin temperatures, oxygen consumption, and carbon dioxide production are being measured.

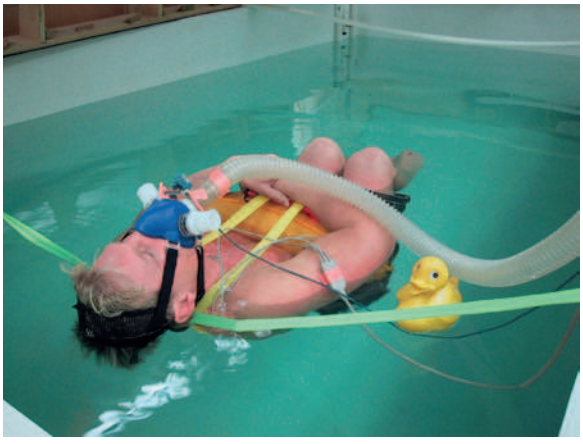


**FIGURE 8-27** Participant adopting the heat escape lessening position (HELP) while wearing a prototype inflatable personal flotation device in a study to assess the relative contributions of the dorsal head and the body to core-temperature decline and cognitive function in cold-water immersion.

**FIGURE 8-28** Investigator testing the flotation posture of a prototype inflatable personal flotation device in an "unconscious" survivor.

**FIGURE 8-29** Participant emerging from cooling tank after a dorsal head, full-body immersion in a study to assess the relative contributions of the dorsal head and the body to core-temperature decline in cold water. Note the peripheral vasodilation. Participant's core temperature was 34°C (93.2°F).

from the head in both head-immersed conditions was only about 60 kilojoules (kJ) compared with 18 kJ to 33 kJ in the two head-out conditions. By contrast, total body heat loss in the body-exposed configurations was about 1100 kJ and 1260 kJ, respectively, for head-out and back-of-the-head-in conditions. Thus, the head accounted for only about 3% and 5% of the total body heat loss, respectively, in the body-exposed conditions. The majority of the difference in heat loss in the body-immersed conditions came from immersion of the anterior thorax rather than from the dorsal head and neck. Nevertheless, it is important to recognize that, although no significant increase occurred in heat loss through the head, there was a disproportionate increase in $T_{co}$ cooling. The mechanisms for this disparity have not yet been determined, but the implications are clear for manufacturers and survivors. During long-term cold-water immersion, it is advantageous to keep the head out of the water. If this is not possible (i.e., most survival suits place the victim in a supine position), the survival ensemble should include a hood with as much insulation as practical (Box 8-5).

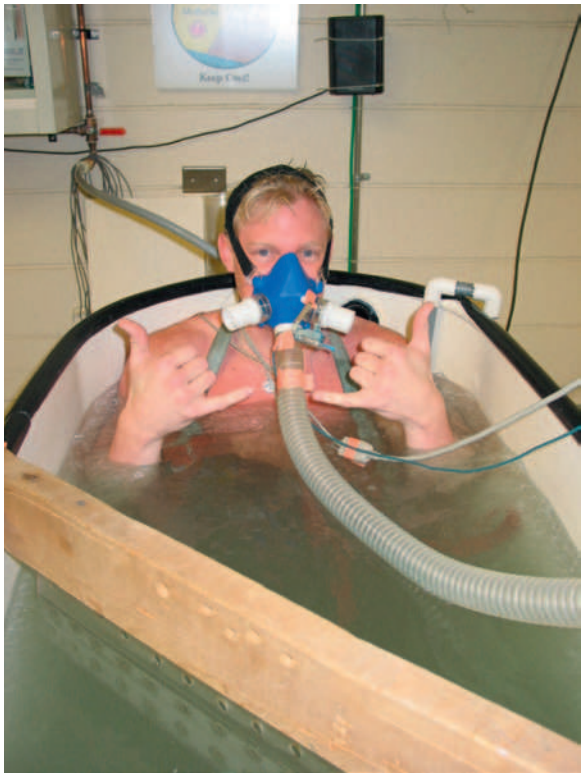


**FIGURE 8-30** Participant rewarming in a circulating warm-water bath in a study to assess the relative contributions of the dorsal head and the body to core-temperature decline and cognitive function in cold-water immersion.

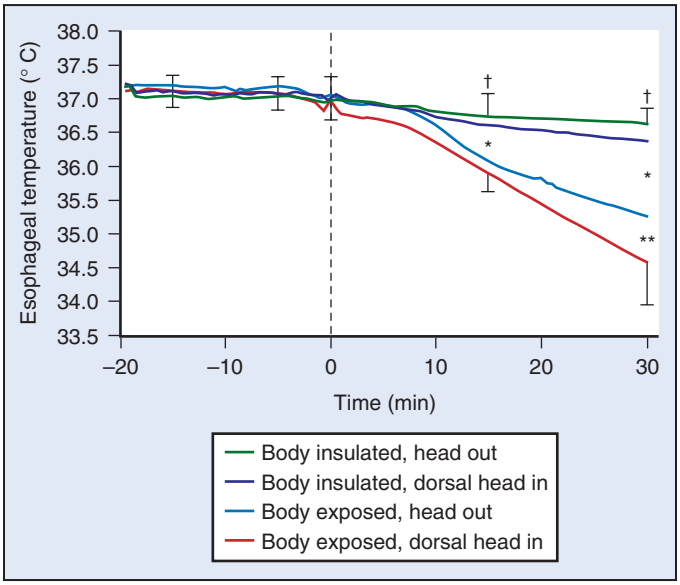



**FIGURE 8-31** Core-temperature response to immersion in 12°C (54°F) water with the head out or the dorsum immersed in body-insulated and body-exposed conditions; shivering was inhibited with meperidine to mimic a severely hypothermic, nonshivering victim. Error bars = standard deviation. *(From Giesbrecht G, Lockhart T, Bristow G, et al: Thermal effects of dorsal head immersion in cold water on non-shivering humans,* J Appl Physiol *99:1958, 2005.)*

**BOX 8-5 Controversy Box: You Lose Most of Your Heat Through Your Head**

This common belief has caused many incorrect and even dangerous actions, such as going to extreme lengths to retrieve hats or to removing clothing when immersed to place it on the head for thermal protection. In a cold-water immersion scenario, 90% to 95% of heat loss occurs through the cold-exposed body. It has been demonstrated that, under similar thermal stresses, relative heat loss from the head (per unit of surface area) is not that much higher than that from other areas of the body. However, under certain conditions, increased heat loss from the head can cause a disproportionate decrease in body core temperature. Thus, head contact with cold water should be minimized whenever possible by changes in posture and maximum practical insulation.

## BEHAVIOR AND POSTURE OF THE BODY IN COLD WATER

Behavioral variables also affect $T_{co}$ cooling rate. Hayward and colleagues[85] used infrared thermography to demonstrate that, despite marked peripheral vasoconstriction, heat losses are high in the groin, the lateral and central thorax, and the neck. In the groin and neck, which are regions with relatively thin layers of peripheral soft tissue, blood flow through the large and relatively superficial femoral vessels, carotid arteries, and jugular veins potentiates heat flow to the cold water. In the lateral and central thorax, the relative absence of tissue (muscle and subcutaneous fat) insulation in combination with the high thermal conductivity of rib bone potentiates heat loss from the relatively warm lungs to the cold environment. Furthermore, exercise or excessive movement in the water greatly increases heat loss from active muscles.

The effect of activity on total heat balance depends on the balance among the many factors illustrated in Figure 8-32. In normothermic circumstances, heat produced locally in peripheral muscles is transferred to the core by venous return. By contrast, during cold-water immersion, physical activity may actually increase heat loss through increased blood flow to the periphery. This is especially true when immersed victims engage in excessive movement in the water (e.g., swimming, performing the vigorous extremity movements that are necessary to maintain airway freeboard in rough seas).

Hayward and colleagues[86] demonstrated that minimizing both voluntary activity and exposure of major heat loss areas of the skin to cold water are the most effective ways to minimize a decline in $T_{co}$. They showed that treading water and drownproofing significantly increased the cooling rate. Despite increased metabolic heat production during exercise, the increased surface heat loss resulted in faster $T_{co}$ cooling during exercise in cold water. They also developed two well-known cold-water survival techniques: HELP and the group huddle (see Figure 8-8). These adaptive behaviors reduce $T_{co}$ cooling by 69% and 66% of that of control conditions, respectively.[82] When the sea is not calm, it may be difficult to perform the group huddle with complete thermal efficiency. However, other advantages of this position include the maintenance of group contact and morale. Sagawa and colleagues[145] concluded that the lowest water temperature in which humans could maintain normal $T_{co}$ by generating body heat through muscular activity is 25°C (77°F), although there may be individual variations.

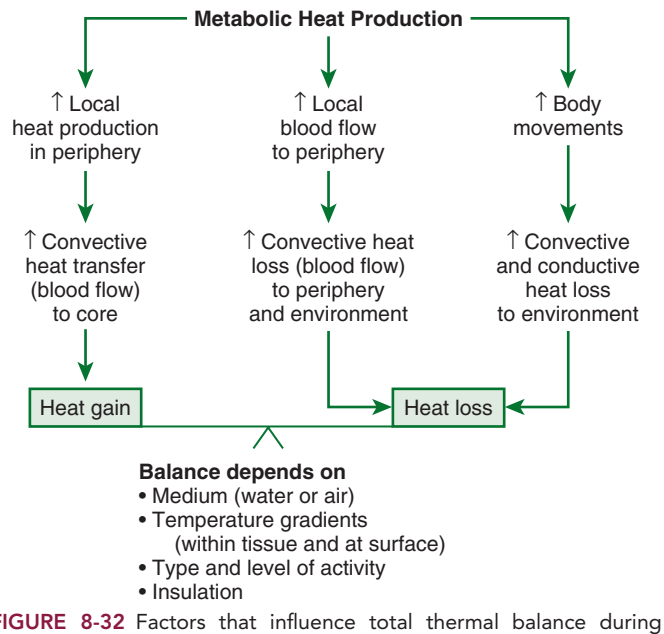



**FIGURE 8-32** Factors that influence total thermal balance during increases in metabolic heat production (i.e., voluntary exercise and involuntary shivering).

## EXERCISE

Normally, the advice is not to exercise while awaiting rescue in cold water. Although metabolic heat production will increase, exercise increases blood flow to muscles and causes increased heat loss to the water, with a net result of increased $T_{co}$ cooling. Færevik and colleagues[39] studied participants wearing neoprene survival dry suits in a wave tank with water temperature of 0°C (32°F) and air temperature of −5°C (23°F). When they remained still, $T_{co}$ dropped more during 3 hours of immersion than it did during 6 hours of immersion during which they performed leg exercises for 5 minutes every 20 minutes (Figure 8-33). Thus, if enough insulation is worn, the heat of exercise can be contained within the insulation, which attenuates the drop in $T_{co}$.

## SHIVERING

Shivering is a thermoregulatory function during which involuntary muscle contraction increases heat production in an effort to

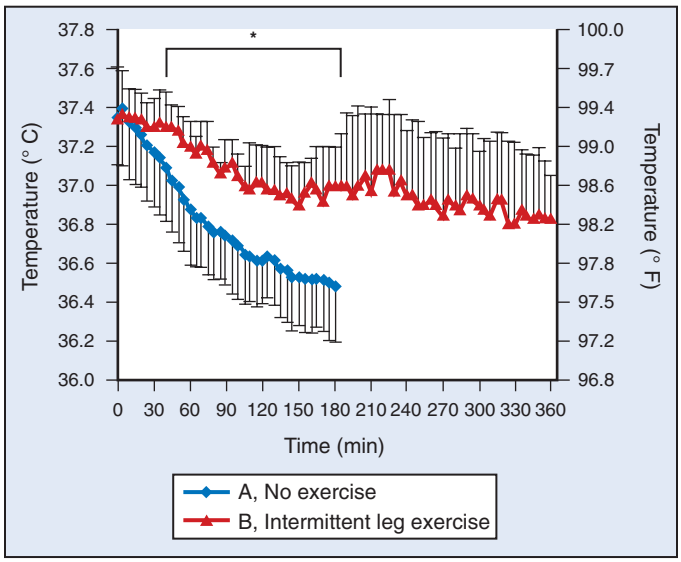



**FIGURE 8-33** Rectal temperature for six volunteers during immersion in 0°C (32°F) water and −5°C (23°F) air. *A*, No exercise, and *B*, intermittent leg exercise for 5 minutes every 20 minutes (mean ± standard deviation). Asterisk (*) indicates significantly higher rectal temperature in condition *B* compared with condition *A* from 40 to 180 minutes. Error bars = standard deviation. *(From Faierevik H, Reinertsen RE, Giesbrecht GG: Leg exercise and core cooling in an insulated immersion suit under severe environmental conditions,* Aviat Space Environ Med *81:1, 2010.)*

prevent or minimize $T_{co}$ cooling. Shivering intensity increases as $T_{co}$ and skin temperatures decrease. Generally, shivering intensity is maximal at a $T_{co}$ of 32° to 33°C (89.6° to 91.4°F) and a skin temperature of approximately 20°C (68°C). However, shivering heat production is lower at any given skin temperature among individuals with higher levels of subcutaneous fat.[108,199]

Thermal balance during shivering depends on the same factors as it does during voluntary activity (see Figure 8-32). Figure 8-34 illustrates how shivering heat production can maintain $T_{co}$ in cold air and how it can arrest the fall in $T_{co}$ in both cool and colder water. In colder water, the combination of shivering thermogenesis and body insulation (as a result of peripheral vasoconstriction) may result in maintenance of a steady-state $T_{co}$, although below normothermic levels. At even lower water temperatures, $T_{co}$ will continue to decrease. This decrease accelerates when shivering thermogenesis eventually stops as a result of hypothermia-induced thermoregulatory impairment (this occurs when $T_{co}$ ≤30°C [86°F]). The power of shivering is especially important during consideration of the clinical classification of hypothermia and rewarming therapies, because this valuable heat source is an efficient mechanism for rewarming the core during postimmersion recovery and resuscitation (see Rescue [Self-Initiated or Assisted] and Medical Management, later).

## NONTHERMAL FACTORS

Underwater divers often experience "symptomless" or "undetected" hypothermia. Several factors contribute to increased cooling. Heat is lost through direct conduction to cold water and through the breathing of compressed air. Breathing compressed air at depth alters human thermoregulation. Mekjavic and Sundberg[117] studied the effects of hyperbaric nitrogen at 6 atm;[117] these researchers also simulated inert gas or "nitrogen" narcosis with the inhalation of 30% nitrous oxide.[136] They demonstrated a

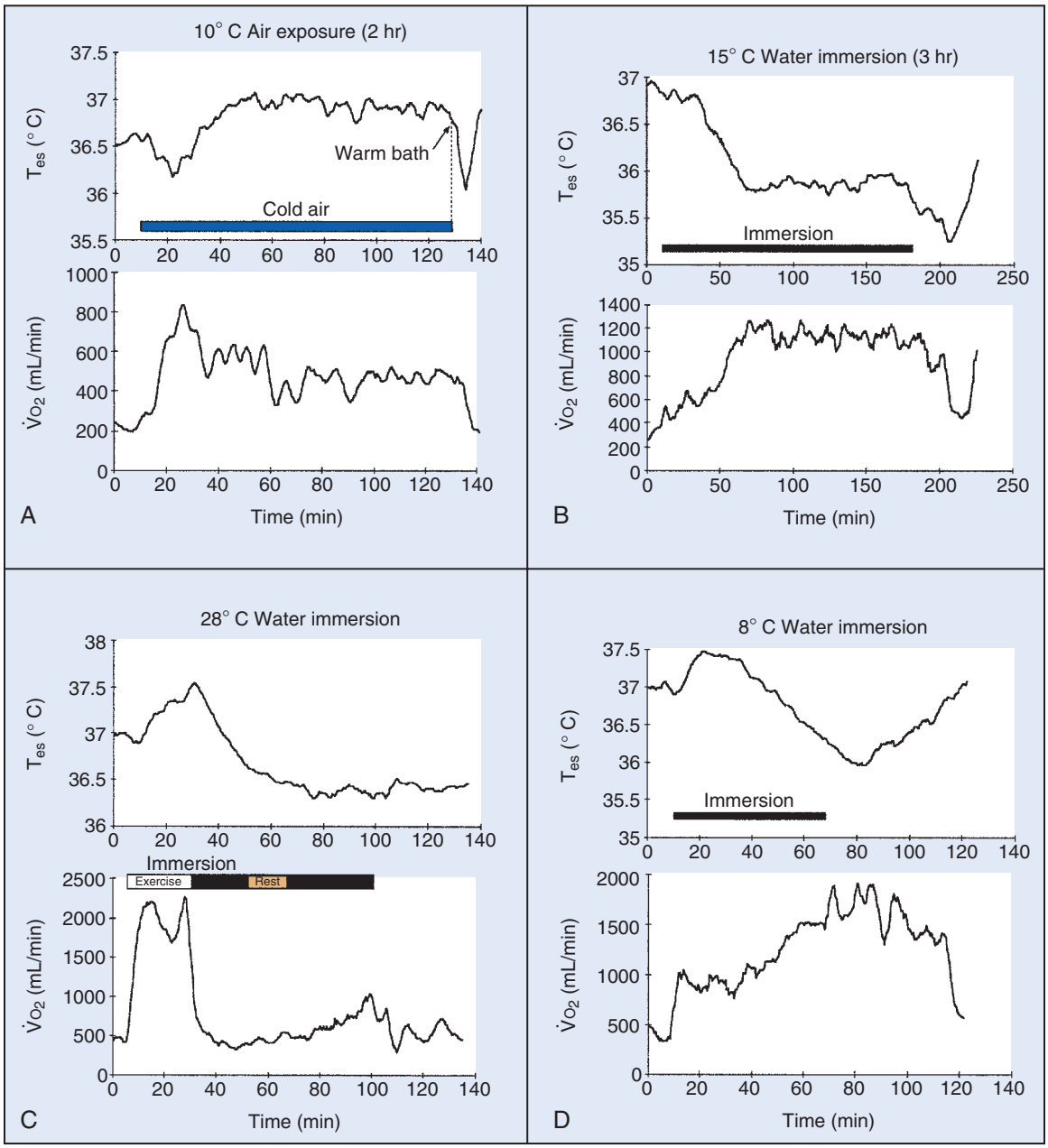



**FIGURE 8-34** Effectiveness of shivering heat production for preventing the onset of hypothermia during exposure to **A,** 10°C (50°F) air; **B,** 28°C (82°F) water; **C,** 15°C (59°F) water; and **D,** 8°C (46°F) water. $T_{es}$, Esophageal temperature.

decrease in the $T_{co}$ threshold for shivering and an increase in the rate of $T_{co}$ cooling of up to twofold under these conditions. In a separate study, this group demonstrated qualitatively similar effects of insulin-induced hypoglycemia.[137]

Hypercapnia and hypoxia may also be present in various underwater scenarios. Hypercapnia has been shown to lower the shivering threshold[94] and transiently inhibit shivering. Both hypercapnia[94] and hypoxia[95] have also been shown to accelerate $T_{co}$ cooling.

Alcohol consumption is frequently associated with immersion hypothermia, because ethanol impairment of mental and motor performance is often the cause of accidental immersion. Social drinking can result in carelessness. Intoxicated mariners or others near water often fall from a boat, ship, gangway, wharf, or bridge into the water. Drunken drivers capsize or collide. On the basis of the frequency of occurrence alone, the consequences of alcohol ingestion warrant special considerations.

Studies of the effects of moderate doses of ethanol (i.e., blood alcohol levels of 50 to 100 mg/dL, which is the range associated with legal impairment) on cold stress have established the following:

1. The rate of heat loss is not significantly increased. Alcohol has a primary vasodilatory effect under normothermic conditions.[38,83,100] Under hypothermic conditions, where vasoconstriction predominates, alcohol lowers the vasoconstriction threshold during the moderate cold stress of 28°C (82.4°F) water immersion, but does not affect the shivering threshold or the rate of $T_{co}$ cooling.[93]
2. The rate of heat production is slightly decreased. For immersion in water colder than 28°C (82.4°F), a moderate ethanol dose inhibits the metabolic response to cold.[42,115] Shivering thermogenesis is reduced in cold water by approximately 10% to 20%.
3. The cooling rate is not significantly increased.[42,93,115] Because the body's cooling rate in cold water is influenced more by the rate of heat loss than by the rate of heat production, the slight reduction in shivering thermogenesis induced by moderate ethanol ingestion is outweighed by factors that affect heat loss (e.g., peripheral vasoconstriction, body fat). Because these do not vary with alcohol use when the person is cold stressed, the cooling rate does not change.
4. Fatigue potentiates thermoregulatory impairment by alcohol. Exhaustive exercise leading to fatigue (which is characterized by hypoglycemia and the depletion of glycogen reserves) in combination with a moderate dose of ethanol significantly reduces resistance to cold.[78,96] Alcohol inhibits gluconeogenesis,[76,96] so the ability to provide glucose to maintain shivering is reduced. If a person enters cold water in this condition, his or her cooling rate is likely to be greater than in the absence of ethanol.
5. The perception of cold is diminished. Experimental studies of humans in cold water show that moderate alcohol dose to some extent relieves feelings of intense cold.[42,101] This cognitive alteration may be functionally related to the reduced shivering response.
6. Cold-induced diuresis is increased. Alcohol inhibition of antidiuretic hormone augments immersion diuresis.[26] During the first hour of cold-water immersion, the urine flow rate can be more than six times normal (i.e., up to approximately 8 mL/min). For longer immersions (>1 hour), alcohol potentiates the development of dehydration and hypovolemia.

For most humans, high doses of alcohol (i.e., blood level >200 mg/dL) have an anesthetic effect. Major impairment of mental, motor, and involuntary function (including thermoregulation) occurs. Alcoholic persons who "pass out" in cold locations (i.e., "urban hypothermia") rapidly and passively become hypothermic.[28,121] When highly intoxicated persons enter cold water (usually by falling in), hypothermia is seldom a problem, because such persons usually drown quickly.

# COLD-WATER SURVIVAL

Cold-water survival depends on avoidance of drowning and hypothermia and on the many factors related to these risks, including ability to control the cold shock response; ability to swim and maintain airway freeboard; availability and type of a PFD; availability of a life raft or other floating object to increase buoyancy; behavior of the survivor in water; decision to swim for shore or to wait for rescue; availability of signaling devices (e.g., whistles, flares, dye, smoke, strobe lights, radios, mirrors) and the ability to use them; and proximity of rescue personnel.[154,155,159]

## ABILITY TO CONTROL THE COLD SHOCK RESPONSE

As previously discussed, sudden immersion in cold water initiates a cardiorespiratory cold shock response that significantly potentiates the risk of drowning. This response and the resulting incapacitation have been suspected as the primary causes of drowning after short-term (<10 minutes) immersion in cold water.[165] Abrupt tachycardia and hypertension induced by sudden immersion in cold water can produce incapacitating cardiac dysrhythmias in susceptible individuals and myocardial infarction or cerebrovascular accident (stroke) in persons with arterial disease or hypertension.[165] In addition, reflex gasping and hyperventilation[165,174] significantly shorten the duration of breath holding.[84,88,165] Figure 8-35 illustrates this phenomenon. Loss of breath-holding capacity can have severe consequences for survivors attempting underwater egress from a submerged vehicle or from a capsized vessel or aircraft, or for survivors who are simply trying to maintain airway freeboard in a rough sea or white-water river.[88,144,169]

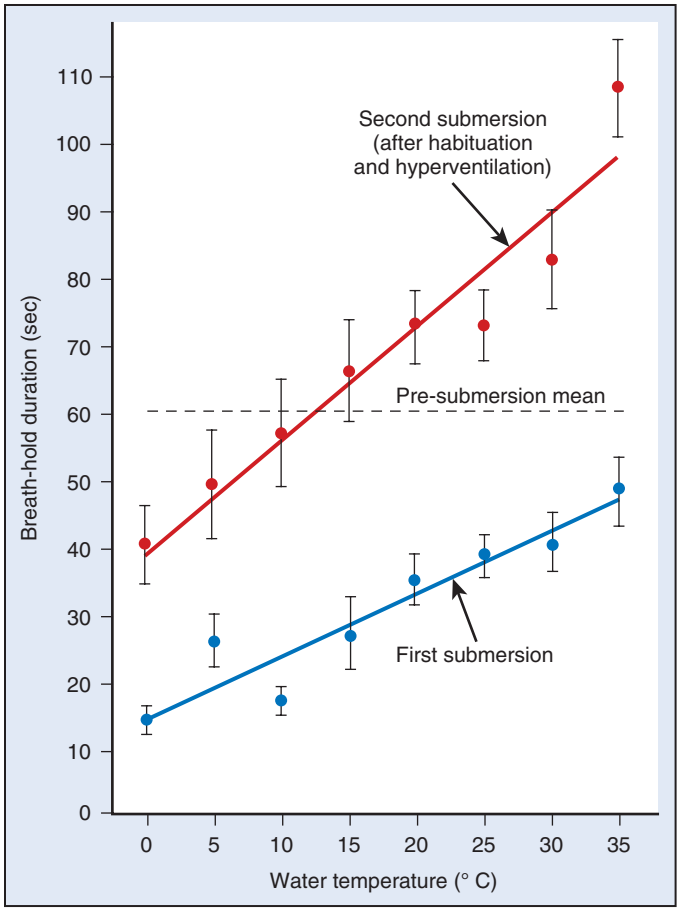



**FIGURE 8-35** Effect of water temperature on maximum breath-hold duration in young, physically fit participants (80 men and 80 women). The first submersion was sudden after sitting comfortably in air at a mean temperature of 11.3°C (52.3°F). The second submersion followed 2 minutes of acclimatization to the water. The last 10 seconds of the acclimatization was accompanied by 10 seconds of hyperventilation. Error bars = standard deviation. *(From Hayward JS, Matthews BR, Overweel CH, et al: Temperature effect on the human dive response in relation to cold-water near-drowning,* J Appl Physiol *56:202, 1984.)*

Respiratory difficulties induced by the cold shock reflexes make breathing while swimming extremely difficult. Golden and Hardcastle[70] have demonstrated "swim stroke/respiration asynchrony" that leads to water inhalation and swimming failure. Even persons who are considered good swimmers (at least in warm water) can only swim for a few minutes in cold water. Swimming ability and survival time in cold water are further diminished by the subjective perception of shortness of breath and panic reactions from unexpected cold-water immersion.[165] The work that is required to swim in cold water is greater than that in warm water because of cold water's higher viscosity (e.g., water at 4.7°C [40.5°F] has a viscosity that is 67% higher than that of water at 23.7°C [74.7°F]).[104] The increased work of swimming in cold water potentiates the onset of fatigue. All these factors combined may incapacitate even physically fit and capable swimmers. Keating and colleagues[104] observed sudden incapacitation in two experimental volunteers (both good swimmers) who were immersed in 4.7°C (40.5°F) water. One inhaled water because of respiratory difficulty and fatigue after swimming for 7.5 minutes and had to be pulled from the water. The second volunteer lasted only 1.5 minutes before he "floundered and sank without managing to reach the side of the pool, which was about one meter from his head, and had to be pulled" out of the water. The observed frequency of such swimming failures and unexpected submersions has led the USCG to coin the term "sudden disappearance syndrome" to describe the phenomenon.[178]

The magnitude of the cold shock response can be attenuated through increased insulation, graded immersion (see Figure 8-6), and habituation to cold immersion. Tipton and colleagues[171] demonstrated that habituating participants to 10°C (50°F) water resulted in a 16% reduction in respiratory rate during the first 30 seconds of immersion in 10°C (50°F) water and a 26% reduction in respiratory rate during the 30- to 180-second interval after immersion in 10°C (50°F) water. Tidal volume and heart rate response demonstrated similar declines in habituated individuals. Habituation through cold-water survival training may thus be an important safety measure for workers in cold-water environments.

Protective clothing also diminishes the cold shock response that occurs as a result of the initial immersion in cold water. Clothing (e.g., well-fitted wet suits, dry suits with adequate seals) that limits the amount and ingress velocity of water that reaches a person's skin significantly decreases cardiorespiratory reflex responses to sudden immersion.[118,172,173,175] Tipton and Golden[172] demonstrated that individuals wearing wet suits that protected the torso but that left the limbs exposed had significantly reduced respiratory reflex responses but not reduced heart rate responses, compared with controls with neither torso nor limbs protected. They concluded that the limbs may be more important than the torso with regard to the cardiac response to sudden cold-water immersion. Tipton and colleagues[173] also demonstrated that even loose-fitting and poorly insulated clothing can attenuate the magnitude of the cold shock response compared with immersion in swimming trunks only. When volunteers were immersed in 10°C (50°F) water wearing either conventional clothing or conventional clothing plus windproof/showerproof foul-weather clothing, cardiopulmonary and thermal responses were significantly less than those in individuals with swimming trunks alone.

Mental preparation should be used to avoid panic, to decrease emotional response, and to make a conscious effort to control breathing.

## ABILITY TO SWIM AND MAINTAIN AIRWAY FREEBOARD

Drowning is the most immediate survival problem after water entry. To maintain airway freeboard and to avoid drowning, a survivor must possess the physical skills and psychological aptitude to combat the effects of wave action.[155,169] Although a PFD assists with maintenance of airway freeboard, any combination of flotation posture and sea state in which water can enter the nose or mouth can lead to aspiration and possible drowning. If waves are present, it is usually necessary for a survivor to actively combat a potential loss of airway freeboard through effective swimming motion, something an unconscious survivor cannot do or a survivor at night cannot do if waves are not visible.[65,154,178] To reduce risk of drowning in rough seas, a survivor can increase effective airway freeboard by partially exiting the water (e.g., clinging to an overturned vessel or other debris floating in the water) or by climbing totally out of the water onto a life raft or a capsized vessel. In both these environments, the survivor may still have to cope with the effects of cold wind, spray, and waves (Figure 8-36; see also Figure 8-20).

## BEHAVIOR OF THE SURVIVOR IN THE WATER

Survivor location has a significant effect on $T_{co}$ cooling rate and survival time. The USCG and other rescue organizations recommend that a survivor of a maritime accident in cold seas get as much of his or her body out of the water as possible to minimize the cooling rate and maximize survival time.[159,178] This recommendation derives from the higher thermal conductivity of water compared with air at the same temperature. However, survivors who are exposed to cold air are still at risk from hypothermia as a result of convective, evaporative, and radiant heat losses. In a rough sea environment, wind increases the magnitude of convective heat loss, and spray and periodic wetting from breaking waves result in conductive heat loss.[162,164] Steinman and Kubilis[159] confirmed these observations. The cooling rates of thin male volunteers wearing different types of protective clothing were compared for three survival situations:

1. Immersion in 6°C (42.8°F) water with 1.5-m (4.9-foot) breaking waves.
2. Exposure to 7.7°C (45.9°F) air, continuous water spray at 6°C (42.8°F), continuous 28 to 33 km/hr (17.40 to 20.50 miles/hr) wind, and occasional breaking waves while sitting atop an overturned boat (see Figure 8-36).
3. Exposure to 7.7°C (45.9°F) air and occasional breaking waves while sitting in an open one-man life raft.

The results of the study are shown in Figure 8-37. For each type of garment worn, cooling rates were considerably faster in the water than atop the boat (despite the effects of wind, spray, and breaking waves) or within the raft.

These experimental conditions were tragically reproduced in real life for the four football players whose boat capsized in the Gulf of Mexico, as described previously. Only one of the men survived the heavy seas, high winds, and 18°C (65°F) water. He survived for 43 hours, primarily by exiting the water and sitting atop the capsized boat (see Figure 8-20). The other three men spent much more time immersed and wore less insulation; thus they cooled faster and perished (see Survival Modeling, later).

Survivors should attempt to lift as much of their bodies out of the water as possible, even if it means exposure to cold wind and spray. Even rescue and medical personnel who frequently work in wilderness environments poorly understand this recommendation. A widespread misunderstanding of the concept of windchill[128] causes many to conclude that survivors have higher heat losses if they are exposed to wind, especially if they are wet, than if they are immersed in water.[159] The term *windchill,* which was originally used by Siple and Passel[151] to describe the increase in heat loss from unprotected skin exposed to wind, is frequently used in the communication media without regard to the difference between exposed and unexposed skin. This leads many to believe erroneously that windchill temperature applies to both clothed and unclothed areas of the body. Furthermore, common experiences during recreational activities at the beach, lake, or swimming pool, where people subjectively feel colder after leaving the water (because of evaporative heat loss from the skin) than they do while swimming, reinforce this misunderstanding. This has occasionally led survivors to abandon a position of relative safety atop a capsized vessel and to reenter the water, usually with tragic results. The sensation of coldness, which is skin dependent, does not reliably convey information about rate of heat loss when two radically different environments (e.g., air and water) are compared.


**FIGURE 8-36** Testing protective clothing in rough seas: **A,** atop an overturned boat; **B,** in a one-person life raft; **C,** free swimming with only a personal flotation device. *(Courtesy Alan Steinman)*

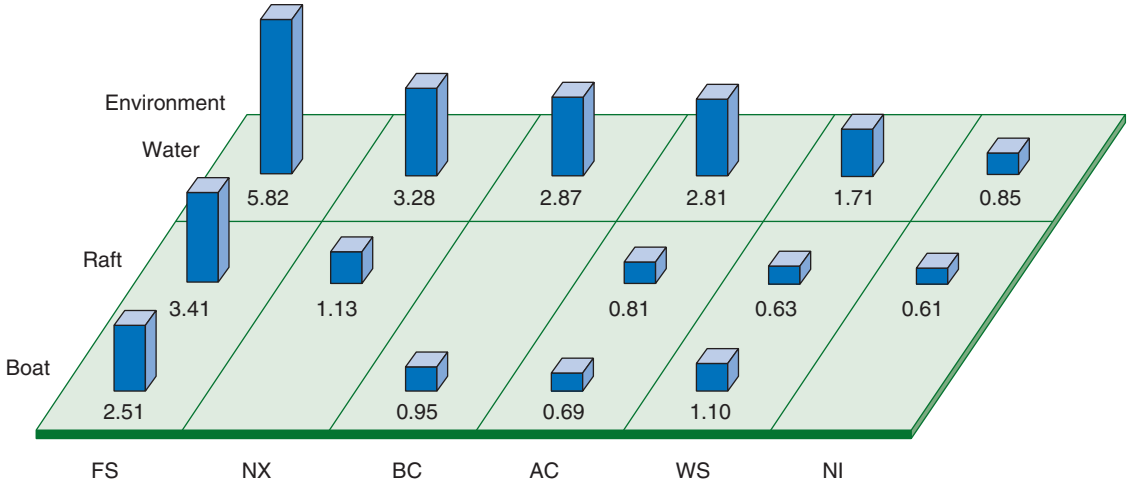



**FIGURE 8-37** Mean linear cooling rates (°C/hr) for lean males in three survival environments: (1) *water* = immersion in 6.1°C (43.0°F) breaking waves; (2) *boat* = 5-minute immersion in 6.1°C (43.0°F) water followed by exposure to 7.7°C (45.9°F) air atop an overturned boat with continuous 28 to 33 km/hr (17.4 to 20.5 miles/hr) wind, water spray, and occasional breaking waves; and (3) *raft* = exposure to 7.7°C (45.9°F) air in an open, one-man life raft preceded by 5-minute immersion in 6.1°C (43.0°F) water. *AC,* Air-crew coveralls; *BC,* boat-crew coveralls; *FS,* flight suit (lightweight clothing); *NI,* intact, non–foam-insulated "dry" coveralls; *NX,* NI with a 5-cm tear in the left shoulder, thus permitting water to leak into the suit and degrade its insulation; *WS,* wet suit. *Blank squares* indicate combinations of garments and environments that were not tested. *(From Steinman AM, Kubilis P:* Survival at sea: The effects of protective clothing and survivor location on core and skin temperature, *USCG Rep No CG-D-26-86, Springfield, Va, 1986, National Technical Information Service.)*

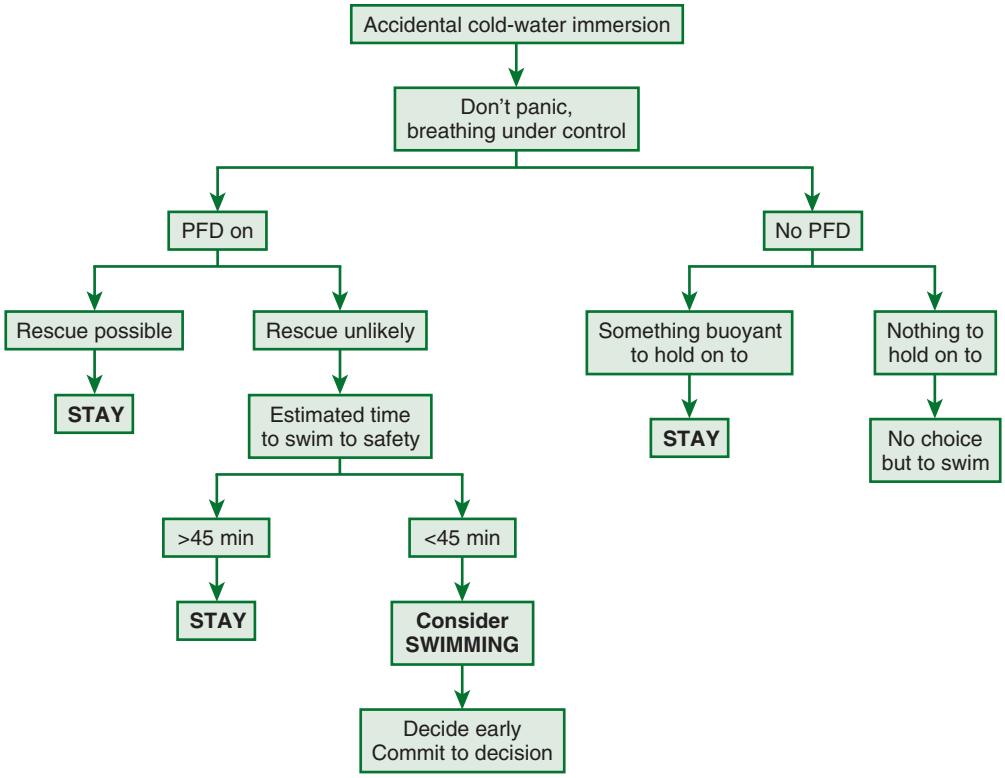



**FIGURE 8-38** Algorithm for making the decision to stay or swim when immersed in cold water. *PFD,* Personal flotation device.

## DECISION TO SWIM FOR SHORE OR TO WAIT FOR RESCUE

During cold-water immersion, physical activity increases heat loss through increased blood flow to the periphery. This is especially pertinent when immersed victims engage in excessive movement in the water (e.g., swimming, performing the vigorous extremity movements necessary to maintain airway freeboard in rough seas).

The decision to swim for shore or to wait for rescue is crucial for a survivor of cold-water immersion. The increased cooling rate associated with swimming might lead one to conclude that holding still is preferable to an attempt to swim for safety. However, if the survivor can make it to shore or even to shallow water, survival is likely to be prolonged, despite the risk of lower $T_{co}$. Ducharme and Lounsbury[32] specifically evaluated this issue by comparing the cooling rates and swimming distances for both novice and expert swimmers in a swimming plume. Experimental participants, who were wearing average clothing (i.e., no specific insulation against cold-water immersion) and PFDs, were immersed in 10°C (50°F) water and either remained still in a HELP position or swam against a current that was matched with their swimming ability. Swimming resulted in a 17% faster rate of $T_{co}$ cooling compared with holding still. The novice swimmers traversed about 800 m (2625 feet) and the expert swimmers about 1400 m (4593 feet) during their swim. Thus, swimming may well have allowed the participants to achieve safety ashore, despite the faster cooling rate. The researchers also found that the probability of a successful survival outcome depended on the decision to swim for safety early during a survival event. If the participants had cooled for 30 minutes before attempting to swim, the likelihood of success was significantly reduced.

The decision to swim or to remain still ultimately depends on the immersed individual's understanding of the many variables that affect a successful outcome, including body morphology and cooling rate; water temperature; wave conditions and currents; proximity of shore; proximity of rescue personnel; swimming ability; and availability of signaling devices, flotation devices, and protective clothing. There is no uniformly correct answer to the question, "Should I swim for it?" Each survival situation must be evaluated individually (Figure 8-38 and Box 8-6).

## SURVIVAL MODELING

When a rescue organization is tasked with searching for victims in cold water, it is important to have an accurate estimate of how long the victims might survive and thus continue to warrant search resources. Various prediction models have been devised to assist with these difficult estimates.

The Cold Exposure Survival Model was devised by Tikuisis[162,163] to provide a sophisticated set of survival-time estimates for individuals who are immersed in cold, rough seas and for survivors who are partially immersed or exposed to cold wind under wet conditions. The model was developed on the basis of experimental data about cooling with different types of flotation devices and thermal protective clothing (Figure 8-39),[158,159] shivering control and capacity,[38] body composition (Figure 8-40), and other factors.

The Cold Exposure Survival Model has been used for many years by both the Canadian and U.S. Coast Guards. Recently, the USCG started using a new decision tool: the Probability of Survival Decision Aid (PSDA), which was developed by Xu and

**BOX 8-6 Controversy Box: Always Stay with Your Boat**

For many scenarios in which warmer water temperature allows for longer survival and in which rescue is likely to occur, this is good advice. However, in colder water in secluded areas, the decision is not as clear, especially if rescue is unlikely. First, the decision to swim to safety should be made **only if the victim is wearing a personal flotation device,** if the likelihood of rescue is low, and if the victim can reach shore within 45 minutes. With a PFD, if swim failure occurs, the victim will still remain afloat. Without a PFD, swim failure will result in drowning (see Figure 8-38).

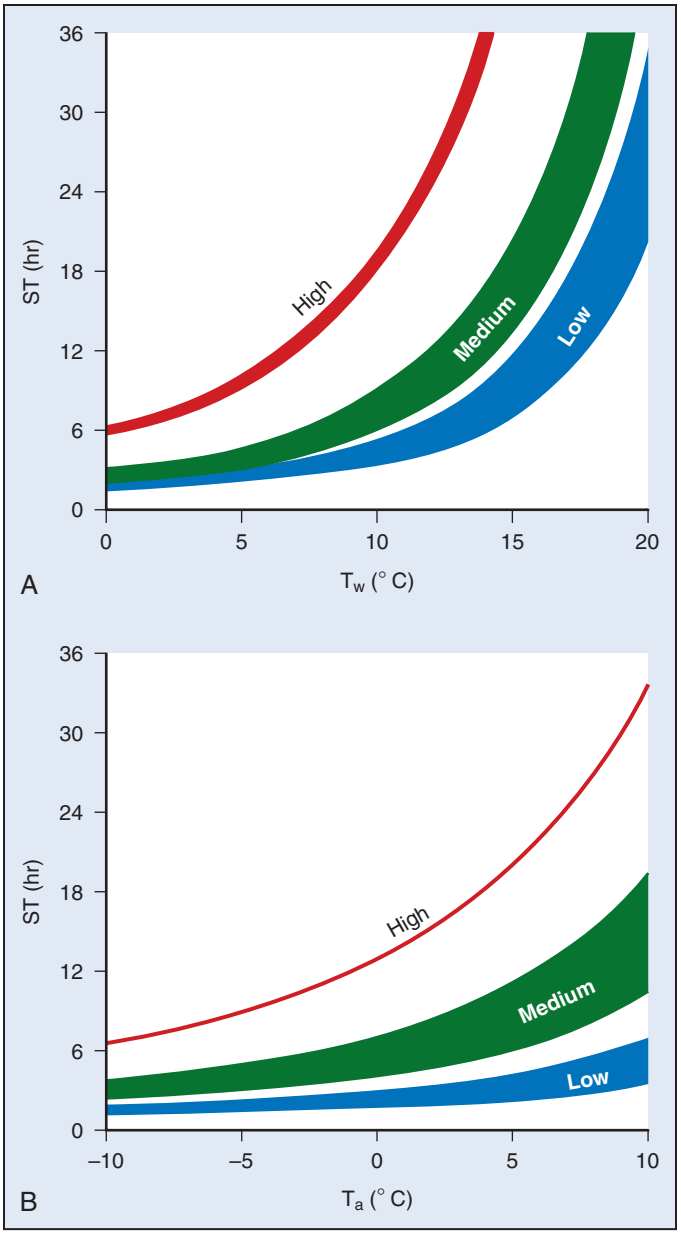



**FIGURE 8-39** Prediction of survival time *(ST)* for an average individual under varying degrees of clothing protection (see Figure 8-15). **A,** For immersion in rough seas versus water temperature, *low* = nude, flight suit, float coat, aviation coveralls, boat-crew coverall, or torn coverall); *medium* = short wet suit or full wet suit; and *high* = dry coverall or dry suit. **B,** For exposure to air at 20 km/hr (12.4 miles/hr) under wet conditions versus air temperature, *low* = nude, flight suit, or aviation coverall; *medium* = float coat, boat-crew coverall, short wet suit, full wet suit, dry coverall, or torn coverall; and *high* = dry suit. *(From Tikuisis P: Predicting survival time at sea based on observed body cooling rates,* Aviat Space Environ Med *68:441, 1997.)*

colleagues.[205] Although the Cold Exposure Survival Model is based on a one-cylinder model, which assumes that most heat loss comes from the torso in cold victims, the PSDA includes six cylinders that represent the head, torso, arms, hands, legs, and feet. For example, Figure 8-41 shows predicted survival times for victims in varying water temperatures. Presently, the PSDA predicts the time required for $T_{co}$ to drop to 34°C (93.2°F) (i.e., functional time) and to 30°C (86°F) (i.e., survival time).

When the PSDA was applied to the four football players whose boat capsized (as described previously in Recreational Activities and Cold Water), the survival-time predictions for the first and third fatalities (13.5 and 25.7 hours, respectively) were very close to the actual survival times of approximately 13.0 and 25.5 hours. The heaviest victim (the second fatality) died much sooner (13.5 hours) than was predicted (37.3 hours). However, his symptoms were much different and indicated that more than hypothermia was involved. Instead of the expected hypothermia-induced gradual loss of physical abilities and the expected level of mental abilities and responsiveness, he was very agitated and aggressive, and he vigorously and continuously tried to get away from the boat. He eventually took off his lifejacket and forcefully dove under the surface and drowned. Therefore, it is likely that some other factors also contributed significantly to his death. Because this victim spent so much more time immersed in the water than did the others, he may have ingested significant

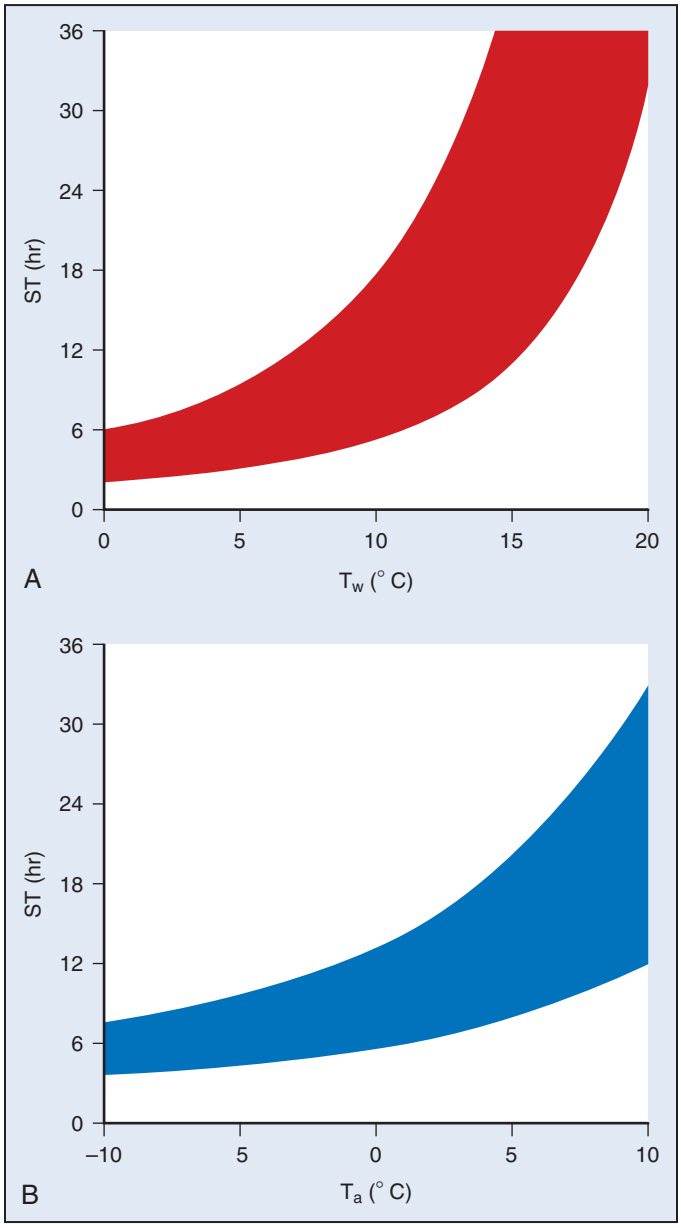



**FIGURE 8-40** Predicted survival time *(ST)* for individuals wearing boat-crew coveralls (see Figure 8-15) for **A,** immersion in rough seas versus water temperature; and **B,** exposure to air at 20 km/hr (12.4 miles/hr) under wet conditions (i.e., clothing wetness of 1550 g/m$^2$) versus air temperature. The lower and upper boundaries of the shaded regions represent predictions for lean and fat individuals, respectively. *(From Tikuisis P: Predicting survival time at sea based on observed body cooling rates,* Aviat Space Environ Med *68:441, 1997.)*

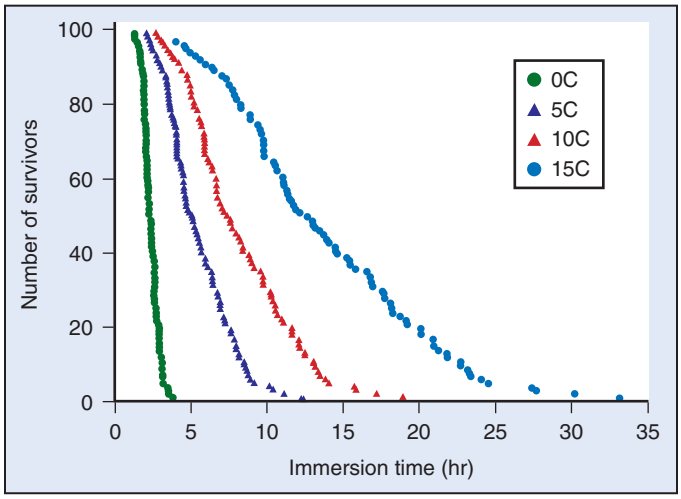



**FIGURE 8-41** Effect of water temperature on predicted number of survivors using the Probability of Survival Decision Aid. *(From Xu X, Amin M, Santee WR:* Probability of Survival Decision Aid (PSDA), *USARIEM Technical Report T08-05, Natick, Mass, 2008, US Army Research Institute of Environmental Medicine.)*

amounts of seawater; this was described and would be consistent with some of his actions and symptoms. The lone survivor lasted longer than predicted with a $T_{co}$ of approximately 32°C (89.6°F) after 43 hours; the PSDA predicted he would cool to 28°C (82.4°F) after 41 hours. Interestingly, at this point, he was still shivering vigorously, likely as a result of his excellent physical condition; normally he would have been expected to stop shivering many hours before rescue. This long-lasting and high-intensity shivering heat production would have a significant effect in attenuating the drop in $T_{co}$. Predictive modeling has many inherent complications, but the PSDA results indicate the value of modeling as well as of providing some insight into the thermophysiology and pathophysiology present during this epic struggle.

## SIGNALS

Effective signals can greatly increase the chance of survival by bringing rescue and shortening the duration required to survive. Figures 8-42 and 8-43 show various types of signals, including dye, smoke, group formations, streamers, and flares. One inherent signal can be the clothing that is worn. It is a great advantage to wear colorful PFDs or other colorful clothing. For example, USCG rescue personnel found Nick Schuyler after 43 hours of immersion in the Gulf of Mexico because of his bright-orange jacket (see Figure 8-20).

# PHYSIOLOGIC RESPONSES TO COLD-WATER SUBMERSION WITH THE HEAD UNDER WATER

Drowning is covered in detail in Chapter 69. However, a brief discussion is included here to provide a more complete description of cold-water immersion. There have been several recent advances in our understanding of why individuals can survive cold-water submersion for as long as 66 minutes[8] with full or partial neurologic recovery (i.e., cold-water drowning). The most important factors in these unusual cases are low water temperature and subsequent brain cooling. This principle has been used in clinical practice for years. For example, cardiopulmonary bypass used to cool neurosurgical patients to a $T_{co}$ of approximately 9°C (48.2°F) made it possible to arrest brain blood flow for at least 55 minutes, with full neurologic recovery.[135] The full explanation for these recoveries relates to both (1) the mechanisms for and amounts of brain and body cooling and (2) the mechanisms for the protective effect of this cooling.

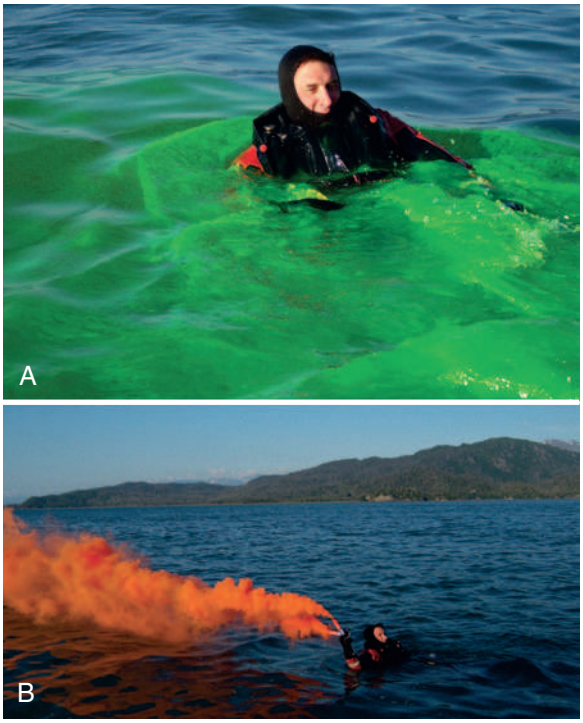



**FIGURE 8-42** Dye marker **(A)** and smoke flare **(B)** signals. *(Courtesy Gordon G. Giesbrecht.)*

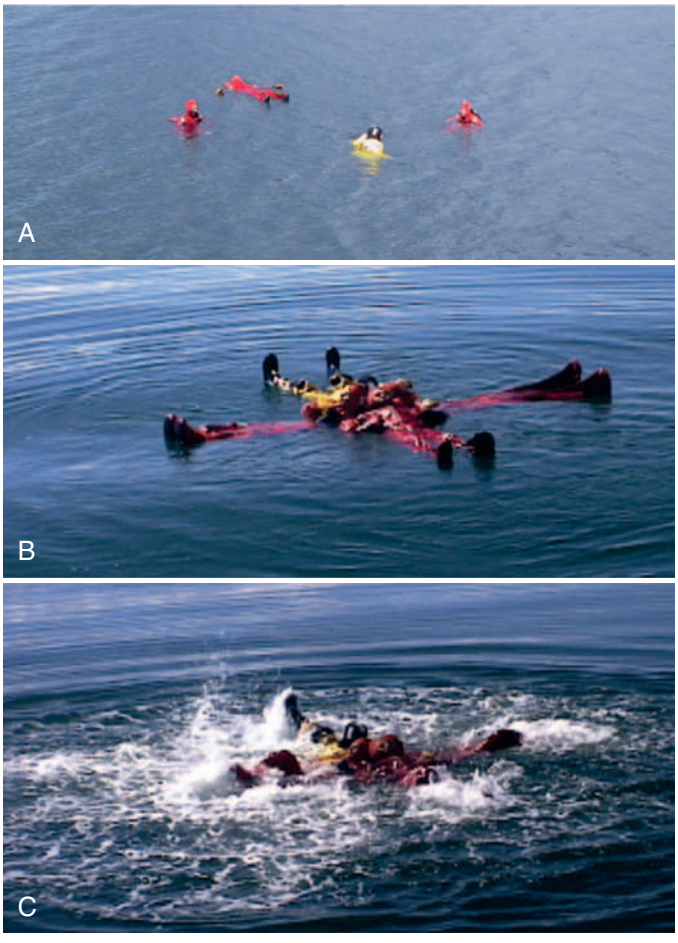



**FIGURE 8-43** Differences in visibility in water based on suit color **(A)** and whether a group is stationary in a star formation **(B)** or kicking the legs **(C).** *(Courtesy Gordon G. Giesbrecht.)*

## MECHANISMS FOR BRAIN AND BODY COOLING

Children have an advantage in cold-water submersion incidents, because their greater surface area–to–mass ratio allows for faster conductive cooling, which provides cerebral protection on the basis of decreased cerebral metabolic requirements of oxygen ($CMR_{O2}$). The mammalian dive reflex, which initiates intense bradycardia and shunts blood flow to important core organs such as the heart and brain, has also been implicated. A third factor that has recently been explored is the possibility that cold-water ventilation may result in rapid and extensive cooling during submersion.

The effectiveness of the human dive reflex, especially the breath-hold response, is controversial. Nemiroff,[129,130] who reported one of the largest series of successful resuscitations of submersion victims, believes the dive reflex plays an important role, particularly in children and infants and especially in neonates. Hayward and colleagues[88] believe that the enhanced success of resuscitation associated with cold-water submersion is more a result of hypothermia than of the dive reflex.[138]

It is important to note that the protective effect of cooling depends on the $T_{co}$ at cessation of oxygen delivery and the subsequent rate and extent of the decrease of $T_{co}$. Because $T_{co}$ is likely to be near normal at the onset of an accidental submersion, rapid cooling after the onset of ischemia is important for survival. Conduction alone probably cannot account for the rapid decrease in $T_{co}$ that occurs during cold-water submersion incidents. Conn and colleagues[22] studied cold-water (4°C [7.2°F]) drowning in shaved and anesthetized dogs and found that submersed dogs continued to breathe the cold water for an extended period. $T_{co}$ decreased by 11°C (19.8°F) after 4 minutes in the completely submersed dogs, compared with only 3°C (5.4°F) in the control dogs, which were immersed with their heads out and did not breathe cold water. It is likely that the rapid cooling was the result of convective heat exchange in the lungs compared with only surface conduction in the control dogs. The general conclusion that brain cooling is accelerated considerably by respiration of cold water has been proposed by others[54,68,74] and mathematically predicted by Xu and colleagues.[206] Although breath holding may occur during submersion, a physiologic break point occurs, at which time involuntary breathing movements predominate.[4] This factor, when coupled with unconsciousness, could reasonably be expected to result in the respiration of water, at least under certain circumstances. Experimental and anecdotal evidence in humans is rare. However, one helicopter crash survivor reported that, after being trapped underwater for some time, he recalled feeling that he was about to die and that he was breathing water in and out just before escaping the cockpit.[12] Whether or not this occurred has not been confirmed.

## MECHANISMS FOR THE PROTECTIVE EFFECT OF BRAIN COOLING

Hypothermia provides an advantage during anoxic periods, such as cold-water submersion, because of what is known as the "metabolic icebox." Whole-body or focal hypothermia has long been used to extend biologic survival time during surgery under ischemic conditions. Cerebral protection under hypothermic conditions has commonly been attributed to decreased $CMR_{O2}$, according to the temperature coefficient ($Q_{10}$) principle. Although the $Q_{10}$ of the whole body is about 2, the $Q_{10}$ of the brain increases from approximately 3 between 27° and 37°C (80.6° and 98.6°F) to 4.8 between 17° and 27°C (62.6° and 80.6°F).[120] On the basis of these values, if the brain could survive an ischemic insult for 5 minutes at 37°C (98.6°F), cooling to 27°C (80.6°F) or to 17°C (62.6°F) would provide 15 and 72 minutes of protection, respectively, based solely on the decreased $CMR_{O2}$ (Figure 8-44). Although long survival times at brain temperatures less than 20°C (68°F) may be predicted on the basis of increasing $Q_{10}$ and diminishing $CMR_{O2}$, some additional mechanisms may be required to explain intact survival after prolonged submersion, when reported core temperatures are often above 30°C (86°F). These factors are schematically shown in Figure 8-45. Since the early 1990s, several studies that have been directed mainly toward the protection of the brain during or after cerebral ischemic events have demonstrated that even moderate brain cooling of 3° to 5°C (5.4° to 9°F) provides substantial cerebral protection from ischemic insult.[14,15,64,123,146,204]

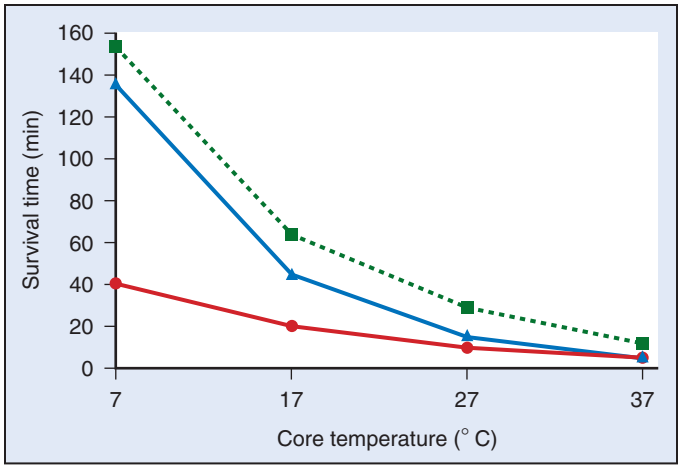



**FIGURE 8-44** Schematic presentation of survival time at different core and brain temperatures. *Red,* Prediction based on a temperature coefficient ($Q_{10}$) of 2. *Blue,* Prediction based on a $Q_{10}$ of 3. *Green,* Prediction based on the $Q_{10}$ effect plus other factors, such as changes in neurotransmitter release (i.e., glutamate and dopamine). Actual survival times from both neurosurgical and accidental hypothermia cases fall outside of the range predicted based on $Q_{10}$ alone; thus some other factors must also contribute to survival.

Submersion likely promotes cerebral death as tissue ischemia depletes high-energy phosphates and leads to membrane depolarization. This stimulates release into the extracellular space of excitatory neurotransmitters such as glutamate and dopamine, which mediate postsynaptic depolarization and cause calcium entry into the cell. Calcium influx mediates production of oxygen and hydroxyl free radicals (which may be involved in reperfusion injury) and release of free fatty acids, which results in eicosanoid

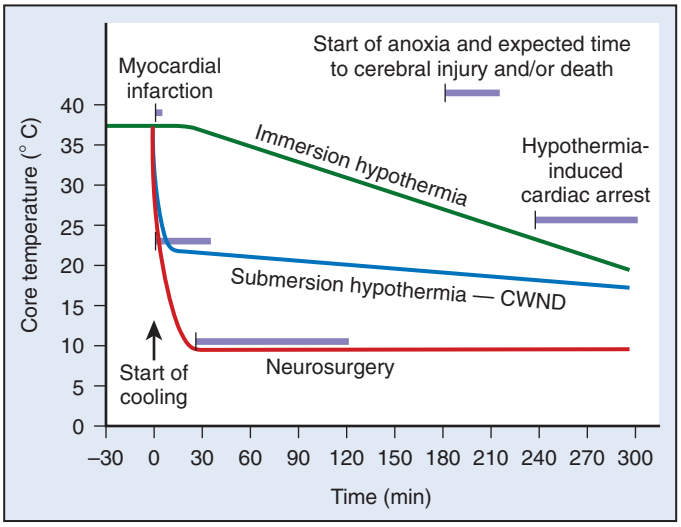



**FIGURE 8-45** Schematic representation of theoretical times to cerebral injury or death after the sudden onset of anoxia. Examples include anoxia induced by myocardial infarction at normal core temperatures, hypothermia-induced cardiac arrest during immersion hypothermia, ischemia-induced cardiac arrest after cold-water drowning *(CWND),* and electrically induced arrest after protective cooling for neurosurgery. Note that the times shown here are representational; actual survival times may vary.

synthesis.[176] Various animal studies have shown that cooling the brain by only 3° to 5°C (5.4° to 9°F) before ischemia delays terminal depolarization and does the following: reduces the initial rate of rise of extracellular potassium;[97] results in complete suppression of glutamate release and 60% reduction in the peak release of dopamine;[15] attenuates ischemia-induced damage to endothelial cells;[29,30] reduces hydroxyl radical production;[66] and improves postischemia glucose use.[64] These results relate to mechanisms other than decreased $CMR_{O2}$, which may explain cerebral protection during cold-water drowning.

In summary, these findings indicate the following: (1) if the brain cools even by only 3° to 5°C (5.4° to 9°F), it is protected in excess of what would be predicted from decreased $CMR_{O2}$ alone; (2) protection results from additional protective mechanisms of cooling related to neurotransmitter release, calcium flux, eicosanoid synthesis, and perhaps other phenomena; (3) the mammalian dive reflex may result in cold-induced circulatory adjustments that favor conservation of oxygen for the heart and the brain; and (4) cold-water ventilation may accelerate brain cooling and provide further protection.

### IMPLICATIONS FOR SURVIVAL

The paradox of whether $T_{co}$ cooling is an advantage or a disadvantage depends on whether there is cessation of oxygen delivery, and, if so, what $T_{co}$ is when anoxia occurs and how much the $T_{co}$ subsequently declines. These factors are schematically illustrated in Figure 8-45. If oxygen delivery is not compromised (i.e., during immersion hypothermia), $T_{co}$ cooling will eventually lead to death from cardiac arrest. However, if oxygen delivery is compromised (i.e., during submersion hypothermia and cold-water drowning), $T_{co}$ and brain cooling will prolong survival compared with a condition in which $T_{co}$ cooling does not occur (i.e., myocardial infarction). These factors are important to understanding whether children have a survival advantage over adults during cold stress. Because children cool faster, their body size would be an advantage when oxygen supply is compromised during cold-water submersion. However, when the oxygen supply is uninterrupted during head-out immersion or in cold air, the small body size becomes a disadvantage, because the onset of severe hypothermia is faster.

## RESCUE (SELF-INITIATED OR ASSISTED)

### SELF-RESCUE FROM OPEN WATER OR AN ICE HOLE

Most people have a poor understanding of how their bodies will react during cold-water immersion. Although there is individual variability, the following general principles apply. First, get breathing under control, because gasping and hyperventilation may result in gulping water or even drowning. One should be able to control breathing within 30 seconds. In ice-cold water, loss of arm control and the ability to grasp is progressive and begins to occur within the first 3 to 15 minutes. In open water, self-rescue may involve pulling oneself onto a floating object and out of the water as much as possible. If a person has fallen through the ice, it is usually best to turn and face the direction from which he or she came. The ice traveled over has already been proved capable of holding one's weight. Swim to the ice ledge on the entry side of the hole.

The self-rescue exit is illustrated in Figure 8-46 and can be seen in *Cold Water Boating* (Video 8-7). It is initiated by putting the arms up on the ice and pulling as much of the upper body out of the water as possible. Kick the legs vigorously to bring the body into a horizontal position. Next, kick and pull yourself forward and get on top of the ice. Once up on the ice edge, it is best to crawl or roll away from the hole until the ice is thick enough to stand on. Use ice picks, a knife, or any other available object to get a better grip on the ice.

Once on solid ice, remember that hypothermia and frostbite pose threats to survival. The first thing to do is to wring the water out of clothing. It might seem that this would make one colder, but wringing out the clothing increases its insulation value, which

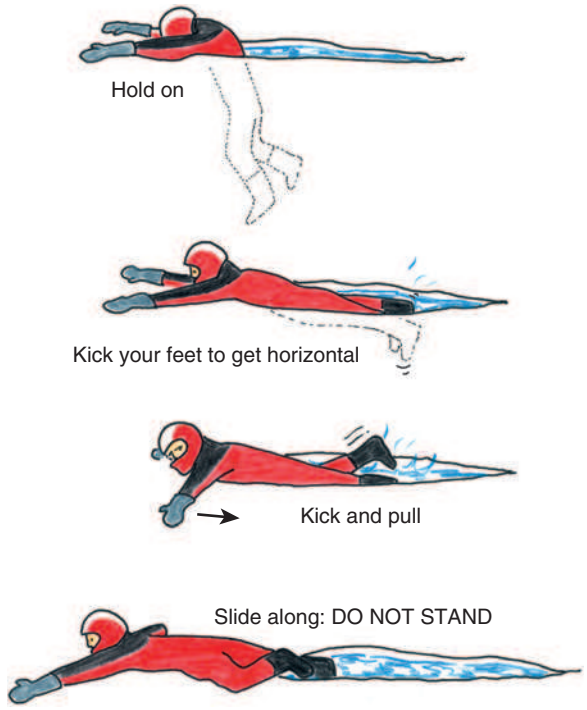



**FIGURE 8-46** Self-rescue technique after falling through ice. Place the arms on the ice and kick the feet (i.e., flutter kick) until the body is horizontal with the water surface, then kick vigorously with the legs and pull the body along the ice surface. Slide or roll away from the hole, and do not stand up until it is certain that the ice is thick enough to hold body weight. *(Courtesy* Wilderness Medicine Newsletter. *www.wildernessmedicinenewsletter.com.)*

is best in the long run. Next, decide whether to stay and try to get warm and dry by a fire or to seek shelter. If shelter is reasonably close (i.e., <30 minutes of exposure to the cold air), it may be beneficial to walk to safety. If it is more than 30 minutes away, it may be better to stay and build an emergency fire and campsite.

It is extremely important to protect the hands from becoming frostbitten. Wring water from gloves or mittens. If the fingers are still very cold, place each hand in the opposite armpit. If necessary, pull the arms inside the jacket to place the hands directly against the skin of the armpit. When the hands have recovered, it is imperative to start a fire to warm up and dry the clothing.

Although a person who cannot exit the cold water unaided might not yet be very hypothermic, physical incapacitation will become worse within 10 to 15 minutes. Consciousness will remain for an hour or so, until $T_{co}$ decreases from 37°C to about 30°C (99°F to about 86°F), so one should work to extend survival time to widen the window of opportunity for rescue. Recall the 1-10-1 principle for responses during cold-water immersion (but remember that time estimates are subject to individual variability): you have 1 minute to get your breathing under control, 10 minutes of meaningful movement, and 1 hour until you become unconscious as a result of hypothermia (see Box 8-2).

Swimming should be minimized, because it causes the body to lose heat much faster than remaining as still as possible, and it also causes exhaustion. Clothes should be kept on in the water, because they help to conserve body heat. Although the air initially trapped in clothing will eventually be forced out, it helps with flotation while it remains. Wet clothing does not cause a person to sink. The main effect of water in clothing is that its inertia makes movement difficult. The weight of water in clothing becomes a problem only when trying to exit the water.

In all cases (even if wearing a thermal protection suit or a PFD), use the ice edge for support. Extend the arms over the ice and press the legs together to help to conserve body heat. Keep the head and upper body as far out of the water as possible to

conserve as much body heat as possible. Remain as still as possible. This will decrease heat loss, but it may also result in the arms freezing to the ice. After about 1 hour, when consciousness is lost from severe hypothermia, drowning occurs unless the head is prevented from slipping beneath the water. If one is frozen to the ice, drowning will be prevented, and a victim might survive yet another hour before the heart stops beating (generally at a $T_{co}$ <25° to 28°C [77° to 82°F]). Thus, this could double the survival time and perhaps allow rescue.

## ASSISTED RESCUE OF A VICTIM WHO HAS FALLEN THROUGH THE ICE

Self-rescue and assisted rescue both have three guidelines: (1) acknowledge the danger of the situation, (2) assess the situation, and (3) follow the rescue sequence.

### Recognize the Danger

1. Recognize that ice conditions are unsafe and that no one else should approach the area.
2. Recognize that the victim is in an urgent situation that is potentially life threatening but that, if proper action is taken, there is more time than might be expected to make safe and effective decisions.
3. Recognize your own limitations in terms of training and equipment.

### Assess the Situation

1. Assess the victim's physical and emotional condition.
2. Assess the ice and water conditions (e.g., ice thickness, water current).
3. Assess the equipment that you have that might be useful in a rescue.
4. Assess the rescue skills that are possessed by you and by those who are with you.

### Follow the Rescue Sequence

The rescue sequence progresses from lowest-risk actions to highest-risk actions. Low-risk actions should be taken first. Progression to higher-risk actions is dictated by training level and available equipment.

1. Shore-assisted rescues involve talking, throwing, and reaching; untrained bystanders should limit themselves to these techniques.
2. Platform-assisted rescues involve working from or with a flotation platform (e.g., an inflatable boat or other buoyant device).
3. In a "go" rescue, the rescuer approaches and contacts the victim. This should only be done by trained personnel wearing PFDs and thermally protective dry suits (Figure 8-47).

Rescuers should always perform the lowest-risk rescue first and then contact professional authorities, if possible.

## UNTRAINED-BYSTANDER RESCUE

Every year, newspaper articles describe the death of well-meaning bystanders who rush to help victims who have fallen through the ice. It is extremely important that untrained bystanders apply the acronym *STOP* to their actions: *stop, think, observe,* and *plan*. *Stop* the urge to rush up to help the victim, because you are likely to fall through the ice and become another victim. *Think* and *observe* the victim and the surrounding conditions, including any material that might be used in a rescue attempt. Lastly, *plan* how to assist the victim out of the water. Untrained bystanders should limit themselves to techniques that progress from talking to throwing to reaching.

### Talk

Encourage the victim to calm down and not to panic. Direct the victim to an area of strong ice, and instruct the victim to execute a self-rescue by placing the arms on the ice, kicking until the body is horizontal near the water surface, and then kicking and pulling up onto the ice. Direct the victim to crawl and roll away from the hole until stronger ice is reached.

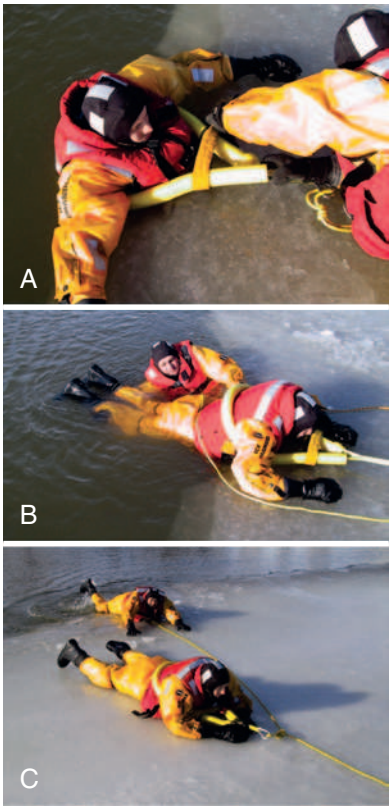



**FIGURE 8-47** Professional rescue of a volunteer from ice water. A rescue sling is placed around the victim's chest **(A),** and the rescuer then enters the water to help the victim out of the water **(B).** Both individuals are then pulled along the ice to safety **(C).** *(Courtesy Gordon G. Giesbrecht.)*

### Throw

Any buoyant item can be thrown to the victim to assist him or her with remaining buoyant, especially if the ice is continually breaking and not providing a secure base of support. If possible, tie a rope or cord to the object; this could allow you to pull the victim out of the water. If only a cord or rope is available, tie a large loop at the end to make it easier for the victim to hold on to it. After the rope has been grabbed, instruct the victim to put the loop over the body and under the arms, to put an arm through the loop and bend the elbow around the rope, or simply to hold on to the loop.

### Reach

It may be possible to reach a victim with some implement, such as a tree branch, ladder, or any object that can be pushed out on the ice. Care must be taken to not get too close to the hole when trying to reach the victim with any object. Any rescue that requires the rescuer to approach the hole in the ice should be left to trained personnel.

An untrained bystander who cannot perform a rescue with the use of these techniques should help the victim to widen the window of opportunity for trained rescuers to arrive. Instruct the victim to stop struggling and to hold the arms still on the ice. The objective is to let the arms freeze to the ice. Make sure that someone contacts emergency personnel. Wait with the victim, and provide continuous encouragement that the person can survive; emphasize that help is on the way.

## RESCUE BY TRAINED PERSONNEL

This discussion is not meant to provide in-depth training for professional rescue workers, but rather to describe some of the basics of high-risk rescues. The techniques used by any

professional rescuer should follow the policies and procedures of their local jurisdictions.

Trained personnel should first use the lower-risk techniques described earlier. If these do not work, personnel should implement the higher-risk techniques described by many ice-rescue training institutions.[48] Briefly, trained rescuers must not go on the ice unless they are wearing a thermal protective dry suit and PFD. The rescuers should also be secured by a safety rope that is operated by a trained colleague.

Platform-assisted rescues involve working from or with a flotation platform, such as an inflatable boat or another buoyant device. These techniques involve pushing or being transported on the buoyant platform. The first choice is to push the platform toward the victim and to use it as a reaching device. Alternatively, the rescuer can make contact with the victim directly from the platform.

Finally, during a "go" rescue, the rescuer approaches and contacts the victim directly. Standard lifesaving techniques should be used to ensure that a panicking victim does not pose a threat to the rescuer. After the victim is securely contacted, the victim and the rescuer can be pulled toward shore by the attendants on shore (see Figure 8-47).

## RESCUE FROM OPEN WATER

Retrieval of a victim from cold-water immersion must be performed with caution. Sudden reduction of the "hydrostatic squeeze" applied to tissues below the water's surface may potentiate hypotension, especially orthostatic hypotension.[73] Because a hypothermic patient's normal cardiovascular defenses are impaired, the cold myocardium may be incapable of increasing cardiac output in response to a hypotensive stimulus. A victim's vertical posture may also potentiate hypotension. Hypovolemia as a result of combined cold- and immersion-induced diuresis as well as increased blood viscosity potentiate these effects.[27] Peripheral vascular resistance may be incapable of increasing, because vasoconstriction is already maximal as a result of cold stress. The net result of the sudden removal of a hypothermic patient from the water is similar to sudden deflation of antishock trousers on a patient in hypovolemic shock: abrupt hypotension. This has been demonstrated experimentally in mildly hypothermic human volunteers,[72] and it has been suspected as a cause of post-rescue death in many immersion hypothermia victims.[73,157] Accordingly, rescuers should attempt to maintain hypothermic patients in a horizontal position during retrieval from the water and aboard the rescue vehicle[3,73,157] (Figure 8-48). If rescuers cannot recover the patient horizontally, they should place the victim in a supine posture as soon as possible after removal from cold water (Box 8-7).[157]

Hoist extractions can be done from a helicopter (Figure 8-49) or boat. Two slings can be used to keep the patient close to horizontal compared to a single sling (Figure 8-50).

**BOX 8-7 Controversy Box: A Hypothermic Patient Presents an Emergency That Must Be Dealt with Quickly**

Although severe hypothermia is a critical condition, rescue and treatment do not necessitate rapid and reckless actions. Rescuers and medical providers should take the time required to safely remove the victim from the cold stress and then do as much as possible to be gentle and to keep the patient horizontal. The patient's core has been cooling gradually for a long time (i.e., hours or even days), and a delay of a few minutes to get organized for treatment will not make the patient's condition worse. However, rushing may result in patient jostling that induces ventricular fibrillation and cardiac arrest.

**FIGURE 8-49** U.S. Coast Guard helicopter hoist rescue with a rescue swimmer and a victim. *(Courtesy Gordon G. Giesbrecht.)*

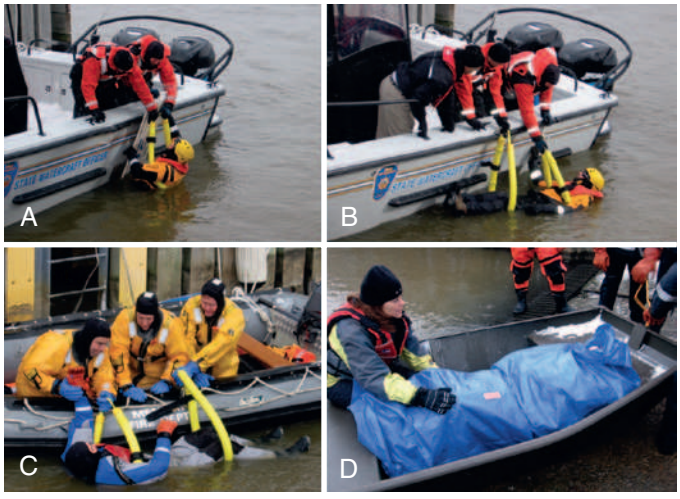



**FIGURE 8-48** Single **(A)** and double **(B** and **C)** sling techniques affect how vertical the victim is during extraction from the water. The rescue slings provide a leverage advantage, especially when there is high freeboard **(A** and **B).** A wet victim is wrapped in a makeshift vapor barrier to minimize evaporative and convective heat loss during boat transport **(D).** *(Courtesy Gordon G. Giesbrecht.)*

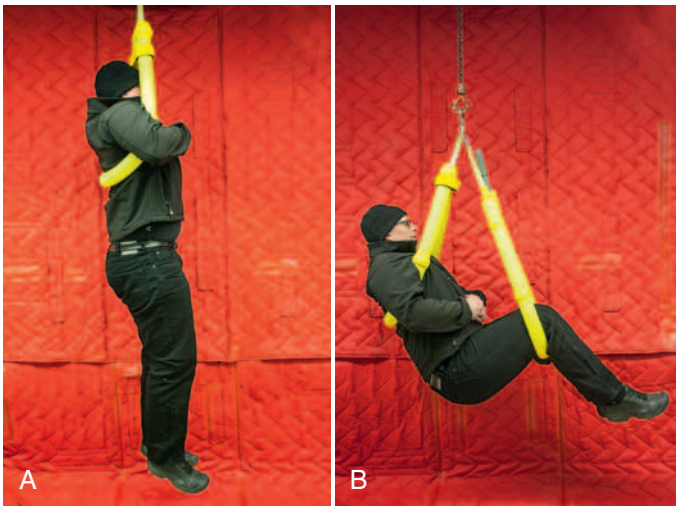



**FIGURE 8-50** Comparison between single **(A)** and double **(B)** sling methods for hoisting to a helicopter or boat. The double sling method places the patient in a more horizontal position. *(Courtesy Garrick Kozier.)*

The patient's $T_{co}$ may continue to decline—depending on the quality of insulation provided, the patient's endogenous heat production, active or passive manipulation of extremities, and the site of $T_{co}$ measurement—even after the person has been rescued as a result of the physiologic processes described earlier as "afterdrop." To diminish this effect, the patient's physical activity must be minimized. Conscious patients should not be required to assist with their own rescue (e.g., by climbing up a scramble net or a ship's ladder) or to ambulate when they are out of the water (e.g., by walking to a waiting ambulance or helicopter).[49,122,157] Physical activity increases afterdrop, presumably by increasing perfusion of cold muscle tissue with relatively warm blood.[11,52,53,55] As this blood is cooled, venous return (the circulatory component of afterdrop) contributes to a decline in myocardial temperature, thereby increasing the risk for VF.[87] Experiments on moderately hypothermic volunteers with esophageal temperatures of 33°C (91.4°F) demonstrated a threefold greater afterdrop during treadmill walking than while lying still.[10,56] Such an exercise-induced enhancement of afterdrop could precipitate post-rescue collapse. Throughout the rescue procedures and during subsequent management, hypothermic patients must be handled gently.[3,77,122] Excessive mechanical stimulation of the cold myocardium is another suspected cause of death after rescue.[110,192]

Several extraction techniques are presented in Figure 8-48 and Videos 8-7 and 8-8. The technique depends on the number of rescuers, the design of the boat platform and the resultant freeboard, and the equipment on hand. Victims can be pulled by their clothing or PFDs; placed into single or double rescue slings, rescue nets, or even hoists; and extracted either headfirst or horizontally. It is easier to be gentle and to keep the victim horizontal if there are low gunnels or if the boat has a rescue port on the side. If possible, the method that will be used to package the patient (see Packaging, later) should be prepared ahead of time. Regardless of the technique used, care should be taken to be as gentle as possible and to lift the patient directly into the packaging system.

## MEDICAL MANAGEMENT

This section describes prehospital management of hypothermia with specific reference to immersion pathophysiology. Chapter 7 describes the hospital management of both accidental immersion and land-based hypothermia. Prehospital management of hypothermia patients, both in the field and during transportation to a site of definitive medical care, varies with the patient's level of hypothermia, the rescuer's level of training, the resuscitative equipment available, type of transportation, and time required for delivery to definitive care.[208] Medical personnel must exercise good clinical judgment to balance all these factors to select appropriate therapeutic modalities (Box 8-8).

The primary goals of prehospital management of victims of accidental immersion hypothermia are prevention of cardiopulmonary arrest; prevention of continued $T_{co}$ decline; moderate, safe core rewarming, if practicable; and transportation to a site of definitive medical care.[33,79,105,112,152,157] Aggressive rewarming in the field has been contraindicated in the past, because the means to diagnose or manage the many potential complications of severe hypothermia are unavailable in this setting.[122] However, in the prehospital scenario of cold-water immersion, there is no source of heat that could be considered too aggressive. Figure 8-51 indicates the levels of aggressiveness and effectiveness of various sources of heat for hypothermia and frostbite treatment. When transportation to a site of definitive care will take more than 30 minutes or is impossible, rewarming in the field with the use of the principles and techniques of management described next may be appropriate (Box 8-9).

**BOX 8-8 Controversy Box: Prehospital Warming Is Dangerous and Should Be Avoided**

For many decades, it was believed that warming would cause massive vasodilation and result in cardiac arrest as a result of a precipitous drop in blood pressure or core temperature or the return of noxious metabolites from the periphery. Many studies have demonstrated that a very cold patient will display intense vasoconstriction such that only massive heating from warm-water immersion could override this thermoregulatory response. Any heat source (other than a warm-water bath) that is available in a prehospital setting will likely be safe. Thus, it is now widely accepted that gradual core rewarming through the application of heat to the chest and axillae is valuable as long as cardiovascular stability is maintained.

**BOX 8-9 Controversy Box: Afterdrop Is an Artifact and Is Unimportant**

Rescuers and emergency medical personnel should be aware that core temperature will continue to drop after an individual has been removed from the cold stress (see Figure 8-12). Although some decrease is inevitable, the understanding is that anything that increases blood flow to cold tissue (e.g., the legs) will increase afterdrop. Thus, patients should be kept from walking and should remain horizontal, and the arms and legs should not be rubbed or massaged in an effort to warm the patient.

### EXAMINATION, TRIAGE, AND LIFE SUPPORT

Because hypothermia affects virtually every physiologic process, rescuers should manage a severely hypothermic patient as they would a victim of multiple trauma.[156,157] Rescuers should not focus solely on $T_{co}$ to the exclusion of other potentially life-threatening problems. Conversely, when the incident includes cold exposure, care must be taken not to focus solely on trauma injuries. Several patients have died of hypothermia when treatment focused only on non–life-threatening physical injuries.

It is rarely possible to measure $T_{co}$ in the field. However, a diagnosis can be made on the basis of the patient's history (to confirm that the main insult is cold exposure) and the signs and symptoms (see Figure 8-13). Generally, if mentally alert and shivering vigorously, the patient can be considered mildly hypothermic. If shivering is waxing and waning or absent, or if consciousness is diminished or absent, the patient can be considered moderately to severely hypothermic.

In accordance with standard emergency medical procedures, the ABCs of first aid—airway, breathing, and circulation—are essential.[3,157] Rescuers should ensure an open airway and confirm the presence of adequate ventilation and circulation. If the patient is severely hypothermic, respirations and pulse may be slow, shallow, and difficult to detect;[3,156] therefore, rescuers should take 60 seconds to assess these vital signs.[3] If neither the pulse nor breathing is detectable, rescuers should commence cardiopulmonary resuscitation (CPR) in accordance with normal basic life support (BLS) protocols.[3,156] Figure 8-52 is a field algorithm for assessment and treatment of a cold patient by search/emergency personnel.[152,208]

Cardiac rhythm should be carefully monitored. Percutaneous electrodes may be required to overcome interference from muscle fasciculations or shivering. Endotracheal intubation and administration of heated and humidified air or oxygen are useful for management of apnea or hypoventilation and for reduction of further respiratory heat loss.[3] Mouth-to-mouth or mouth-to-mask ventilation also provides heated and humidified air; if available, oxygen may supplement ventilation. Mouth-to-mouth or mouth-to-mask ventilation has the added advantage of providing a small amount of carbon dioxide ($CO_2$) for the patient's inspired gases. This may be useful for prevention of hypocapnia caused by relative hyperventilation in a severely hypothermic patient whose metabolic $CO_2$ production is diminished.[28] This is important because hypocapnia may decrease the threshold for VF.

Hypothermic patients with any detectable pulse or respiration do not require the chest compressions of CPR, although severe

| Power source | Heat source | | Heat level/ aggressive | Treatment effectiveness | |
|---|---|---|---|---|---|
| | Prehospital | Hospital | | Hypothermia | Frostbite |
| Non-electric | Fire | | Low-to-moderate heat<br>**Nonaggressive** | XX | XXX |
| | Chemical pack | | | – | √ |
| | IV fluid | | | √ | – |
| | Warm sweet drink | | | √ | – |
| | Inhalation warming | | | – | – |
| | Warm water bottles | | | √ | √ |
| | Warm body | | | √ | √ |
| | **Charcoal HeatPac** | | | √√ | √ |
| Electric 120 VAC | Electric blanket | Electric blanket | | √ | √ |
| | Water blanket | Water blanket | | √ | √ |
| | **Forced air warming** | Forced air warming | | √√ | √ |
| | Warm shower | | High heat<br>**Aggressive** | XX | – |
| | Warm bath | Warm bath | | XXX | – |
| | | Lavage | | √√√ | – |
| | | CAVR | | √√√ | – |
| | | Fem-fem | | √√√ | – |
| | | Bypass | | √√√√ | – |

√, Effectiveness  –, Not effective or applicable  X, Harmful

**FIGURE 8-51** Heat sources that could be used for hypothermia rewarming classified by location, heat level or aggressiveness, and treatment effectiveness for hypothermia and frostbite. Drinks should only be given to a patient who is alert and unlikely to choke (i.e., mild hypothermia). Inhalation warming will reduce respiratory water loss but will add little heat to the body core. *CAVR,* Continuous arteriovenous rewarming.

bradycardia and bradypnea may be present.[3,156] This differs from normothermic CPR protocols, when chest compressions may be indicated if bradycardia fails to provide sufficient cardiac output or systolic blood pressure.[3] Because the metabolic requirements of hypothermic patients are reduced, bradycardia and bradypnea may still meet tissue oxygen requirements.[29,49] Inappropriate administration of chest compressions in an attempt to augment cardiac output may precipitate VF from mechanical stimulation of the irritable myocardium[29] (Box 8-10).

If a victim of cold-water immersion is found floating face-down, drowning should be suspected and managed accordingly (see Chapter 69). In this case, correction of anoxia is paramount, and consideration of hypothermia is of secondary importance.[3,130] Normal advanced cardiac life support (ACLS) protocols should not be routinely applied to severely hypothermic patients in cardiac arrest, because management beyond BLS differs from that used for normothermic patients.[3,29] Defibrillation and pharmacologic interventions are usually ineffective for myocardial temperatures of less than 30°C (86°F).[3,7,29] Furthermore, repeated defibrillatory shocks may damage the myocardium.[3,156] Defibrillation should be limited to three shocks at 200, 300, and 360 joules, consecutively, for patients who are colder than 30°C (86°F).[3] Administered medications are ineffective, and they may accumulate to toxic levels, because drug metabolism by the hypothermic liver and kidneys is reduced.[29,196] For hypothermic patients with a $T_{co}$ of more than 30°C (86°F), normal ACLS protocols may be used.[3] All intravenous (IV) fluids should be warmed before administration. However, it may be necessary to extend the recommended interval for IV medications because of the patient's reduced metabolic rate.

For the unconscious hypothermic patient who is not in cardiopulmonary arrest, endotracheal or nasotracheal intubation should be performed gently. The insertion of pacemaker wires and central venous catheters has been suspected of precipitating VF, but prior ventilation with 100% oxygen has been associated with a decreased risk for VF.[27,28] Rescuers should not withhold endotracheal intubation, if indicated, for fear of precipitating VF.[3]

If the patient does not require immediate life support intervention, a thorough and systematic examination must be performed as quickly as possible before the initiation of treatment for hypothermia. Because severely hypothermic patients may have a greatly depressed mental status, they may not respond normally to painful stimuli. Victims of immersion hypothermia may have suffered trauma before entering or while in the water. Central nervous system (CNS), skeletal, and soft tissue injuries may be overlooked unless a careful examination occurs.

Attention should be paid to the patient's mental status and other CNS signs. Rescuers should evaluate the level of

**BOX 8-10 Controversy Box: Cardiopulmonary Resuscitation (CPR) Should Be Started Rapidly if a Pulse Cannot Be Found Quickly**

A hypothermic patient has been cooling for a long time, and it will likely not affect the outcome if a few minutes are taken to ensure that the heart is not functioning before commencing CPR. Premature chest compressions can cause an irritable heart to fibrillate. An initial pulse check should be done for 60 seconds. If no pulse is found, 3 minutes of rescue breathing might oxygenate the heart enough to strengthen contractions. If a pulse still cannot be found after another 60-second check, it can be assumed that the heart is not functioning, and chest compressions can be started in accordance with local jurisdiction protocols (see Figure 8-52).[152]

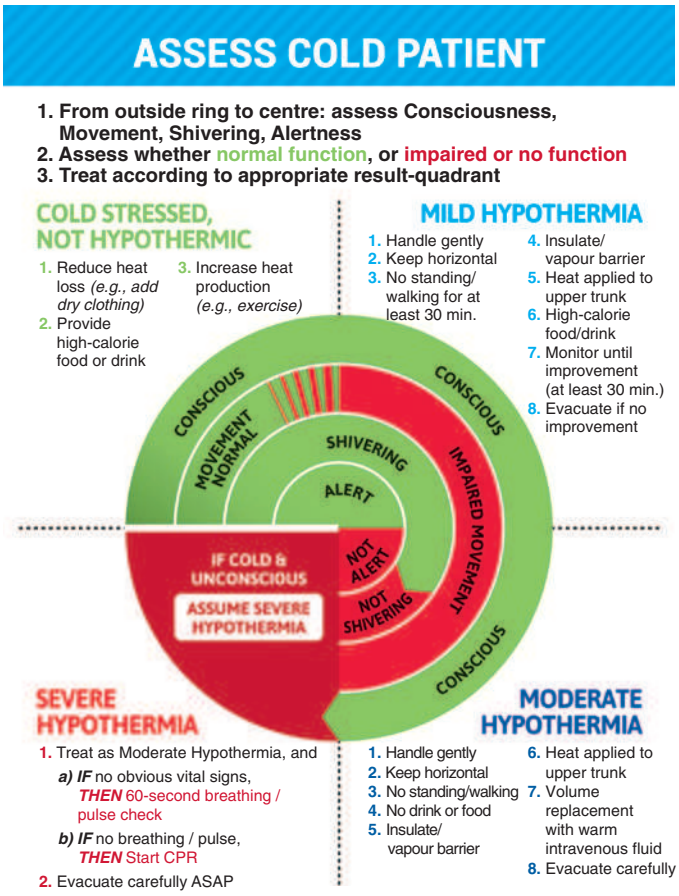



**FIGURE 8-52** Algorithm for field assessment and treatment of a cold patient. *(Copyright 2016 Baby It's Cold Outside; PDF can be downloaded from www.BICOrescue.com.)*

consciousness, presence or absence of shivering, and pupillary size and light reflex. Pupils may appear fixed and dilated in an unconscious and severely hypothermic patient, thus simulating the appearance of death. The diagnosis of death should not be made in a hypothermic patient, particularly in a field setting, unless resuscitation efforts fail after adequate rewarming efforts.

The vital signs should be carefully measured, with particular attention paid to the $T_{co}$. A low-reading thermometer that is capable of recording down to 20°C (68°F) is required. Esophageal temperature at the level of the atria is the most clinically useful $T_{co}$ obtainable, because this site most closely parallels cardiac temperature.[56,87] However, most rescue personnel are not equipped to measure esophageal temperature. Rectal temperature is not easily obtained, as rescuers often show reluctance to obtain a recording from this site in the field, and incorrect thermometer placement may cause an erroneous reading. If neither esophageal nor rectal temperature is taken, oral or axillary temperature is of limited value; neither will accurately reflect $T_{co}$ in a victim of immersion hypothermia. Facial cooling affects oral temperature, and cold skin temperature affects axillary recordings. However, the patient's $T_{co}$ will not be lower than that indicated by an oral or axillary recording. Thus, rescuers can use even superficial temperatures in a limited way to monitor the patient's status, although this is not ideal.

Hemorrhage should be controlled in the usual manner. Antishock trousers are normally contraindicated, because they are likely to be ineffective in the face of the maximal vasoconstriction already present in a severely hypothermic patient. Because hypothermia itself can cause hypotension without massive fluid losses, antishock trousers should be used only if required for temporary stabilization of a suspected pelvic fracture.[29]

## INSULATION, STABILIZATION, AND REWARMING

After removal of the patient from the water and management of immediate life-threatening emergencies, the next objectives are prevention of further heat loss and efforts at moderate rewarming (i.e., 1° to 2°C/hr [1.8° to 3.6°F/hr]). Strategies for moderate rewarming in the field vary with the equipment available, training of rescue personnel, environmental conditions, and length of time required for transport to a site of definitive care. Maximum insulation of the whole body from any further environmental cooling is an obvious first requirement. The main goals for rescue personnel are to maintain or improve cardiorespiratory stability and to minimize $T_{co}$ afterdrop, which can depress cardiac temperature and potentiate VF.

### Packaging

The purpose of packaging a patient in the field or during prehospital transport is to minimize all sources of heat loss: evaporation, conduction, convection, and radiation. Rescuers should maintain the patient in a horizontal position to prevent hypotension, and movement of the patient must be kept to a minimum. Clothing should be cut away if it is wet but only if the patient is in a sheltered area. The patient's skin should be dried with gentle blotting motions (no rubbing), and the patient should be protected by dry and insulating clothing and blankets, a sleeping bag, or a specialized rescue bag (Figure 8-53). This protection must include the head and neck. Incorporation of a windproof and waterproof layer or vapor barrier assists in prevention of convective and evaporative heat loss. This is particularly important for patients who require helicopter evacuation, because downwash from helicopter rotor blades can reach wind speeds

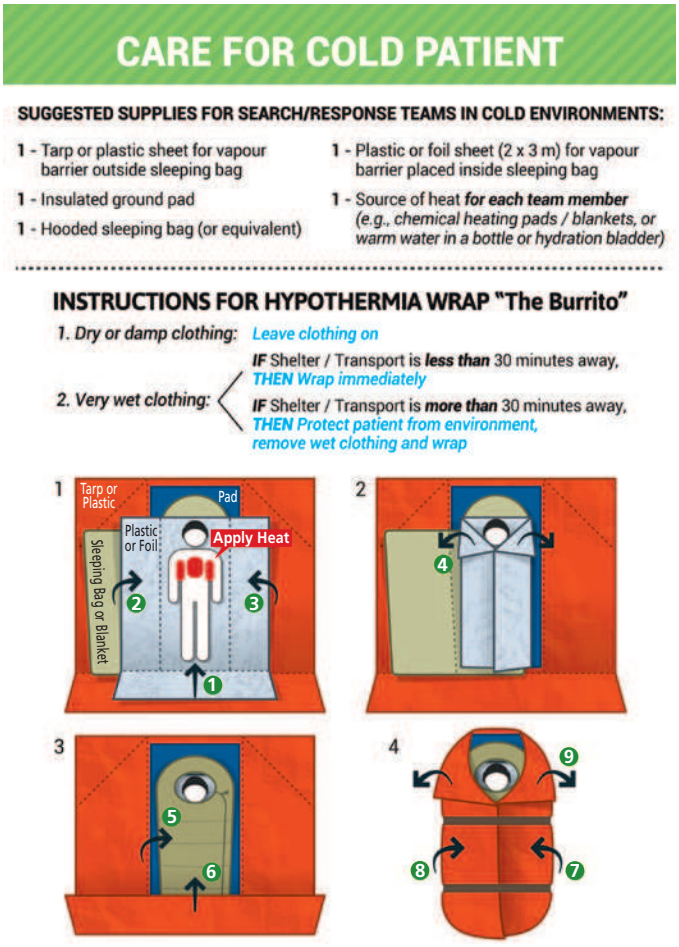



**FIGURE 8-53** Instructions for hypothermia wrap (The Burrito) for a cold patient. *(Copyright 2016 Baby It's Cold Outside; PDF can be downloaded from www.BICOrescue.com.)*

**FIGURE 8-54** Patient is exposed to strong rotor wash when being hoisted to U.S. Coast Guard helicopter. *(Courtesy Art Allen.)*

in excess of 160 km/hr (100 miles/hr), thereby potentiating significant heat loss from windchill (Figure 8-54). It is important to note that the vapor barrier should also protect the insulation from becoming wet. Therefore, if the patient is dry, the vapor barrier can be wrapped around the outside of the insulation. However, if the patient is wet and clothing cannot be changed (e.g., a survivor picked up by a small rescue boat), the vapor barrier should be placed around the patient inside the insulation layers.

### Spontaneous Rewarming

Patients who are only mildly hypothermic (i.e., exposed to cold water for a relatively short time, fully conscious, and vigorously shivering with $T_{co}$ >32°C [89.6°F]) are usually capable of rewarming themselves without difficulty. Heat production from shivering can reach levels that are five to six times that of the resting metabolic rate.[38] Shivering is thus a highly effective means of rewarming, particularly if rescuers insulate the patient's body and head with vapor-barrier garments to minimize evaporative heat loss.[56] Vigorous shivering has been shown to produce rewarming rates of as high as 3° to 4°C/hr (5.4° to 7.2°F/hr).[49,56,62] Patients who are conscious and vigorously shivering are generally not a medical emergency and usually do not require immediate transportation for definitive care. However, rescuers should be aware that prolonged periods of shivering consume the patient's endogenous energy reserves. Thus, rescuers should administer oral glucose-containing fluids to conscious patients who have adequate cough and gag reflexes. Attention to energy reserves in unconscious and severely hypothermic patients is also important. Warmed IV glucose solutions are useful for these patients as part of definitive resuscitative and rewarming protocols, as described later.[3,29] Alcoholic beverages are contraindicated in all cases.

### Inhalation Warming

Rescuers should attempt to minimize respiratory heat losses. Hypothermic patients lose up to 11 to 13 kcal/hr through inhalation of relatively cold and dry air and through exhalation of water-saturated air at near $T_{co}$.[65,200] Administration of heated and humidified air or oxygen at approximately 42° to 46°C (108° to 115°F) can result in net positive gain of 17.1 kcal/hr. Although this is a relatively small amount of heat compared with the total kilocalories required to rewarm the hypothermic patient completely, heated and humidified ventilation helps to insulate the airway from further evaporative heat loss. However, some studies have shown that inhalation rewarming reduces metabolic heat production provided by shivering.[54] In experimental volunteers whose shivering was pharmacologically inhibited, inhalation warming did not appear to provide any advantage over spontaneous rewarming.[67] Other suggested benefits of inhalation warming include rehydration, stimulation of mucociliary activity in the respiratory tract, and direct heat transfer from the upper airways to the hypothalamus, brainstem, and other brain structures. Any warming of the respiratory, cardiovascular, or thermoregulatory centers could be of benefit. Although research continues regarding efficacy of airway rewarming, most hypothermia treatment protocols continue to recommend inhalation warming as an adjunct to overall rewarming strategies.[3,27,29,33,49,157,195]

### Warmed Intravenous Fluids

Administration of warmed IV fluids (40-42°C [104-108°F]) is beneficial for reversing hypothermia-induced dehydration and hypovolemia.[29,156] Replacement of fluids before rewarming has been shown in dogs to augment cardiac output.[140] Dextrose 5% in water or normal saline and normal saline alone are preferable to lactated Ringer's solution, because a hypothermic liver may be unable to metabolize lactate normally.[157] Administration of 300 to 500 mL should occur fairly rapidly, with the remainder of the liter administered over the next hour.[5] In no case should IV fluids (at room temperature or colder) be administered. Plastic IV fluid bags can be easily carried inside of a rescuer's clothing (preferably next to the skin) to keep the fluids warm and to supply some perfusion pressure.

### Controversy Box: Airway Warming Effectively Warms the Core

It is important for an emergency medical provider to know that airway warming does not significantly warm the body core (see Figure 8-12). However, the method does have some advantages. Most of the heat transfer occurs in the upper airways and may warm certain areas in the brainstem. Moisture loss is eliminated. It is important to know that some additional warming techniques—preferably application of heat to the chest and axillae—are necessary to actually raise the temperature of the heart.

### Body-to-Body Rewarming

Body-to-body warming of the hypothermic patient has long been advocated as an acceptable field treatment. Sir John Franklin, in his 1823 text *Narrative of a Journey to the Shores of the Polar Sea in the Years 1819, 20, 21*, describes this technique for resuscitation of an expedition member who was recovered from ice-filled water.[41] When wrapped together in a blanket or sleeping bag, a rescuer can transfer body heat to a hypothermic patient. However, experimental studies on human volunteers have failed to demonstrate a rewarming advantage with this technique for shivering individuals. When volunteers were cooled to an average $T_{co}$ of 34.6°C (94.3°F), body-to-body rewarming proved no better than shivering alone.[62] In this study, the heat donated by the rescuers was only sufficient to offset the heat lost by the inhibition of shivering. The following theoretical arguments mediate against the routine use of body-to-body rewarming for shivering patients in the field:

1. The large heat loss of an immersion hypothermic victim (e.g., 300 kcal in cooling an average normothermic adult to $T_{co}$ of 33°C [91.4°F]) is unlikely to be reversed by the relatively small amount of heat provided by the donor (i.e., a resting, nonshivering adult produces only about 100 kcal/hr).[62]
2. External heat from body-to-body contact will inhibit the hypothermic victim's endogenous heat production through shivering.[56]
3. Once body-to-body rewarming is initiated, transport of the patient and heat donor will be difficult, if not impossible.

However, for severely hypothermic and nonshivering victims or for victims whose shivering thermogenesis is inhibited by alcohol, medications, age, or other factors, body-to-body rewarming may be used. Furthermore, body-to-body rewarming may provide important psychological support to the patient. For these reasons, rescuers should weigh the likelihood of effective rewarming against the advantages and disadvantages of body-to-body rewarming when devising a field rewarming strategy for any particular hypothermic patient.

### Heating Pads

The application of external moderate heat sources to hypothermic patients has been a traditional method of field rewarming.

**FIGURE 8-55** Placement of a charcoal heater on the chest. Warming ducts are wrapped over the shoulders and touching the neck, under the axillae, and over the chest. This configuration provides heat to important areas for heat transfer (surrounding or near the heart) to a cold patient.

Particularly when applied to the patient's thorax, including axillae, chest, and upper back, (areas with high potential for conductive heat transfer),[85] hot-water bottles, chemical and charcoal heat packs (Figure 8-55), heating pads, and other warmed objects have been used to attempt to stabilize the patient's $T_{co}$. If a patient is shivering vigorously, $T_{co}$ will warm at a similar rate as with external heat.[21,56,80,113,160] For more severely hypothermic patients who are not shivering, these types of external heat sources would help to stabilize and even increase the patient's $T_{co}$, which would likely remain low if no heat were added. A recent study demonstrated that charcoal heating provides a significant rewarming advantage for hypothermic individuals when shivering was pharmacologically inhibited.[92]

Rescuers should be aware of several potential hazards with this rewarming technique. Hypothermic skin is very sensitive to heat and easily injured. All sources of external heat must be separated from direct contact with the patient's skin to prevent severe thermal burns.[156] Third-degree burns have resulted from the application of a lukewarm hot-water bottle directly to a hypothermic child's skin.[129] Furthermore, heat packs that make use of burning charcoal as a heat source can create a carbon monoxide hazard within an enclosed space.[160]

### Arteriovenous Anastomoses Rewarming

The arteriovenous anastomoses (AVA) rewarming technique relies on the physiologic AVAs that exist in human digits and on the superficial venous rete in the forearms and the lower legs. Warming these areas opens the AVAs and increases superficial venous return via the rete. Warmed venous blood thus reaches the core without excessive countercurrent heat loss to cold arteries (superficial veins are not in close contact with arteries). As a result of the pioneering work of Vanggaard and Gjerloff,[189] who proposed AVA rewarming, the Royal Danish Navy has been using this technique since 1970.[187] Experimental studies have confirmed the efficacy of this technique.[188] Mildly hypothermic participants with an esophageal temperature of 34.2°C (93.6°F) whose hands, forearms, feet, and lower legs were immersed in either 42°C (108°F) or 45°C (113°F) water had a smaller postcooling afterdrop than with shivering alone (0.4°C [0.7°F] vs. 0.6°C [1.1°F]) and a significantly faster rate of rewarming (6.6°C/hr [11.9°F/hr] and 9.9°C/hr [18°F/hr]) than with shivering alone (3.4°C/hr [6.1°F/hr]). Although this technique may be difficult to implement in some field settings, it may be practical for mildly hypothermic victims on rescue vessels or other locations where a source of warm water is available.

As with heating pads and other sources of external heat, however, rescuers should be concerned about the possibility of thermal burns. In the previously described study, no burns were observed in the experimental volunteers, even when their extremities were immersed in 45°C (113°F) water, although some complained of initial discomfort at this temperature. Rescuers opting to use AVA rewarming should consider starting with a water temperature of 42°C (108°F) and gradually raise the temperature to 44°C (111°F).[188]

Another concern with AVA rewarming involves potential cardiovascular instability. Hypotension may result from an increase in peripheral blood flow in a hypovolemic patient. If the patient is required to be in a semiupright position to receive AVA rewarming, orthostatic hypotension could potentially add to cardiovascular instability. No experimental data support these potential cardiovascular problems, but studies of AVA rewarming have been performed only on mildly hypothermic individuals.[188] Further research is required to evaluate the efficacy and safety of AVA warming on severely hypothermic patients.

### Forced-Air Warming

Forced-air warming (FAW) is derived from a treatment modality used to prevent or reverse hypothermia in surgical patients.[106,149] Convective heat transfer is provided by warm air blown into warming covers over the patient's body. Both experimental and clinical data support the efficacy of this technique on mildly, moderately, and severely hypothermic subjects. In mildly hypothermic experimental patients, FAW was associated with a 30% smaller afterdrop compared with shivering alone. Furthermore, during the initial 35 minutes of rewarming, shivering patients experienced net heat loss of 30 to 50 W, compared with net heat gain from FAW of 163 to 237 W.[61] In moderately to severely hypothermic patients with a mean rectal temperature of 28.5°C (83.3°F) who were treated in an emergency department, FAW (in conjunction with warmed IV fluids and inhalation warming) achieved a rewarming rate of 2.4°C/hr (4.3°F/hr), which was almost twice that of patients treated only with warmed IV fluids and inhalation warming (1.4°C/hr [2.5°F/hr]).[153]

In another series of human experiments, a FAW device designed for field use was associated with a significantly higher $T_{co}$ rewarming rate (5.8°C/hr [10.4°F/hr]) than with shivering alone (3.4°C/hr [6.1°F/hr]), but it showed no advantage over shivering with regard to decreasing afterdrop.[35] When shivering was inhibited with meperidine in volunteers,[57] FAW was associated with a 50% decrease in afterdrop and a 600% increase in rewarming rate compared with spontaneous rewarming alone.[67] A different prototype FAW device that used a collapsible rigid patient cover and that was evaluated experimentally on nonshivering volunteers was associated with a smaller afterdrop and faster rewarming rate than with spontaneous rewarming alone.[60]

In summary, FAW has shown significant promise as both a field and a hospital treatment modality. It is a safe, noninvasive technique that can both decrease afterdrop and increase the $T_{co}$ warming rate of immersion hypothermic patients. Figure 8-56 schematically illustrates $T_{co}$ responses to various rewarming methodologies under mild (i.e., shivering intact) and severe (i.e., shivering absent) hypothermic conditions.

## TRANSPORTATION

Stabilization, insulation, and rewarming of the hypothermic patient should be started during transport of the patient to an appropriate medical center for definitive rewarming. If possible, the receiving facility should be selected on the basis of its knowledge of and experience with management of hypothermic patients. In the same manner that victims of multiple trauma are most appropriately managed in trauma centers, severely hypothermic patients are best managed in hospitals equipped to handle potential complications and provide core rewarming therapies. For example, a hospital with cardiac bypass rewarming capabilities may be a better choice for management of a severely hypothermic patient than a hospital without such qualifications, even if the former may require a longer transport time.

During transport to a site for definitive medical care, emergency medical personnel should frequently monitor the patient's $T_{co}$ and other vital signs. In addition, they should attach an

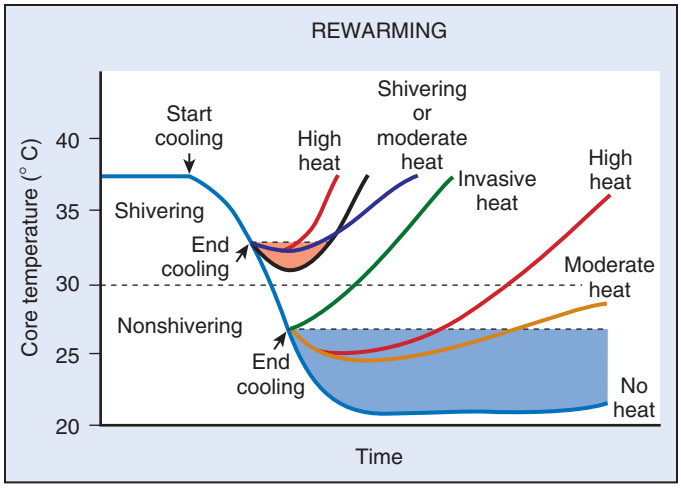



**FIGURE 8-56** Effectiveness of various rewarming techniques under shivering and nonshivering hypothermic conditions. The dashed line indicates the approximate core temperature at which shivering is spontaneously abolished.

electrocardiography monitor and continue administration of warmed IV fluids, heated and humidified air or oxygen, and other rewarming efforts discussed previously. Rescuers should maintain the hypothermic patient in a horizontal posture and restrict the voluntary movements of conscious individuals. At the receiving facility, rescuers should ensure that the patient is carried (rather than allowed to walk) to the treatment location.

In summary, prehospital rescue and management of immersion hypothermia patients requires understanding the physiologic events that occur during cooling and recovery. With such understanding, medical personnel can better prepare for and manage this potentially difficult environmental exposure. When prehospital care is performed safely and effectively, definitive hospital care is more likely to have a successful outcome.

Finally, it should be noted that, if you are from a Nordic country, you are oblivious to cold, and this chapter is likely irrelevant to you (Figure 8-57).

**FIGURE 8-57** Norwegian ice breaker.

## REFERENCES

***Complete references used in this text are available online at expertconsult.inkling.com.***

# CHAPTER 9
# Frostbite

LUANNE FREER, CHARLES HANDFORD, AND CHRISTOPHER H.E. IMRAY

Frostbite is a true freezing injury, and depending on the severity, ice crystals will tend to form in deep and superficial tissues. The degree of injury is a complex interaction of many factors, including environmental (e.g., temperature, windchill, length of exposure, altitude) and individual (e.g., genetics, comorbidities, medications/drugs, clothing, skin products, previous frostbite injury).

This chapter reviews current understanding of the history, epidemiology, physiology, pathophysiology, and classification of frostbite, as well as risk factors, clinical presentation, field and hospital evaluation, treatment, prevention, and consultation strategies. Although the principles of prevention and treatment transfer from urban to wilderness settings, the time to definitive treatment of frostbite is often prolonged, and resources are almost always limited in the wilderness setting. Therefore, wherever possible, we incorporate special considerations for wilderness management. Hypothermia and nonfreezing cold-induced injuries are discussed in Chapters 7 and 10.

## HISTORY OF FROSTBITE

A 5000-year-old pre-Columbian mummy discovered in the Chilean mountains is widely recognized as the earliest documented evidence of human frostbite.[151] In 218 BC, Hannibal lost almost half his army of 46,000 to cold injuries in only 15 days when crossing the Pyrenean Alps. Dr. James Thatcher wrote in 1778 that 10% of George Washington's colonial army had been left to perish in the winter cold during his campaign against the British soldiers.[164]

Although frostbite was a known consequence of military campaigns in the cold for thousands of years, the first authoritative report of mass casualties was by Baron Larrey, surgeon-in-chief of Napoleon's army during the invasion of Russia in the winter of 1812-1813.[105] Larrey introduced the concept of friction massage with ice or snow, avoidance of heat during thawing, and the idea that cold injuries were similar to burn injuries. These concepts are better understood against the background as

## REFERENCES


1. Abocar A. Canadian snowmobilers falling victim to thin ice. Reuters 1998;23.
2. Alexander L. The treatment of shock from prolonged exposure to cold, especially in water. Washington, DC: Office of the Publication Board, Department of Commerce; 1946 (Combined Intelligence Objectives Sub-committee).
3. American Medical Association. Standards and guidelines for cardiopulmonary resuscitation and emergency cardiac care. J Am Med Assoc 1992;268:2172.
4. Andersson J, Schagatay E. Effects of lung volume and involuntary breathing movements on the human diving response. Eur J Appl Physiol 1998;77:19.
5. Bagian JP. Effectiveness of the space shuttle anti-exposure system in a cold water environment. Aviat Space Environ Med 1990;61:753.
6. Baumgartner FJ, Janusz MT, Jamieson WR, et al. Cardiopulmonary bypass for resuscitation of patients with accidental hypothermia and cardiac arrest. Can J Surg 1992;35:184.
7. Bjornstad H, Tande PM, Refsum H. Cardiac electrophysiology during hypothermia: Implications for medical treatment. Arctic Med Res 1991;50:71.
8. Bolte RG, Black PG, Bowers RS, et al. The use of extracorporeal rewarming in a child submerged for 66 minutes. JAMA 1988;260:377.
9. Bowen HM. Diver performance and the effects of cold. Hum Factors 1968;10:445.
10. Bristow GK, Giesbrecht GG. Contribution of exercise and shivering to recovery from induced hypothermia (31.2°C) in one subject. Aviat Space Environ Med 1988;59:549.
11. Bristow GK, Sessler DI, Giesbrecht GG. Leg temperature and heat content in humans during immersion hypothermia and rewarming. Aviat Space Environ Med 1994;65:220.
12. Brooks CJ. Personal communication 1999.
13. Burton AC. Man in a cold environment. London: Edward Arnold Ltd; 1955.
14. Busto R, Dietrich WD, Globus MY-T, et al. Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. J Cereb Blood Flow Metab 1987;7:729.
15. Busto R, Globus MY, Dietrich WD, et al. Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rate brain. Stroke 1989;20:904.
16. Carlson LD, Hsieh AC, Fullington F, et al. Immersion in cold water and body tissue insulation. J Aviat Med 1958;29:145.
17. Castellani JW. Eighty-four hours of sustained operations alter thermoregulation during cold exposure. Med Sci Sports Exerc 2003;35:175.
18. Choi JS, Ahn DW, Choi JK, et al. Thermal balance of man in water: Prediction of deep body temperature change. Appl Human Sci 1996;15:161.
19. Coleshaw SR, Van Someren RN, Wolff AH, et al. Impaired memory registration and speed of reasoning caused by low body temperature. J Appl Physiol 1983;55:27.
20. Collins KJ, Easton JC, Exton-Smith AN. Body temperature afterdrop: A physical or physiological phenomenon? J Physiol 1982;328:72P.
21. Collis ML, Steinman AM, Chaney RD. Accidental hypothermia: An experimental study of practical rewarming methods. Aviat Space Environ Med 1977;48:625.
22. Conn AW, Miyasaka K, Katayama M, et al. A canine study of cold water drowning in fresh versus salt water. Crit Care Med 1995;23:2029.
23. Cooper KE. Hypothermia. In: Strauss RM, editor. Diving medicine. New York: Grune & Stratton; 1976.
24. Cotter JD, Taylor NA. Physiological assessment of the RNZAF constant wear immersion suit: Laboratory and field trials. Aviat Space Environ Med 1995;66:528.
25. Covino BG. Pharmacology of local anaesthetic agents. Br J Anaesth 1986;58:701.
26. Cupples WA, Fox GR, Hayward JS. Effects of cold water immersion and its combination with alcohol intoxication on urine flow rate of man. Can J Physiol Pharmacol 1980;58:319.
27. Danzl DF, Pozos RS. Accidental hypothermia. N Engl J Med 1994; 331:1756.
28. Danzl DF, Pozos RS, Auerbach PS, et al. Multicenter hypothermia survey. Ann Emerg Med 1987;16:1042.
29. Danzl DF, Pozos RS, Hamlet MP. Accidental hypothermia. In: Auerbach PS, editor. Wilderness medicine: Management of wilderness and environmental emergencies. St Louis: Mosby; 1995.
30. Dietrich WD, Busto R, Halley M, et al. The importance of brain temperature in alterations of the blood-brain barrier following cerebral ischemia. J Neuropathol Exp Neurol 1990;49:486.
31. Ducharme MB, Brooks CJ. The effect of wave motion on dry suit insulation and the response to cold water immersion. Aviat Space Environ Med 1998;69:957.
32. Ducharme MB, Lounsbury DS. Self-rescue swimming in cold water: The latest advice. Appl Physiol Nutr Metab 2007;32:799.
33. Ducharme MB, Steinman AS, Giesbrecht GG. Prehospital management of immersion hypothermia. In: Bierens JJLM, editor. Handbook on drowning. Berlin: Springer-Verlag; 2006.
34. Ducharme MB, Tikuisis P. Role of blood as heat source or sink in human limbs during local cooling and heating. J Appl Physiol 1994; 76:2084.
35. Ducharme MB. The effect of wave motion on dry suit insulation and the responses to cold water immersion. Aviat Space Environ Med 1998;69:957.
36. Edmonds C, Lowry C, Pennefather J. Cold and hypothermia. In: Diving and subaquatic medicine. Oxford: Butterworth-Heinemann; 1992.
37. Reference deleted in proofs.
38. Eyolfson D, Tikuisis P, Xu X, et al. Measurement and prediction of peak shivering intensity in humans. Eur J Appl Physiol 2001;84:100.
39. Færevik H, Reinertsen RE, Giesbrecht GG. Leg exercise and core cooling in an insulated immersion suit under severe environmental conditions. Aviat Space Environ Med 2010;81:1.
40. Ferretti G. Cold and muscle performance. Int J Sports Med 1992; 13:S185.
41. Forgey WW. The basic essentials of hypothermia. Merrillville, IN: ICS Books; 1991.
42. Fox GR, Hayward JS, Hobson GN. Effect of alcohol on thermal balance of man in cold water. Can J Physiol Pharmacol 1979;57: 860.
43. Fox JB, Thomas F, Clemmer TP, et al. A retrospective analysis of air-evacuated hypothermia patients. Aviat Space Environ Med 1988;59:1070.
44. Franks CM, Golden FS, Hampton IFG, et al. The effect of blood alcohol on the initial responses to cold water immersion in humans. Eur J Appl Physiol 1997;75:279.
45. Froese G, Burton AC. Heat loses from the human head. J Appl Physiol 1957;10:235.
46. Giesbrecht G, Lockhart T, Bristow G, et al. Thermal effects of dorsal head immersion in cold water on nonshivering humans. J Appl Physiol 2005;99:1958.
47. Giesbrecht G, Pretorius T. Survey of public knowledge and responses to educational slogans regarding cold water immersion. Wilderness Med Newslett 2008;19:261.
48. Giesbrecht G, Wilkerson J. Hypothermia: Frostbite and other cold injuries. 2nd ed. Seattle, Wash: The Mountaineers Books; 2006.
49. Giesbrecht GG. Cold stress, near drowning and accidental hypothermia: A review. Aviat Space Environ Med 2000;71:733.
50. Giesbrecht GG, Arnett JL, Vela E, et al. Effect of task complexity on mental performance during immersion hypothermia. Aviat Space Environ Med 1993;64:206.
51. Giesbrecht GG, Bristow GK. Decrement in manual arm performance during whole body cooling. Aviat Space Environ Med 1992;63:1077.
52. Giesbrecht GG, Bristow GK. A second postcooling afterdrop: more evidence for a convective mechanism. J Appl Physiol 1992;73:1253.
53. Giesbrecht GG, Bristow GK. Influence of body composition on rewarming from immersion hypothermia. Aviat Space Environ Med 1995;66:1144.
54. Giesbrecht GG, Bristow GK. Recent advances in hypothermia research. In: Blatteis CM, editor. Thermoregulation: Tenth International Symposium on the Pharmacology of Thermoregulation. New York: New York Academy of Sciences; 1997.
55. Giesbrecht GG, Bristow GK. The convective component for postcooling afterdrop during exercise is decreased by a previous period of shivering. Aviat Space Environ Med 1998;69:17.
56. Giesbrecht GG, Bristow GK, Uin A, et al. Effectiveness of three field treatments for induced mild (33.0°C) hypothermia. J Appl Physiol 1987;63:2375.
57. Giesbrecht GG, Goheen MSL, Johnston CE, et al. Inhibition of shivering increases core temperature afterdrop and attenuates rewarming in hypothermic humans. J Appl Physiol 1997;83:1630.
58. Giesbrecht GG, Hayward JS. Problems and complications with cold water rescue. Wilderness Environ Med 2006;17:26.
59. Giesbrecht GG, McDonald GK. Exit strategies and safety considerations for heavy machinery occupants following ice failure. Aviat Space Environ Med 2011;82:52.
60. Giesbrecht GG, Pachu P, Xu X. Design and evaluation of a portable rigid forced-air warming cover for prehospital transport of cold patients. Aviat Space Environ Med 1998;69:1200.
61. Giesbrecht GG, Schroeder M, Bristow GK. Treatment of mild immersion hypothermia by forced-air warming. Aviat Space Environ Med 1994;65:803.
62. Giesbrecht GG, Sessler DI, Mekjavic IB, et al. Treatment of mild immersion hypothermia by direct body-to-body contact. J Appl Physiol 1994;76:2373.
63. Giesbrecht GG, Wu MP, White MD, et al. Isolated effects of peripheral arm and central body cooling on arm performance. Aviat Space Environ Med 1995;66:968.

64. Ginsberg MD, Globus MY, Dietrich WD, et al. Temperature modulation of ischemic brain injury: A synthesis of recent advances. Prog Brain Res 1993;96:13.
65. Girton TR, Wehr SE. An evaluation of the rough-water performance characteristics of personal flotation devices (life-jackets). Springfield, VA: National Technical Information Service; 1984.
66. Globus MY, Busto R, Lin B, et al. Detection of free radical activity during transient global ischemia and recirculation: Effects of intraischemic brain temperature modulation. J Neurochem 1995;65:1250.
67. Goheen MSL, Ducharme MB, Kenny GP, et al. Efficacy of forced-air and inhalation rewarming using a human model for severe hypothermia. J Appl Physiol 1997;83:1635.
68. Golden FS. Mechanisms of body cooling in submersed victims. Resuscitation 1997;35:107.
69. Golden FS, Tipton M. Essentials of sea survival. Windsor, ON: Human Kinetics; 2002.
70. Golden FS, Hardcastle PT. Swimming failure in cold water. J Physiol 1982;330:60P.
71. Golden FS. Death after rescue from immersion in cold water. J R Nav Med Serv 1973;59:5.
72. Golden FS. Problems of immersion. Br J Hosp Med 1980;23:371.
73. Golden FS, Hervey GR, Tipton MJ. Circum-rescue collapse: Collapse, sometimes fatal, associated with rescue of immersion victims. J R Nav Med Serv 1991;77:139.
74. Golden FS, Tipton MJ, Scott RC. Immersion, near-drowning and drowning. Br J Anaesth 1997;79:1.
75. Golden FS, Hervey GR. The mechanism of the after-drop following immersion hypothermia in pigs. J Physiol 1977;272:26.
76. Graham T, Baulk K. Effect of alcohol ingestion on man's thermoregulatory responses during cold water immersion. Aviat Space Environ Med 1980;51:155.
77. Hackett P. State of Alaska hypothermia and near-drowning guidelines. Juneau, Alaska: Alaska Dept of Health and Human Services, EMS Section; 1989.
78. Haight JSJ, Keatinge WR. Failure of thermoregulation in the cold during hypoglycaemia induced by exercise and ethanol. J Physiol 1973;229:87.
79. Hamilton RS, Paton BC. The diagnosis and treatment of hypothermia by mountain rescue teams: A survey. Wilderness Environ Med 1996;7:28.
80. Harnett RM, O'Brien EM, Sias FR, et al. Initial treatment of profound accidental hypothermia. Aviat Space Environ Med 1980;51:680.
81. Hayes PA: Reactions to cold water immersion with and without waves, Farnborough, UK, 1985, Royal Air Force Institute of Aviation Medicine.
82. Hayward J. The physiology of immersion hypothermia. In: Poroz R, Wittmers LE, editors. The nature and treatment of hypothermia. Minneapolis: University of Minnesota Press; 1983. p. 3–19.
83. Hayward JS. Thermal protection performance of survival suits in ice water. Aviat Space Environ Med 1984;55:212.
84. Hayward JS, editor. Immersion hypothermia. Seattle: The Mountaineers Books; 1986.
85. Hayward JS, Collis M, Eckerson JD. Thermographic evaluation of relative heat loss areas of man during cold water immersion. Aerosp Med 1973;44:708.
86. Hayward JS, Eckerson JD, Collis ML. Effect of behavioral variables on cooling rate of man in cold water. J Appl Physiol 1975;38: 1073.
87. Hayward JS, Eckerson JD, Kemna D. Thermal and cardiovascular changes during three methods of resuscitation from mild hypothermia. Resuscitation 1984;11:21.
88. Hayward JS, Matthews BR, Overweel CH, et al. Temperature effect on the human dive response in relation to cold water near-drowning. J Appl Physiol 1984;56:202.
89. Hayward JS. Design concepts of survival suits for cold-water immersion and their thermal protection performance. In Proceedings of the 17th Symposium of the SAFE (Survival and Flight Equipment) Association, Van Nuys, Calif, 1980.
90. Holmer I. Prediction of responses to cold. Arctic Med Res 1995; 54:48.
91. Howell MW. Report by provincial judge on inquest respecting the death of: Calvin Sean Wood. Winnipeg: Provincial Court of Manitoba; 2005.
92. Hultzer M, Xu X, Marrao M, et al. Efficacy of torso rewarming using a human model for severe hypothermia (abstract). In Proceedings of the World Congress on Wilderness Medicine, Whistler, Canada, 1999, Wilderness Medical Society.
93. Johnston CE, Bristow GK, Elias DA, et al. Alcohol lowers the vasoconstriction threshold in humans without affecting core cooling rate during mild cold exposure. Eur J Appl Physiol 1996;74:293.
94. Johnston CE, Elias DA, Ready AE, et al. Hypercapnia lowers the shivering threshold and increases core cooling rate in humans. Aviat Space Environ Med 1996;67:438.
95. Johnston CE, White MD, Wu M, et al. Eucapnic hypoxia lowers human cold thermoregulatory response thresholds and accelerates core cooling. J Appl Physiol 1996;80:422.
96. Kalant H, Le AD. Effects of ethanol on thermoregulation. Pharmacol Ther 1984;23:313.
97. Katsura K, Minamisawa H, Ekholm A, et al. Changes of labile metabolites during anoxia in moderately hypo- and hyperthermic rats: Correlation to membrane fluxes of $K^+$. Brain Res 1992;590:6.
98. Kaufman JW, Bagian JP. Insidious hypothermia during raft use. Aviat Space Environ Med 1990;61:569.
99. Kaufman JW, Dejneka K: Cold water evaluation of constant wear anti-exposure suit systems, Warminster, PA, 1985, Naval Air Development Center.
100. Keatinge WR. Death after shipwreck. Br Med J 1965;25:1537.
101. Keatinge WR. Survival in cold water. 2nd ed. Oxford: Blackwell Scientific Publications; 1969.
102. Keatinge WR. Survival in cold water: The physiology and treatment of immersion hypothermia and of drowning. Oxford and Edinburgh: Blackwell Scientific Publications; 1969.
103. Keatinge WR, McIlroy MB, Goldfien A. Cardiovascular responses to ice-cold showers. J Appl Physiol 1964;19:1145.
104. Keatinge WR, Prys-Roberts C, Cooper KE, et al. Sudden failure of swimming in cold water. Br Med J 1969;1:480.
105. Kempainen RR, Brunette DD. The evaluation and management of accidental hypothermia. Respir Care 2004;49:192.
106. Kurz A, Kurz M, Hackl W, et al. Forced-air warming maintains intraoperative normothermia better than circulating-water in infants and children. Anesth Analg 1993;77:89.
107. Layton R, Mints WJ, Annis J, et al. Calorimetry with heat flux transducers: Comparison with a suit calorimeter. J Appl Physiol 1983; 54:1361.
108. LeBlanc J. Subcutaneous fat and skin temperature. Can J Biochem Physiol 1954;32:354.
109. Light IM. Immersion suit insulation: the effect of dampening on survival estimates. Aviat Space Environ Med 1987;58:964.
110. Lloyd EL. Accidental hypothermia. Resuscitation 1996;32:111.
111. Lockhart T, Jamieson C, Steinman A, et al. Life jacket design affects dorsal head and chest exposure, body core cooling and mental performance in 10°C water. Aviat Space Environ Med 2005;76:954.
112. Long WB III, Edlich RF, Winters KL, et al. Cold injuries. J Long Term Eff Med Implants 2005;15:67.
113. Lundgren J, Henriksson O, Pretorius T, et al. Field torso-warming modalities for severe hypothermia: a comparative study using a human model. Prehosp Emerg Care 2008;13:371.
114. Marino F, Booth J. Whole body cooling by immersion in water at moderate temperatures. J Sci Med Sport 1998;1:73.
115. Martin S, Cooper KE. Alcohol and respiratory and body temperature changes during tepid water immersion. J Appl Physiol 1978;44:683.
116. McCance RA, Ungley CC, Crosfill JWL, et al. The hazards to men in ships lost at sea, 1940-44. Medical Research Council Special Report Series. Report 291, London, 1956, Her Majesty's Stationery Office.
117. Mekjavic IB, Sundberg CJ. Human temperature regulation during narcosis induced by inhalation of 30% nitrous oxide ($N_2O$). J Appl Physiol 1992;73:2246.
118. Mekjavic IB, La Prairie A, Burke W, et al. Respiratory drive during sudden cold water immersion. Respir Physiol 1987;70:121.
119. Mersey L. Report of a formal investigation into the circumstances attending the foundering on 15th April 1912 of the British Steamship 'Titanic' of Liverpool after striking ice in or near latitude 41 deg 46' N, longitude 50 deg 14' north Atlantic Ocean, whereby loss of life ensued. His Majesty's Stationery Office, London, 1912.
120. Michenfelder JD, Milde JH. The relationship among canine brain temperature, metabolism, and function during hypothermia. Anesthesiology 1991;75:130.
121. Miller JW, Danzl DF, Thomas DM. Urban accidental hypothermia: 135 cases. Ann Emerg Med 1980;9:456.
122. Mills WJ. Field care of the hypothermic patient. Int J Sports Med 1992;13:S199.
123. Minamisawa H, Nordstrom CH, Smith ML, et al. The influence of mild body and brain hypothermia on ischemic brain damage. J Cereb Blood Flow Metab 1990;10:365.
124. Molnar GW. Survival of hypothermia by men immersed in the ocean. JAMA 1946;131:1046.
125. Nadel E. Energy exchanges in water. Undersea Biomed Res 1984; 11:149.
126. National Center for Environmental Prediction. Sea surface temperature—25 April 2005, 2005, Space Science and Engineering Center, University of Wisconsin–Madison.
127. National Technical Information Service. Maritime casualty report, Mobile Offshore Drilling Unit (MODU) Ocean Ranger. Capsizing and sinking in the Atlantic Ocean on 15 Feb 1982 with loss of life: Report number USCG 001 HQS 82, Springfield, Va, 1983, National Technical Information Service.

128. National Weather Service, National Oceanic and Atmospheric Administration. Wind chill temperature index. <http://www.nws.noaa.gov/om/windchill/index.shtml>.
129. Nemiroff M. Personal communication 1999.
130. Nemiroff MJ. Near-drowning. Resp Care 1992;37:600.
131. Niazi SA, Lewis EJ. Profound hypothermia in the dog. Surg Gynecol Obstet 1956;102:98.
132. Nunneley SA, Wissler EH, Allan JR. Immersion cooling: Effect of clothing and skinfold thickness. Aviat Space Environ Med 1985;56:1177.
133. Oksa J, Rintamaki H, Hassi J, et al. Gross efficiency of muscular work during step exercise at −15°C and 21°C. Acta Physiol Scand 1993;147:235.
134. Oksa J, Rintamaki H, Makinen T. Cooling alters force-velocity relationship of upper body and arms. In Proceedings of the International Conference on Human-Environment System, 1991, Tokyo, p 587.
135. Parkinson D. Carotid cavernous fistula: direct repair with preservation of the carotid artery. J Neurosurg 1973;38:99.
136. Passias TC, Mekjavic IB, Eiken O. The effect of 30% nitrous oxide on thermoregulatory responses in humans during hypothermia. Anesthesiology 1992;76:550.
137. Passias TC, Meneilly GS, Mekjavi IB. Effect of hypoglycemia on thermoregulatory responses. J Appl Physiol 1996;80:1021.
138. Ramey CA, Ramey DN, Hayward JS. The dive response of children in relation to cold-water near-drowning. J Appl Physiol 1987;63:665.
139. Rasch W, Samson P, Cote J, et al. Heat loss from the human head during exercise. J Appl Physiol (1985) 1991;71:590.
140. Roberts DE, Barr JC, Kerr D, et al. Fluid replacement during hypothermia. Aviat Space Environ Med 1985;56:333.
141. Romet TT. Mechanism of afterdrop after cold water immersion. J Appl Physiol 1988;65:1535.
142. Romet TT. Immersed clothing insulation in marine work suits using human and thermal manikin data. Aviat Space Environ Med 1991;62:739.
143. Roythorne C, editor. Cold in North Sea operations. Aberdeen, UK: University Press; 1981.
144. Ryack BL, Luria SM, Smith PF. Surviving helicopter crashes at sea: A review of studies of underwater egress from helicopters. Aviat Space Environ Med 1986;57:603.
145. Sagawa S, Shiraki K, Yousef MK, et al. Water temperature and intensity of exercise in maintenance of thermal equilibrium. J Appl Physiol 1988;65:2413.
146. Sano T, Drummond JC, Patel PM, et al. A comparison of the cerebral protective effects of isoflurane and mild hypothermia in a model of incomplete forebrain ischemia in the rat. Anesthesiology 1992;76:221.
147. Savard GK, Cooper KE, Veale WL, et al. Peripheral blood flow during rewarming from mild hypothermia in humans. J Appl Physiol 1985;58:4.
148. Schuyler N, Longman J. Not without hope. New York: HarperCollins; 2010.
149. Sessler DI, Moayeri A. Skin-surface warming: Heat flux and central temperature. Anesthesiology 1990;73:218.
150. Shender BS, Kaufman JW, Ilmarinen R. Cold water immersion simulations using the Wissler Texas Thermal Model: Validation and sensitivity analysis. Aviat Space Environ Med 1995;66:678.
151. Siple PA, Passel CF. Measurements of dry atmospheric cooling in subfreezing temperatures, 1945. Wilderness Environ Med 1999;10:176.
152. State of Alaska Cold injuries guidelines. <http://www.chems.alaska.gov/EMS/documents/AKcoldinj2005.pdf>.
153. Steele MT, Nelson MJ, Sessler DI, et al. Forced air speeds rewarming in accidental hypothermia. Ann Emerg Med 1996;27:479.
154. Steinman AM. A few more thoughts on water survival. On-Scene Nat Maritime Search Rescue Rev 1984;3:14.
155. Steinman AM. A few thoughts on water survival. On-Scene Nat Maritime Search Rescue Rev 1984;2:12.
156. Steinman AM. Cardiopulmonary resuscitation and hypothermia. Circulation 1986;74:IV29.
157. Steinman AM. Prehospital management of hypothermia: Rescue, examine, insulate and transport. Response! 1987;18–19.
158. Steinman AM, Hayward JS, Nemiroff MJ, et al. Immersion hypothermia: Comparative protection of anti-exposure garments in calm versus rough seas. Aviat Space Environ Med 1987;58:550.
159. Steinman AM, Kubilis P. Survival at sea: The effects of protective clothing and survivor location on core and skin temperature. Springfield, VA: United States Coast Guard, National Technical Information Service; 1986.
160. Sterba JA. Efficacy and safety of prehospital rewarming techniques to treat accidental hypothermia. Ann Emerg Med 1991;20:896.
161. Stoneham MD, Squires SJ. Prolonged resuscitation in acute deep hypothermia. Anaesthesia 1992;47:784.
162. Tikuisis P. Predicting survival time for cold exposure. Int J Biometeorol 1995;39:94.
163. Tikuisis P. Prediction of survival time at sea based on observed body cooling rates. Aviat Space Environ Med 1997;68:441.
164. Tikuisis P, Frim J. Prediction of survival time in cold air. North York: Defense and Civil Institute of Environmental Medicine; 1994.
165. Tipton MJ. The initial responses to cold-water immersion in man. Clin Sci 1989;77:581.
166. Tipton MJ. Laboratory-based evaluation of the protection provided against cold water by two helicopter passenger suits. J Soc Occup Med 1991;41:161.
167. Tipton MJ. The relationship between maximum breath hold time in air and the ventilatory responses to immersion in cold water. Eur J Appl Physiol 1992;64:426.
168. Tipton MJ. The concept of an "integrated survival system" for protection against the responses associated with immersion in cold water. J R Nav Med Serv 1993;79:11.
169. Tipton MJ. Immersion fatalities: Hazardous responses and dangerous discrepancies. J R Nav Med Serv 1995;81:101.
170. Tipton MJ, Balmi PJ. The effect of water leakage on the results obtained from human and thermal manikin tests of immersion protective clothing. Eur J Appl Physiol 1996;72:394.
171. Tipton MJ, Eglin CM, Golden FSC. Habituation of the initial responses to cold water immersion in humans: A central or peripheral mechanism? J Physiol 1998;512:621.
172. Tipton MJ, Golden FSC. The influence of regional insulation on the initial responses to cold immersion. Aviat Space Environ Med 1987;58:1192.
173. Tipton MJ, Stubbs DA, Elliott DH. The effect of clothing on the initial responses to cold water immersion in man. J R Nav Med Serv 1990;76:89.
174. Tipton MJ, Stubbs DA, Elliott DH. Human initial responses to immersion in cold water at three temperatures and after hyperventilation. J Appl Physiol 1991;70:317.
175. Tipton MJ, Vincent MJ. Protection provided against the initial responses to cold immersion by a partial coverage wet suit. Aviat Space Environ Med 1989;60:769.
176. Todd MM, Warner DS. A comfortable hypothesis reevaluated: cerebral metabolic depression and brain protection during ischemia. Anesthesiology 1992;76:161.
177. Transport Canada. Trends in motor vehicle traffic collision statistics 1988-1997, 2001, Transport Ottowa, Canada.
178. US Coast Guard. A pocket guide to cold-water survival. Washington, DC: U.S. Coast Guard; 1991.
179. Reference deleted in proofs.
180. US Coast Guard. Commandant (G-NRS) data, 1999.
181. US Coast Guard. Living to fish, dying to fish. Fishing Vessel Casualty Task Force Report. 1999. Available at: <http://homeport.uscg.mil/cgi-bin/st/portal/uscg_docs/MyCG/EditoriaI/20071102/fvctf.pdf?id=becaf871380eedc08f08af6d411c512b68ffef18>.
182. US Coast Guard. Final action message on Station Niagara CG-214341 capsizing, R081306Z Feb 02, COMDT COGARD WASHINGTON DC (G-WKS). Washington, DC, 2002.
183. US Coast Guard. Safety alert—Wearing of life jackets, 2003. Available at: <http://www.uscg.mil/hq/g-m/moa/docs/3-03.htm>.
184. US Coast Guard. Inspection into the circumstances surrounding the sinking of the uninspected fishing vessel, Arctic Rose, 2004.
185. Reference deleted in proofs.
186. Vanggaard L. Physiological reactions to wet-cold. Aviat Space Environ Med 1975;46:33.
187. Vanggaard L. Ny laegebog for sofarende (authorized ship captain's guide). Copenhagen, Denmark: Tellus; 1987.
188. Vanggaard L, Eyolfson D, Xu X, et al. Immersion of distal arms and legs in warm water (AVA rewarming) effectively rewarms hypothermic humans. Aviat Space Environ Med 1999;70:1081.
189. Vanggaard L, Gjerloff CC. A new simple technique of rewarming in hypothermia, Internal Review of the Army. Navy and Air Force Medical Services 1979;52:427.
190. Vaughan WSJ. Distraction effect of cold water on performance of higher-order tasks. Undersea Biomed Res 1977;4:103.
191. Vincent MJ, Tipton MJ. The effects of cold immersion and hand protection on grip strength. Aviat Space Environ Med 1988;59:738.
192. Walpoth BH, Walpoth-Aslan BN, Mattle HP, et al. Outcome of survivors of accidental deep hypothermia and circulatory arrest treated with extracorporeal blood warming. N Engl J Med 1997;337:1500.
193. Webb P. Impaired performance from prolonged mild body cooling. In: Bachrach AJ, Matzen MM, editors. Underwater physiology VIII. Bethesda, Md.: Undersea Medical Society; 1984.
194. Webb P. Afterdrop of body temperature during rewarming: an alternative explanation. J Appl Physiol 1986;60:385.
195. Weinberg AD. The role of inhalation rewarming in the early management of hypothermia. Resuscitation 1998;36:101.
196. Weinberg AD Cold weather emergencies: principles of patient management, Branford, CT, 1990, American.

197. Werner J, Webb P. A six-cylinder model of human thermoregulation for general use on personal computers. Ann Physiol Anthropol 1993;12:123.
198. White GR. Cold water survival suits for aircrew. Aviat Space Environ Med 1979;50:1040.
199. White MD, LeBlanc J. Paradoxical absence of shivering in obese humans. In Proceedings of the Thermal Physiology Conference, 1993 Aberdeen, Scotland, 1993, IUPS.
200. Wilkerson J, Zigler S, Wilkerson E. Heat transfer by heated aerosols. In Proceedings of the First Annual International Forum: Critical Decisions in Hypothermia, 1992.
201. Wintemute GJ, Kraus JF, Teret SP, et al. Death resulting from motor vehicle immersions: The nature of the injuries, personal and environmental contributing factors, and potential interventions. Am J Public Health 1990;80:1068.
202. Wissler EH. Mathematical simulation of human thermal behavior using whole body models. In: Shitzer A, Eberhart RC, editors. Heat transfer in medicine and biology. New York: Plenum Press; 1985.
203. Wolf AH, Coleshaw SRK, Newstead CG, et al. Heat exchanges in wet suits. J Appl Physiol 1985;58:770.
204. Xiao F, Safar P, Radovsky A. Mild protective and resuscitative hypothermia for asphyxial cardiac arrest in rats. Am J Emerg Med 1998; 16:17.
205. Xu X, Amin M, Santee WR. Probability of Survival Decision Aid (PSDA). USARIEM Technical Report T08-05. Natick, Mass.: US Army Research Institute of Environmental Medicine; 2008.
206. Xu X, Tikuisis P, Giesbrecht G. A mathematical model for human brain cooling during cold-water near-drowning. J Appl Physiol 1999; 86:265.
207. Xu X, Werner J. A dynamic model of the human/clothing/environment-system. Appl Human Sci 1997;16:61.
208. Zafren K, Giesbrecht GG, Danzl DF, et al. Wilderness Medical Society practice guidelines for the out-of-hospital evaluation and treatment of accidental hypothermia: 2014 Update. Wilderness Environ Med 2014;25:S66.

viewed by Larrey; soldiers with cold injuries rapidly rewarmed their extremities over roaring fires (65° to 75°C [149° to 167°F]) after long marches, only to renew the trek and refreeze their extremities the next day. Larrey recognized that warming was good, but cautioned against the use of excessive heat and ultimately recognized the freeze-thaw-freeze cycle. Napoleon left France with 250,000 men and returned 6 months later with only 350 effective soldiers. The remainder were casualties to cold or starvation.[105]

During both world wars and the Korean conflict, at least 1 million cases of frostbite occurred.[142,181,198] High-altitude frostbite, first described in 1943, was recognized from the treatment of aviators in World War II, when gunners of aircraft flying between 7620 and 10,668 m (25,000 and 35,000 feet) fired machine guns through open ports, removing their bulky mittens and jackets to improve the dexterity that they thought was crucial to saving their lives.[198]

Until the 1950s, treatment of cold injuries basically followed Larrey's guidelines. In 1956, experimental laboratory work encouraged Meryman, the U.S. Public Health Service district medical officer in Tanana, Alaska, to try rapid rewarming at 37.8°C (100°F) on a patient with frostbite and hypothermia.[25,131] This was the genesis and has become the cornerstone of the method currently used in Alaska and popularized by Mills.[130,131]

## EPIDEMIOLOGY

No comprehensive statistical data are available on the incidence of frostbite, but it is much more prevalent during military campaigns and is a known hazard for mountain climbers and polar explorers. The typical frostbite patient is either working or recreating in cold and/or high-altitude environments, is homeless, or is accidentally trapped outdoors in the winter.[98,101,146] The patient is typically 30 to 49 years old, and in more than half of urban cases, is intoxicated.

### CIVILIAN

In the nonadventurer U.S. civilian population, Mills[129-131] had collected 500 cases in Alaska by 1963, Cook County Hospital in Chicago recorded 843 cases from 1962 to 1972, and Detroit Receiving Hospital reported on 154 patients treated between 1982 and 1985.[17,74,102] The incidence of frostbite in Finland calculated in a 9-year retrospective query of hospital admissions was 2.5 cases per 100,000 inhabitants.[87]

### MILITARY AND OCCUPATIONAL

The mean annual incidence of frostbite in the Finnish military was reported as 1.8 episodes per 1000 persons, with the head, hands, and feet most often affected.[107] In a more recent study of almost 6000 Finnish military recruits, 44% reported at least one episode of frostbite during their lifetime, and the annual incidence was 2.2%; the head, hands, and feet were the sites most frequently afflicted.[47] Among refugees navigating a high-altitude military line of control during December 1988 to March 2003, 2564 cases of frostbite were treated at local hospitals in Muzaffarabad, Azad Kashmir.[92]

### MOUNTAINEERING

A 10-year retrospective review of medical records of the British Antarctic Survey revealed that the incidence of frostbite was approximately 65.6 cases per 1000 persons per year.[28] During a 10-year period in the Karakorum Mountains, 1500 cases of frostbite were treated at tertiary care medical facilities; all victims were males age 17 to 43 years. The incidence is unknown because the total number of potential exposures was unrecorded.[71] In a questionnaire-based study of 637 mountaineers, the mean incidence of frostbite was 366 cases per 1000 persons per year,[70] and of 2219 south-side Mt Everest climbers in 7 years (2001–2007), the base camp medical clinic at Mt Everest saw 35 cases of frostbite (and estimates at least a comparable number of patients not brought for treatment at the facility).[56]

## ANATOMY AND PHYSIOLOGY

Physiologically, humans are tropical animals, better suited to losing heat than retaining it. When naked and at rest, a person's neutral environmental temperature is 28°C (82.4°F). With an environmental drop of 8°C (14.4°F) to 20°C (68°F), the metabolic rate must double to avoid lowering of body temperature.

The rate at which heat is lost by radiation is a function of the temperature of the cutaneous surface, which in turn is primarily a function of the rate of blood flow through the skin. Heat is poorly conducted from warmer internal tissue to the cutaneous surface because adipose tissue is a good heat insulator.

As a result, cutaneous circulation is key to development of frostbite. Because of its role in thermoregulation, normal blood flow of skin far exceeds its nutritional obligation. The skin holds a complex system of capillary loops that empty into a large, subcapillary venous plexus containing the majority of the cutaneous blood volume. Under normothermic conditions, 80% of an extremity's blood volume is in the veins of skin and muscle. Skin blood volume depends in part on tone in resistance and capacitance blood vessels, and tone in turn depends largely on ambient and body temperatures. Under basal conditions, a 70-kg (154.3-lb) person has total cutaneous blood flow of 200 to 500 milliliters per minute (mL/min). With external heating to maintain skin temperature at 41°C (105.8°F), this may increase to 7000 to 8000 mL/min, whereas cooling the skin to 14°C (57.2°F) may diminish it to 20 to 50 mL/min.

Blood flow through apical structures, such as the nose, ears, hands, and feet, is most variable because of richly innervated arteriovenous connections. Blood flow to hand skin can be increased from a basal rate of 3 to 10 mL/min/100 grams (g) of tissue to a maximum of 180 mL/min/100 g of tissue. This cutaneous vascular tone is controlled by both direct local and reflex effects. Indirect heating (warming a distant part of the body) results in reflex-mediated cutaneous vasodilation, whereas direct warming results in vasodilation dominated by local effects. When both types (central and peripheral) of heating or cooling are present, their effects are additive.

Cutaneous vessels are controlled by sympathetic adrenergic vasoconstrictor fibers, and vascular smooth muscles have both α-adrenergic and β-adrenergic receptors. Vasodilation in the hands and feet is passive, so maximal reflex vasodilation occurs after sympathectomy.

When the hand or foot is cooled to 15°C (59°F), maximal vasoconstriction and minimal blood flow occur. If cooling continues to 10°C (50°F), vasoconstriction is interrupted by periods of vasodilation and an associated increase in blood and heat flow. This cold-induced vasodilation (CIVD), or "hunting response," recurs in 5- to 10-minute cycles and provides some protection from the cold. There is considerable individual variation in the amount of CIVD, and it is believed this might explain some of the variation in susceptibility to frostbite. Prolonged repeated exposure to cold increases CIVD and offers a degree of acclimatization. Inuit, Sami, and Nordic fishermen have a strong CIVD response and very short intervals between dilations, which may contribute to maintenance of hand function in the cold environment.[66]

Normal skin maturation and tissue function rely on maintenance of permeability and integrity of all tissue membranes. A steady-state relationship of prostaglandins, particularly prostaglandin $E_2$ ($PGE_2$, vasodilator) and $PGF_{2\alpha}$ (vasoconstrictor), is crucial for normal skin function. Imbalance may disrupt cell membrane equilibrium. This relationship is controlled through $PGE_2$–9-ketoreductase and nicotinamide adenine dinucleotide phosphate (NADPH). Low concentrations of $PGE_2$–9-ketoreductase found in normal skin emphasize an active biologic presence.

It is not difficult to imagine why frostbite tends to affect tissues that are acral (e.g., fingers, toes, ears, nose) and that receive diminished blood supply as a result of vasoconstriction, thereby conserving heat for the core. The nose and corneas may be difficult to protect from cold wind and are particularly vulnerable;

face coverings such as a balaclava and goggles should be considered in extreme conditions. In addition, men who jog, ski, or otherwise exercise in the cold may be prone to penile frostbite, especially if fast speeds create a headwind. Clothing becomes moist with sweat in the groin, and the tip of the penis is vulnerable, especially if unprotected by a wind-resistant or windproof outer layer.[56,76]

# PATHOPHYSIOLOGY OF FROSTBITE

The pathophysiology of frostbite has been categorized in several different ways, illustrating the numbers of variables that affect the extent and depth of tissue damage. Frostbite may be divided into four pathologic phases: prefreeze, freeze-thaw, vascular stasis, and late ischemic. Overlap occurs among these phases. The changes during each phase vary with rapidity of freezing and duration and extent of injury.

Some believe that it is conceptually more clear to divide pathologic changes occurring in frostbite into two categories: those resulting from direct cellular injury and those from indirect cellular effects, or progressive dermal ischemia,[138] a similar pathophysiology described in thermal burn patients.[119,120,163]

## DIRECT CELLULAR INJURY

Regardless of the classification scheme, researchers agree that the changes caused by direct injury include the following[211,212]:

- Extracellular ice formation
- Intracellular ice formation
- Cell dehydration and shrinkage
- Abnormal intracellular electrolyte concentrations
- Thermal shock
- Denaturation of lipid-protein complexes

Cells subjected to a slow rate of cooling (over hours) develop ice crystals extracellularly in the cellular interspaces. Rapid cooling (over seconds to minutes) produces intracellular ice crystals, which are more lethal to the cell and less favorable for cell survival. In a clinical cold injury, the slower rate of freezing does not produce intracellular crystals;[124,125] however, the extracellular ice formed is not innocuous. It draws water across the cell membrane, contributing to intracellular dehydration. The theory of cellular dehydration was originally proposed by Moran in 1929 and subsequently supported by Meryman's study of "ice-crystal nucleation."[124,125,127,136] Cellular dehydration produces modification of protein structure because of high electrolyte concentrations, alteration of membrane lipids, alteration of cellular pH, and imbalance of chemical activity.[116,118,128] This phenomenon subsequently permits a marked and toxic increase of electrolytes within the cell, leading to partial shrinkage and collapse of its vital cell membrane. These events are incompatible with cell survival.

Not all the water within a cell is freezable. A small amount of unfrozen water, "bound water," constitutes up to 10% of the total water content and is held tightly in the protein complex within the cell. Regardless of how rapid or marked the cold injury, this bound water remains liquid. At temperatures below −20° C (−4° F), approximately 90% of available water is frozen.[208] Although the theory of ice crystal disruption of cell structure is attractive, it has yet to be conclusively proven.

"Thermal shock" is the phenomenon of sudden and profound temperature change in a biologic system. Precipitous chilling has been theorized to be incompatible with life, but the severity of this phenomenon is debatable. Another poorly understood concept is the manner in which subzero temperatures produce denaturation of lipid-protein complexes. One proposed theory hypothesizes detachment of lipids and lipid protein from cell membranes as a consequence of the solvent action of a toxic electrolyte concentration within a cell.[42,110] No direct evidence supports an alteration of enzyme activity during freezing, but DNA synthesis is inhibited.[85] On the other hand, there is indirect evidence of ox liver catalase inactivation caused by denaturation and structural alteration of lactic acid dehydrogenase after freezing and thawing.[112,179]

## INDIRECT CELLULAR DAMAGE/PROGRESSIVE DERMAL ISCHEMIA

Indirect cellular damage secondary to progressive microvascular insults is more severe than the direct cellular effect. This is supported by the observation that skin tissue subjected to a standard freeze-thaw injury, which consistently produced necrosis in vivo, survived as a full-thickness skin graft when transplanted to an uninjured recipient site.[197] Conversely, uninjured full-thickness skin did not survive when transferred to a recipient area pretreated with the same freezing injury. Thus, direct skin injury is reversible. The progressive nature of injury is probably secondary to microvascular changes.

Approximately 60% of skin capillary circulation ceases in the temperature range of 3° to 11° C (37.4° to 51.8° F), while 35% and 40% of blood flow ceases in arterioles and venules, respectively.[161] Capillary patency is initially restored in thawed tissue, but blood flow declines 3 to 5 minutes later. Three nearly simultaneous phenomena occur after thawing: momentary and initial vasoconstriction of arterioles and venules, resumption of capillary circulation and blood flow, and showers of emboli coursing through microvessels.[212] Ultimately, there is progressive tissue loss caused by progressive thrombosis and hypoxia. This is similar to the tissue loss seen in the distal dying random flap and the no-reflow phenomenon. For both these, in addition to the effect of arachidonic acid metabolites, oxygen free radicals have been shown to be detrimental and contribute to tissue loss. It has been proposed that this may be the case with frostbite injury.[24]

Emerging concepts, perhaps including the deleterious role of protein kinase C in mitochondrial dysfunction during reperfusion injury and the role of nitric oxide production and activation, will no doubt be incorporated into our understanding of frostbite injury as scientific understanding evolves.

Considerable evidence indicates that the primary alteration caused by cold injury is to vascular endothelium.[210] At 72 hours after a freeze-thaw injury, vascular endothelium is lost in capillary walls, accompanied by significant fibrin deposition. The endothelium may be totally destroyed, and fibrin may saturate the arteriole walls.[134,210,212] Ultrastructural derangement of endothelial cells after the thaw period has been observed by electron microscopy in capillaries of the hamster cheek pouch following subzero temperatures.[156] The endothelial injury was confirmed by demonstrating fluid extravasation from vessels almost immediately after thawing.[212] As in other forms of trauma, vascular endothelial cells swell and protrude inward into the lumen until they lyse.

Venules appear more sensitive to cold injury than do other vascular structures, partly because of lower flow rates. Arterioles, with a rate of flow almost twice that of venules, are less damaged by freezing and develop stasis later than do venules. Capillaries manifest the fewest direct effects of cold injury, but their flow is quickly arrested as a result of their position between arterioles and venules. Generalized stasis and cessation of flow are noted at the point of injury within 20 minutes after freeze and thaw. "White thrombi" (blood cells and fibrin) appear after platelet thrombi as blood flow progressively slows. Sludging and stasis result in thrombosis. Microangiography after cold injury shows that although spasm of the arterioles and venules exists, it is not marked enough to completely account for the decreased flow of progressive microvascular collapse.[4] In the 1950s, Kulka[99,100] observed that vascular thrombosis after cold injury advanced from the capillary level to that of the large vessels and ultimately resulted in ischemic death of progressively larger areas. Viable dermal cells may be observed histologically in cold-injured tissues for up to 8 days or until occlusion of local vessels occurs. This emphasizes that vascular insufficiency plays a major role, and that direct injury to cellular structures and mechanisms may be reversible. It also suggests other mechanisms, such as reperfusion injury.

Because Cohnheim had shown changes in cold injury to be similar to changes seen in other inflammatory states, Robson and Heggers[163] postulated that the progressive ischemia seen in frostbite might be caused by the same inflammatory mediators responsible for progressive dermal ischemia in the burn wound.

They evaluated blister fluid from patients with hand frostbite, measuring levels of $PGE_2$, $PGF_{2\alpha}$, and thromboxane $B_2$ ($TXB_2$). Levels of the vasoconstricting, platelet-aggregating, and leukocyte-sticking prostanoids ($PGF_{2\alpha}$ and thromboxane $A_2$ [$TXA_2$]) were greatly elevated. The investigators postulated that massive edema after cold injury was caused either by leakage of proteins from release of these prostanoids or by leukocyte sludging in the capillaries and increased hydrostatic pressure. Studies have confirmed the similarity between cold injury and the burn wound.[24]

Severe endothelial damage was observed by researchers studying a minimal cold-injury model in the hairless mouse.[18] In addition, the sequence of endothelial damage, vascular dilation, vascular incompetence, and erythrocyte extravasation was confirmed. This led to speculation that arachidonic acid metabolites, which may originate from severely damaged endothelial cells, are important in progressive tissue loss. Significantly absent from in vivo and microscopic observations were vascular spasm, thrombosis, and fibrin deposition, all of which had previously been implicated as pathophysiologic mechanisms. A rabbit ear model demonstrated increased tissue survival after blockade of the arachidonic acid cascade at all levels.[157] The most marked tissue salvage resulted when specific $TXA_2$ inhibitors were used. This has now been shown to be effective in clinical situations.[74]

Reports in the 1940s documenting the histopathology of frostbite injury to the skin were not comprehensive. Historically, studies by several investigators have been limited to skin biopsies without documentation of location, exposure time, temperature, or time elapsed since the injury.[174]

More recently, experimental studies have been able to document the histopathology of skin changes under controlled conditions. In 1988, Schoning and Hamlet[176,177] used a Hanford miniature swine model for frostbite injury (−75° C [−103° F] exposure for up to 20 minutes) to note progressive epithelial damage. Early changes included vacuolization of keratinocytes; loss of intercellular attachments and pyknosis occurred over 1 week or more. This subsequently progressed to advanced cellular degeneration and formation of microabscesses at the dermoepidermal junction. Later changes included epithelial necrosis and regeneration, either separately or together within the same tissue. Such histopathologic data favor the current standard of conservative management of frostbite injury with delayed surgery.

However, Marzella and associates[114] used a New Zealand white rabbit ear model of frostbite injury and proposed that the skin necrosis induced by frostbite injury was merely a reflection of damage to the target cell—the endothelial cell. After submersion of a shaved rabbit ear in 60% ethyl alcohol at −21° C (−5.8° F) for 60 seconds, the entire microvasculature demonstrated endothelial damage within 1 hour; erythrocyte extravasation occurred within 6 hours. These early vascular changes in the rabbit ear model are in contradistinction to the timing of vascular changes in the Hanford miniature swine model; Schoning and Hamlet[177] performed biopsies on animals exposed to frostbite injury (−75° C [−103° F] for up to 20 minutes) and evaluated the specimens for vascular inflammation, medial degeneration, and thrombosis. The earliest change documented both grossly and microscopically was hyperemia. Within 6 to 24 hours, leukocyte migration and vasculitis were noted. However, the most severe vascular changes of thrombosis and medial degeneration were not observed until 1 to 2 weeks after the injury.

Whether or not changes in the epidermis are primary or secondary to damage of underlying endothelial cells, it is clear that these tissues have potential, although limited, capacity for regeneration. Human experience clearly suggests that robust local tissue inflammation and coagulation stimulate microvascular thrombosis and progressive cell death.[138] A perfect representative animal model for frostbite has yet to be found. A wide range of animal models has been used to create and assess the condition. Developing a consistent, reproducible, and appropriate model would facilitate frostbite research.[186] In recent years, both swine and mouse models have been proposed to address this, aiming to be inexpensive and easily reproducible.[9,10,167] Although promising, their true value will be known when proven during further trials.

As early as 1991, Manson and co-workers[111] proposed that frostbite is characterized by acute tissue injury induced by freezing and thawing. Initial complete ischemia is followed by reperfusion and later by tissue necrosis. The authors suggested that the vascular events supported the hypothesis that free radical–mediated reperfusion injury at thawing might contribute to tissue necrosis after frostbite in a manner similar to that seen after normothermic ischemia. Supporting evidence included electron micrographs showing the appearance of severe endothelial cell injury, beginning during freezing and extending through early reperfusion. Later, neutrophil adhesion, erythrocyte aggregation, and microvascular stasis were seen.

## DEFINITIONS AND CLASSIFICATIONS

Classically, frostbite has been described by its clinical presentation, but this can be difficult to predict in the field and before rewarming.[97,131] Mills[136,139] favors the use of two simple classifications: mild (without tissue loss) and severe (with tissue loss). Historically, and following the classification of thermal burn injury, frostbite has been divided into "degrees" of injury based on acute physical findings after freezing and rewarming.

*Frostnip* is superficial and associated with intense vasoconstriction. It is characterized by discomfort in the involved parts (Figure 9-1; see also Figure 9-8). Symptoms usually resolve spontaneously within 30 minutes, and no tissue is lost. There is some question whether this qualifies to be called an injury, because neither frozen extracellular water nor progressive tissue loss is routinely demonstrated.

*First-degree* frostbite injury shows numbness and erythema. There may initially be a firm, white or yellowish plaque in the area of injury. There is no tissue loss, although edema is common (Figure 9-2). *Second-degree* injury results in superficial skin vesiculation (Figure 9-3). Clear or milky fluid is present in the blisters, surrounded by erythema and edema. *Third-degree* injury shows deeper blisters, characterized by purple, blood-containing fluid (Figure 9-4). This indicates that the injury has extended into the reticular dermis and beneath the dermal vascular plexus. *Fourth-degree* injury is completely through the dermis and involves relatively avascular subcuticular tissues (Figure 9-5). This tends to

**FIGURE 9-1** Frostnipped nose. *(Courtesy Tim Glasset.)*

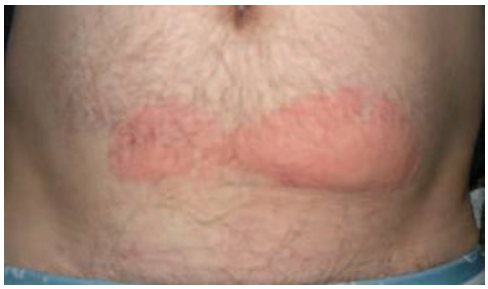


**FIGURE 9-2** Nordic skier with first-degree frostbite (central pallor having cleared after rewarming) of the abdominal skin. This skier reported having skied for 90 minutes in –23.3°C (–10°F) temperature, unaware that his shirt, underneath a parka, had come untucked from his trousers. *(Courtesy Luanne Freer, MD.)*

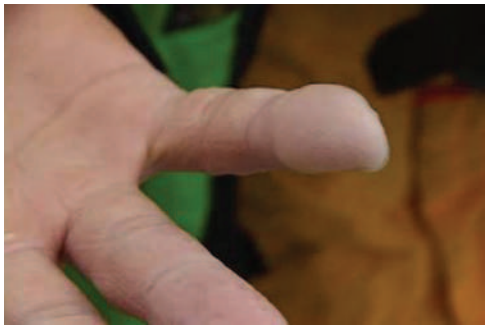


**FIGURE 9-3** Climber with second-degree frostbite of the fifth finger sustained after only several seconds' exposure to –45.6°C (–50°F) windchill when gloves were briefly removed to handle placement of a carabiner to the fixed rope. Clear bullae developed after rewarming. *(Courtesy Luanne Freer, MD.)*

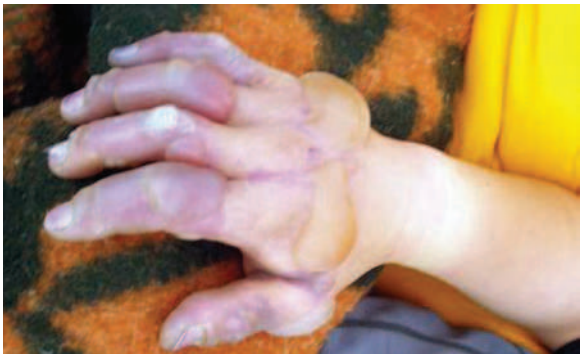


**FIGURE 9-4** Climber with second-, third-, and fourth-degree frostbite of the hand. Note fingers 1 to 4 with hemorrhagic bullae over the areas of third-degree injury, clear bullae over the dorsum of the hand with second-degree injury, and deeply violaceous and unblistered fourth-degree injury of the distal phalanx of the fifth finger. *(Courtesy Luanne Freer, MD.)*

cause mummification, with muscle and bone involvement (Figure 9-6). Less severe bone injury in children may affect the growth plate and result in developmental digital deformities.[21,27]

Cauchy and colleagues[31] proposed a different classification of frostbite injury for the hand and foot based on the risk for amputation of the affected part. An early prognosis prediction for frostbite patients may be delayed by the lack of useful clinical guidelines; this new classification scheme is intended to help resolve such issues (Tables 9-1 to 9-3). The four severity levels proposed provide earlier prediction of the final outcome of frostbite injury by using a technetium-99m ($^{99m}$Tc) bone scan in conjunction with the clinical findings on presentation. The probability of bone amputation for the hand and foot could also be correlated to the extent of frostbite injury seen at the initial presentation and early $^{99m}$Tc bone scanning. In a review of 70 cases of severe frostbite injury, the probability of bone amputation was 1% for involvement of the distal phalanx, 31% when involvement included the middle phalanx, 67% when involvement included the proximal phalanx, and 98% and 100%, respectively, when involvement included the metacarpal/metatarsal and carpal/tarsal bones (see Table 9-3). Grade 1 lesions do not require hospitalization or bone scans. Grade 2 lesions may require brief hospitalization and bone scans. Rapid rewarming and treatment with antibiotics and oral vasodilators appear to be sufficient for healing. Grade 3 lesions are connected with a significant risk for amputation and require rapid rewarming, antibiotics, aspirin, and intravenous (IV) vasodilators. Grade 4 lesions have high risk for amputation and complications such as thrombosis, sepsis, and other systemic problems (see Table 9-3). Cauchy's clinical/$^{99m}$Tc-based classification scheme appears particularly useful in its ability to predict at a very early stage the outcome of a frostbite injury.[31]

## CONTRIBUTING FACTORS

### TEMPERATURE AND WINDCHILL

Air alone is a poor thermal conductor, and cold air alone is not nearly as dangerous a freezing factor as a combination of wind and cold.[208] Wind velocity in combination with temperature establishes the windchill index. For example, an ambient temperature of –6.7°C (–19.9°F) with a 72-km/hr (45-mph) wind has the same cooling effect as a temperature of –40°C (–40°F) with a 3.2-km/hr (2-mph) breeze (Figure 9-7).[198,200,203] Thus, it is important to think in terms of heat loss, not cold gain. Frostbite occurs when the body is unable to conserve heat or protect against heat loss.

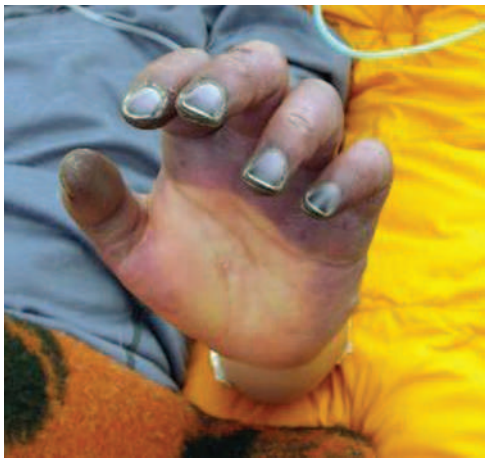


**FIGURE 9-5** Climber with fourth-degree or severe frostbite injury just hours after rewarming. Note absence of any blistering. Fingers are insensate, and capillary refill is absent. *(Courtesy Luanne Freer, MD.)*

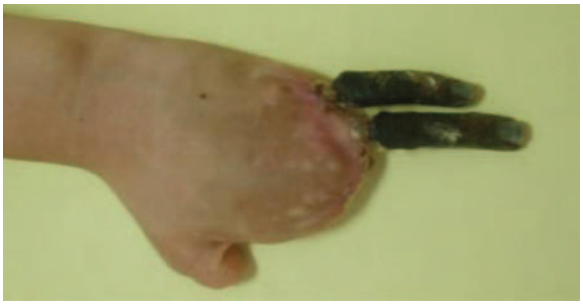


**FIGURE 9-6** Photographs of 8-week follow-up of hand pictured in Figure 9-5, showing complete mummification and autoamputation of remaining digits. *(Courtesy Luanne Freer, MD.)*

**TABLE 9-1** Proposed Classification for Severity of Frostbite Injuries of the Extremities

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Extent of initial lesion at day 0 after rapid rewarming | Absence of initial lesion | Initial lesion on distal phalanx | Initial lesion on intermediary (and) proximal phalanx | Initial lesion on carpal/tarsal |
| Bone scanning at day 2 | Useless | Hypofixation of radiotracer uptake area | Absence of radiotracer | Absence of radiotracer uptake area on the carpal/tarsal |
| Blisters at day 2 | Absence of blisters | Clear blisters | Hemorrhagic blisters on the digit | Hemorrhagic blisters over carpal/tarsal |
| Prognosis at day 2 | No amputation | Tissue amputation | Bone amputation of the digit | Bone amputation of the limb ±systemic involvement ±sepsis |
| Sequelae | No sequelae | Fingernail sequelae | Functional sequelae | Functional sequelae |

From Cauchy E, Chetaille E, Marchand V, et al: Retrospective study of 70 cases of severe frostbite lesions: A proposed new classification scheme, *Wilderness Environ Med* 12:248, 2001.

**TABLE 9-2** Management of Frostbite Injuries of the Extremities

On day 0, treatment consists of rapid rewarming for 2 hours in 38°C (100.4°F) water bath, with intravenous infusion of 400 mg chlorohydrate of buflomedil and 250 mg aspirin. Subsequent treatment depends on the extent of the initial lesion, as follows:

| Grade 1*: Absence of Initial Lesion | Grade 2: Initial Lesion over Distal Phalanx | Grade 3: Initial Lesion over Intermediary (and) Proximal Phalanx | Grade 4: Initial Lesion over Carpal/Tarsal |
|---|---|---|---|
| No hospitalization | Hospitalization 2 days | Hospitalization 8 days | Hospitalization intensive care unit |
| Oral treatment for 1 week (aspirin, vasodilator) | Possibly a bone scan at day 2 | Bone scan at day 2 | Bone scan at day 2 |
| — | Oral treatment for 3 weeks (aspirin, vasodilators), dressing | IV administration for 8 days (aspirin, vasodilators), dressing | IV administration for 8 days (aspirin, vasodilators), dressing |
| — | — | Bone scan near day 8 | Possibly antibiotics |
| — | — | Bone amputation near day 30 | Early bone amputation near day 3 if sepsis |
| Recovery | Recovery with moderate sequelae | Bone amputation of digit with functional sequelae | Bone amputation of limbs with systemic involvement |

From Cauchy E, Chetaille E, Marchand V, et al: Retrospective study of 70 cases of severe frostbite lesions: A proposed new classification scheme, *Wilderness Environ Med* 12:248, 2001.
*IV,* Intravenous.
*See Figure 9-2.

**TABLE 9-3** Probability of Amputation Based on the Extent of the Initial Lesion

| | Extent (Level of Involvement) | Probability of Bone Amputation (95% CI) |
|---|---|---|
| Hand | 5 (carpal/tarsal) | 100— |
| | 4 (metacarpal/metatarsal) | 100— |
| | 3 (proximal phalanx) | 83 (66;100) |
| | 2 (intermediary phalanx) | 39 (25;52) |
| | 1 (distal phalanx) | 1 (00;03) |
| Foot | 5 (carpal/tarsal) | 100— |
| | 4 (metacarpal/metatarsal) | 98 (93;100) |
| | 3 (proximal phalanx) | 60 (45;74) |
| | 2 (intermediary phalanx) | 23 (10;35) |
| | 1 (distal phalanx) | 0— |
| Hand and foot | 5 (carpal/tarsal) | 100— |
| | 4 (metacarpal/metatarsal) | 98 (95;100) |
| | 3 (proximal phalanx) | 67 (55;79) |
| | 2 (intermediary phalanx) | 31 (22;41) |
| | 1 (distal phalanx) | 1 (00;02) |

From Cauchy E, Chetaille E, Marchand V, et al: Retrospective study of 70 cases of severe frostbite lesions: A proposed new classification scheme, *Wilderness Environ Med* 12:248, 2001.
*CI,* Confidence interval.

**FIGURE 9-7** Jet stream on Mt Everest, premonsoon. Caudwell Xtreme Everest Expedition. *(Courtesy Christopher H.E. Imray, MD.)*

## CONDUCTION

The type and duration of cold contact are the two most important factors in determining the extent of frostbite injury.[198,200,203] Touching cold wood or fabric is not nearly as dangerous as direct contact with metal, particularly by wet or even damp hands.[60] This is a result of differences in thermal conductivity between the materials..

Deep, loose snow, which traditionally has been thought to insulate from the cold, may actually contribute to frostbite. Temperature measured beneath deep snow is frequently much lower than that on the surface. Washburn[203] recounts one expedition to Denali, Alaska, when members of his party found it extremely difficult to keep their feet warm, despite a clear, sunny, −16° C (3.2° F) day with little wind. One member inadvertently dropped a thermometer in the snow and noted that it registered −25.6° C (−14.1° F). Feet must be dressed for the temperature at their level of their immersion in the snow, not for surface temperature protection.[203]

## ALTITUDE

Ambient temperature drops by approximately 1.0° C (1.8° F) for every 150 m (492 feet) of altitude gain. Many serious cases of frostbite originate at high altitude, but it is difficult to sort out the independent risk generated by hypobaria/hypoxia versus cold exposure. Hashmi and colleagues[71] reported 1500 cases of high-altitude frostbite and observed a "very steep upward curve" beyond a height of 5182 m (17,000 feet) above sea level. CIVD has been shown to be diminished in non-native visitors to high altitude.[61] Some important sequelae of high-altitude acclimatization—erythrocytosis and high-altitude dehydration—result in hyperviscosity that may make frostbite more likely. Garvey and associates[59] demonstrated that erythremia in the setting of a hypobaric environment provoked procoagulability in a rhesus monkey model.

Recent evidence using a real-time video-imaging technique compared sublingual microcirculation at sea level and altitude.[113] The study showed significant reduction in microcirculatory flow index (MFI) at high altitude (4900 m [16,076 feet]) compared with sea level in small (<25 μm) and medium (26 to 50 μm) blood vessels (Figure 9-8). Larger vessels were not studied because of the relative paucity of their representation in the vascular bed studied. The results showed further reduction in MFI within small and medium vessels at extreme altitude (6400 m [20,997 feet]). The very marked slowing of blood flow in the microcirculation at high altitude is easily appreciated. "Stagnant" hypoxia may occur in tissues as a result of reduced microcirculatory blood flow and consequent failure of oxygen mass transfer. Furthermore, disparity between oxygen supply and demand at the microvascular level could lead to heterogeneous tissue oxygenation and cellular hypoxia.[83] These preliminary data are the first evidence demonstrating clear reduction in microcirculatory blood flow at altitude and may in part explain the apparent increased incidence of frostbite at extreme altitude, because a reduction in flow will be associated with reduction in heat transfer. Further studies to assess the potential reversibility with supplemental oxygen are indicated.

Hypoxic neurologic dysfunction is a feature among nonsurvivors at extreme altitude; failure to adequately protect extremities may contribute to the high incidence of frostbite at extreme altitude.[51] Inadequate fluid intake and poor nutrition are possible risk factors.[133,154]

## COOLANTS

Not all victims of frostbite are exposed to cold environments. Case reports cite toxic dermatologic effects of propane, butane, chloroethane, and liquid oxygen[56,103,185,193,197] application to the skin, either intentionally but exceeding time exposure for cryotherapy, or accidentally (Figure 9-9), as in the case of severe frostbite requiring skin grafting in a child improperly using a toilet air freshener containing propane and butane.[103]

Careless use of ice to cool a soft tissue injury can result in frostbite,[64] so patients should be instructed to place a towel or other fabric between ice packs and bare skin to prevent this complication.

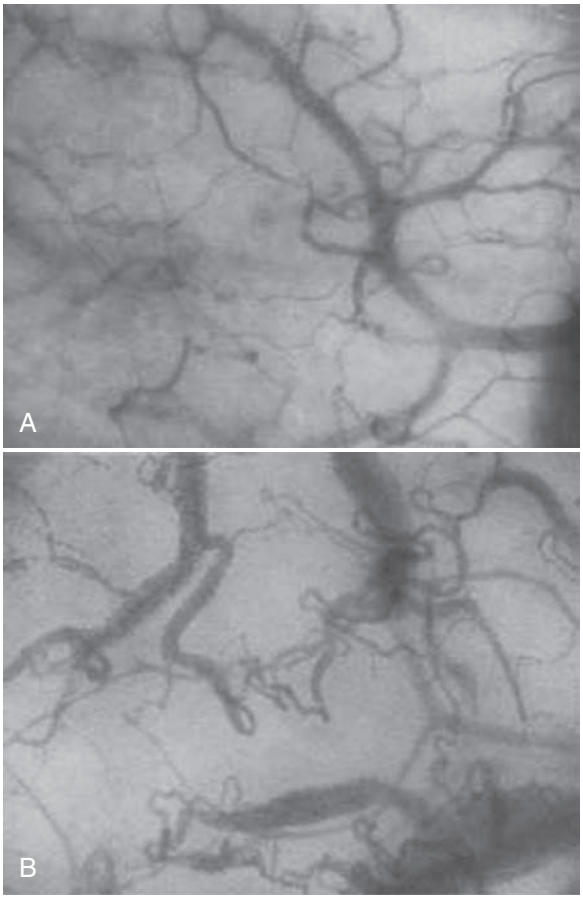



**FIGURE 9-8** Sublingual microcirculatory flow at sea level **(A)** and 4900 m (16,076 feet) **(B)**. There is a significant reduction in microcirculatory flow index at high altitude (4900 m) when compared with baseline in small (<25 μm) and medium (26 to 50 μm) blood vessels. Caudwell Xtreme Everest Expedition. *(From Martin DS, Ince C, Goedhart P, et al: Abnormal blood flow in the sublingual microcirculation at high altitude,* Eur J Appl Physiol *106:473, 2009.)*

## CLOTHING

The degree of inadequacy of protective clothing varies with conditions and may contribute to insufficient conservation of body heat.[40] Tight-fitting clothing may produce constriction, which hinders blood circulation and lessens the benefit of

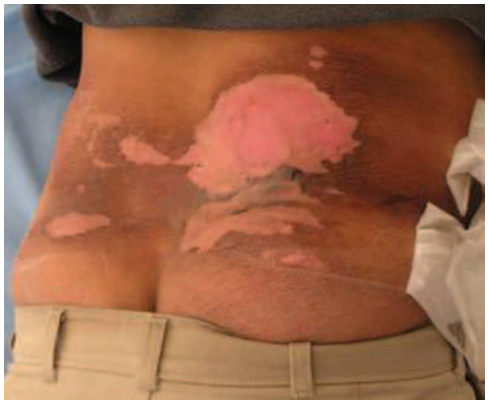


**FIGURE 9-9** Sherpa climber on day 4 of treatment for second-degree frostbite from propane leak in backpack on Mt Everest. *(Courtesy Luanne Freer, MD.)*

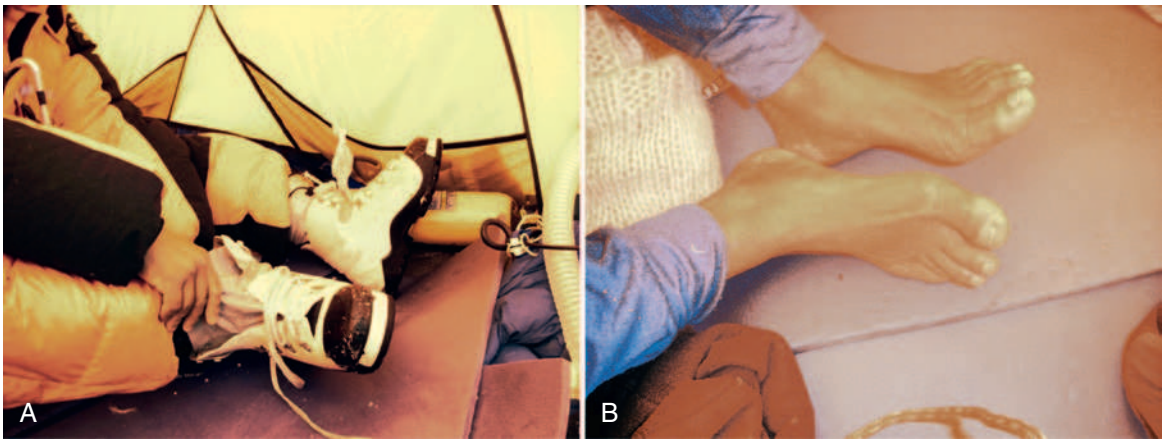



**FIGURE 9-10** Early frostbite at 7950 m (26,083 feet) hours after summiting Mt Everest. Five pairs of socks were being worn. The patient was advised to self-evacuate without rewarming frostbitten feet. Caudwell Xtreme Everest Expedition. *(Courtesy Christopher H.E. Imray, MD.)*

heat-retaining air insulation. Wet clothing transmits heat from the body into the environment, because water is a thermal conductor superior to air by a factor of about 25.[97] Clothing that transmits moisture away from the body may be protective if an outer, wind-resistant layer decreases heat loss. However, this wind-resistant layer must retain the same transmission capabilities; otherwise, clothing will still become moist. Clothes that decrease the amount of surface area may decrease frostbite risk. Mittens are more protective than gloves, because gloves have a greater surface area and prevent air from circulating between fingers. Poorly fitted boots notoriously generate frostbite injuries, even when worn with excess socks (Figures 9-10 and 9-11).

Although up to 40% of total body heat loss can occur through exposed head and neck areas,[3] a study has refuted the widely held belief that the head loses proportionally more heat than the rest of the body. In fact, any uncovered part of the body loses heat in proportion to the body surface area exposed; appropriate protection is important for all exposed skin.[153]

**FIGURE 9-11** Climber on South Col, Mt Everest (7950 m [26,083 feet]) with excess socks in hand, about to descend. Caudwell Xtreme Everest Expedition. *(Courtesy Christopher H.E. Imray, MD.)*

## SKIN WETNESS/UNWASHED SKIN

Development of frostbite does not depend only on ambient temperature and duration of exposure. Windchill, humidity, and wetness predispose to frostbite. Skin wetting adds an increment of heat transfer through evaporation and causes wet skin to cool faster than dry skin.[135] More important, water in the stratum corneum can terminate supercooling by triggering water crystallization not only in this layer but also in underlying tissue. Skin wetness is therefore conducive to frostbite because it allows crystallization to terminate supercooling after approximately one-half the exposure time required by dry skin. This substantiates the following clinical observation:

> It has been found that supercooling displays itself in greater degree in skin that remains unwashed. Washing the skin encourages freezing, whereas rubbing the skin with spirit and anointing it with oil discourages it. The capacity to supercool greatly would seem to be connected with relative dryness of the horny layers of the skin. It is well known that Arctic explorers leave their skin unwashed.[107]

## ALTERED MENTAL STATUS (ALCOHOL, DRUGS, MENTAL ILLNESS)

Putting on clothes in response to cold is not a reflex but requires a conscious decision. When the ability to decide or to act is impaired, there is risk for cold-induced injury; not surprisingly, alcohol has been implicated in up to 53% of nonmilitary frostbite cases.[192] Once the injury had occurred, alcohol intake probably did not significantly alter the course of events. Barillo and associates[13] experimentally demonstrated increased mortality and a detrimental effect of ethanol on tissue perfusion associated with severe murine frostbite. Alcohol consumption promotes peripheral vascular dilation and increases heat loss, making an exposed part more susceptible to frostbite.[162]

In one series of 20 urban frostbite patients, all had overt or covert psychiatric disease.[148] This prompted a retrospective review that suggested between 61% and 65% of urban frostbite patients have psychiatric disease, and some centers now advocate psychiatric screening in all patients with of urban frostbite injury.

## FATIGUE

During World War II and the Korean conflict, clinical studies indicated that cold injuries occurred with higher frequency among soldiers in retreat.[142,207] Fatigue and apathy increase the

incidence of cold injury. When warfare is proceeding toward defeat, or in conditions of starvation, soldiers often become indifferent to personal hygiene and clothing, and the frequency of frostbite increases.[95] Overexertion increases heat loss. A large amount of body heat can be expended by panting, and perspiration further compounds the problem of chilling. Both panting and sweating consume energy, which compounds the fatigue factor.

### TOBACCO SMOKING

Impaired local circulation is a primary contributor to frostbite. Cigarette smoking causes vasoconstriction, decreased cutaneous blood flow, and tissue loss in random skin flaps.[106] Reus and colleagues[160] documented that smoking induced arteriolar vasoconstriction and decreased blood flow in a nude subject. Although red blood cell velocity increased, the net effect was decreased blood flow in cutaneous microcirculation during and immediately after smoking. Curiously, habitual heavy smokers show higher scores on the Resistance Index of Frostbite (RIF), which correlates with lower risk for frostbite.[36] Empirically, one could conclude that smoking, which induces vasoconstriction, should place one at increased risk for frostbite, and research supports this.[37,47,71]

### COMORBIDITIES

Drugs known to have vasoactive properties may predispose to or worsen frostbite injury. Disease states that alter tissue perfusion, such as diabetes, atherosclerosis, arteritis, and Raynaud's disease, predispose to frostbite (Figure 9-12).[41,100]

### PREVIOUS FROSTBITE INJURY

An individual who has experienced prior cold injury is placed in a high-risk category during subsequent cold exposure.[129,207] For undefined reasons, cold injury sensitizes an individual, so that subsequent cold exposure, even of a lesser degree, produces more rapid tissue damage.[96] Cold-induced neuropathy may play an important role in the long-term presence of cold sensitivity after local cold injury. An alteration in somatosensory function was found, and this was more pronounced in lower-limb injuries.[8]

### IMMOBILITY

Military studies emphasize that long periods of immobility contribute to the extent of cold injury.[96,97] Motion produces body heat and improves circulation, especially in endangered limbs.

**FIGURE 9-12** A 54-year-old man had an acute primary episode of Raynaud's disease after surfing for 80 minutes in water that was 21°C (69.8°F). The distinctive asymmetric pallor of the terminal phalanges of the fourth digit on the right hand persisted for 40 minutes. A sharp demarcation between the second and third phalangeal joints was evident, but no other symptoms were apparent. The pallor spontaneously resolved without cyanosis or redness of the affected area. Medical evaluation subsequently revealed no disorder known to cause secondary Raynaud's phenomenon. *(From Bluto MJ, Norman DA: Acute episode of Raynaud's disease,* N Engl J Med *347:992, 2002.)*

### GENETIC PREDISPOSITION

The deletion genotype (DD) for the angiotensin I–converting enzyme (ACE) has been associated with increased vascular reactivity in vivo and in vitro.[23,75] Kamikomaki[88] proposed that a case of frostbite in a climber with ACE DD allele was caused by genetic propensity for vasoconstriction.

Civilian clinical studies are inadequate for statistical evaluation of factors such as race and previous climatic environmental exposure.[96,119,121] In a recent study, African Americans were found to have difficulty generating increased metabolic rate (measured by oxygen consumption [$\dot{V}O_2$] and rectal temperature) after acute cold exposure, and researchers suggest this group may be at greater risk for cold injury.[49] Military studies suggest that women and blacks may be more susceptible to cold injury.[37,61] One author postulates that blacks are three to six times more susceptible to frostbite than are whites because blacks tend to initiate shivering at lower core temperatures and tend to have long, thin fingers and toes, as well as thin arms and legs, which do not conserve heat as efficiently as do their white counterparts. In testing, black fingers cool faster when immersed in cold water and reach a lower temperature before the hunting response ensues.[61] Individuals with type O blood and from warmer climatic regions in the United States tend to be more susceptible.[61,207]

An increased incidence of frostbite was reported in almost 6000 military recruits with cold-provoked white finger syndrome and in those with hand/arm vibration.[47,141]

A low RIF, determined in a simple laboratory test, may be indicative of increased risk for cold injuries during operations in the field.[36]

## CLINICAL PRESENTATION

In most patients, the initial clinical observation is coldness of the injured part, and more than 75% complain of numbness. The involved extremity feels clumsy or "absent" because of ischemia following intense vasoconstriction. When numbness is present initially, it is frequently followed by extreme pain (76% of patients) during rewarming. Throbbing pain begins 2 to 3 days after rewarming and continues for a variable period, even after dead tissue becomes demarcated (22 to 45 days). After about 1 week, the patient usually notices a residual tingling sensation, a result of ischemic neuritis, which explains why this sensation tends to persist longer than other symptoms. Severity of the injury usually defines the extent of neuropathologic damage. Because different injuries are influenced by so many environmental and individual factors, symptoms may vary greatly. In patients without tissue loss, symptoms usually subside within 1 month, whereas in those with tissue loss, disablement may exceed 6 months. In all cases, symptoms are intensified by a warm environment. Other sensory deficits include spontaneous burning and electric current–like sensations. The burning sensation, which is frequently early in presentation, subsides within 2 to 3 weeks and is usually not present in patients with tissue loss. In those without tissue loss, the burning sensation may resume on wearing shoes or increasing activity. The electric current–like shock is almost universal (97%) in patients with tissue loss. It usually begins 2 days after injury, lasts for about 6 weeks, and is particularly unpleasant at night. All frostbite patients experience some degree of sensory loss for at least 4 years after injury and perhaps indefinitely.

The clinical appearance of frostbite depends on how quickly the injured patient presents to care, and it is important to note that this appearance may initially be deceiving.[17,142] In the past, patients in the Alps who arrived by helicopter within minutes of their injury presented quite differently than did Himalayan climbers, who had almost completely rewarmed during self-descent and were fortunate if they were able to arrive at definitive care even several days after injury.[46] Fortunately, helicopter evacuation is being used more widely in the regions with taller mountains. Regardless of venue, only a few patients arrive with tissue still frozen. At first, the extremity appears yellowish white or mottled blue. It may be insensate and may appear frozen solid, regardless of the depth of the injury. With rapid rewarming, there

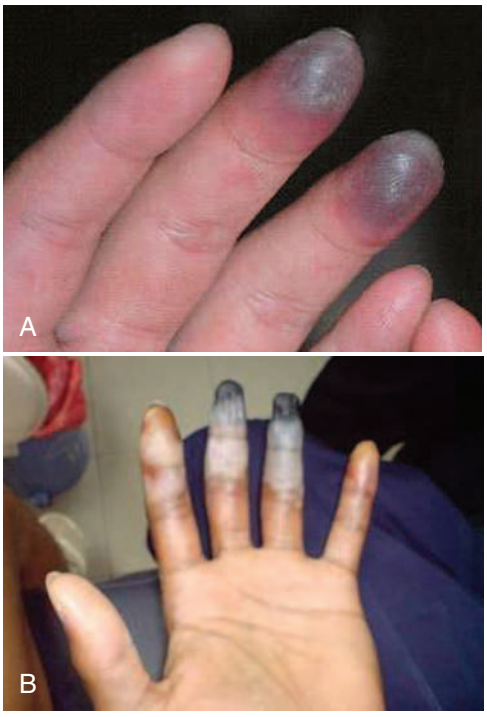



**FIGURE 9-13** Photo of climber 24 hours **(A)** and approximately 2 weeks after **(B)** deep frostbite injury to fingers, showing eschar formation. *(Courtesy Luanne Freer, MD.)*

is almost immediate hyperemia, even in some patients with the most severe injuries. Sensation returns after thawing and persists until blebs appear. At this point, an effort should be made to assess the severity of the injury.

After the extremity is rewarmed, edema appears within 3 hours and lasts 5 days or longer, depending on the severity of the case. Vesicles or bullae appear 6 to 24 hours after rapid rewarming. Clear bullae confer a better prognosis than hemorrhagic bullae, which indicate deeper injury. During the first 9 to 15 days, severely frostbitten skin forms a black, hard, and usually dry eschar, whether or not vesicles are present (Figure 9-13). Mummification forms an apparent line of demarcation in 22 to 45 days.[142]

## FIELD TREATMENT

In 1957, Hurley[78] stated, "Tissue cells can be affected by freezing in three different ways: (1) a certain number of cells are killed; (2) a certain number remain unaffected; and (3) a large number are injured but may recover and survive under the right circumstances." Clearly, the major treatment effort must be to salvage as many cells in the third group as possible. Frostbite treatment is directed separately at the prethaw and postthaw intervals.

### SELF-RESCUE IN THE FREEZING ENVIRONMENT

The International Commission for Alpine Rescue (ICAR) gives specific recommendations for self-rescue to persons working, recreating, or otherwise exposed to a cold environment (Box 9-1). These guidelines advise seeking shelter from cold and wind, drinking warm fluids, removing wet clothing, taking ibuprofen, and attempting self-rewarming for 10 minutes. If at high altitude, supplemental oxygen is advised, and if sensation does not return, the patient is advised to discontinue any further exposure and seek treatment.[187] Although these guidelines may seem common sense to most, climbers appreciate these guidelines for safety and self-rescue when in an exposed, potentially dangerous, and remote setting.

### TREATMENT IN THE PREHOSPITAL FREEZING ENVIRONMENT

The Alaska State guidelines for field treatment and transport of patients with frostbite recommend the following:

**If transport time will be short (1 to 2 hours at most)**, the risks posed by improper rewarming or refreezing outweigh the risks of delaying treatment for deep frostbite.

**If transport will be prolonged (more than 1 to 2 hours)**, frostbite will often thaw spontaneously. It is more important to prevent hypothermia than to rewarm frostbite rapidly in warm water. This does not mean that a frostbitten extremity should be kept in the cold to prevent spontaneous rewarming. Anticipate that frostbitten areas will rewarm as a consequence of keeping the patient warm and protect them from refreezing at all costs.[1]

The Joint Commission of Health and Human Services, emergency medical services, and public health departments for Alaska have published further guidelines for prehospital and bush clinic care of frostbite. These guidelines are widely regarded as state-of-the-art recommendations (Box 9-2). If a patient is referred from a nearby location, no attempt at field rewarming is indicated. Vigorous rubbing is ineffective and potentially harmful. The extremity should not be intentionally rewarmed during transport and should be protected against slow, partial rewarming by keeping the patient away from intense campfires and car heaters. All constrictive and wet clothing should be replaced by dry, loose wraps or garments. The extremity is padded and splinted for protection, and oral ibuprofen, 400 mg twice daily, may be initiated (ibuprofen may be more beneficial than aspirin because aspirin may block more of the inflammatory cascade than is helpful). Although a correlation exists between the length of time tissue is frozen and the amount of time required to thaw that tissue, no direct correlation exists between the length of time tissue is frozen and subsequent tissue damage. Still, "rapid" transport of frostbite patients (within 2 hours) is appropriate, and one should not purposefully keep tissues below freezing temperatures (unless there is risk of refreezing injury).[123] If immediate transport is not feasible, rapid rewarming should be instituted (goal is to see blush of rewarming and/or 15 minutes immersed in rewarming fluid) and the patient transported with protective, dry, and nonadherent dressings to prevent refreezing. Appropriate adequate analgesia should be administered; an IV or intramuscular (IM) opiate may be required. Blisters should be left intact. Patients with long transport times are at greater risk for (refreezing) recurrent injury. All efforts should be made to

**BOX 9-1** Guidelines from ICAR for Self-Treatment of Potential Frostbite

**Emergency Treatment**

***In the Open with Possible Onset of Frostbite***

- Move out of the wind; consider turning back; drink fluids (warm if possible).
- Remove boots, but consider possible problems with replacement if swelling occurs.
- Remove socks/gloves if wet. Exchange for dry clothing.
- Warm by placing foot/hand in companion's armpit/groin *for 10 minutes only.*
- Replace boots.
- Give one dose of aspirin or ibuprofen to improve circulation (if available and not contraindicated).
- Do not rub the affected part because this may cause tissue damage.
- Do not apply direct heat.

If there is sensation, the patient can continue to walk.
If there is no sensation, the patient should go to the nearest warm shelter (hut/base camp) and seek medical treatment.
At high altitude, give oxygen if available.

Modified from Syme D (for ICAR Medical Commission): Position paper: On-site treatment of frostbite for mountaineers. *High Alt Med Biol* 3:297, 2002.
*ICAR*, International Commission on Alpine Rescue.

**BOX 9-2** Alaska State Guidelines for Prehospital Treatment of Frostbite

**First Responder/Emergency Medical Technician—I, II, III/ Paramedic/Small Bush Clinic**

***Evaluation and Treatment***

A. Anticipate, assess, and treat the patient for hypothermia, if present.
B. Assess the frostbitten area carefully because the loss of sensation may cause the patient to be unaware of soft tissue injuries in that area.
C. Obtain a complete set of vital signs and the patient's temperature.
D. Remove jewelry and clothing, if present, from the affected area.
E. Obtain a patient history, including the date of the patient's last tetanus immunization.
F. If there is frostbite distal to a fracture, attempt to align the limb unless there is resistance. Splint the fracture in a manner that does not compromise distal circulation.
G. Determine whether rewarming the frostbitten tissue can be accomplished in a medical facility. If it can, transport the patient while protecting the tissue from further injury from cold or impacts.
H. If the decision is made to rewarm frostbitten tissue in the field, you should prepare a warm water bath in a container large enough to accommodate the frostbitten tissues without them touching the sides or bottom of the container. The temperature of the water bath should be 99° to 102° F (37° to 39° C).
   - Generally, patients with frostbite do not require opiates for pain relief; they occasionally need nonopiate pain medication or anxiolytics. If possible, consult a physician regarding the administration of oral analgesics, such as acetaminophen, ibuprofen, or aspirin. Aspirin or ibuprofen may help improve outcomes by blocking the arachidonic acid pathway.
   - Immersion injury or frostbite with other associated injuries may produce significant edema and high pain levels. These patients may need opiate pain medications for initial treatment. In this case, advanced life support personnel should administer morphine or other analgesics in accordance with physician-signed standing orders or online medical control.

I. A source of additional warm water must be available.
J. Water should be maintained at approximately at 99° to 102° F (37° to 39° C) and gently circulated around the frostbitten tissue until the distal tip of the frostbitten part becomes flushed.
K. Pain after rewarming usually indicates that viable tissue has been successfully rewarmed.
L. After rewarming, let the frostbitten tissues dry in the warm air. Do *not* towel dry.
M. After thawing, tissues that were deeply frostbitten may develop blisters or appear cyanotic. Blisters should not be broken and must be protected from injury.
N. Pad between affected digits and bandage affected tissues loosely with a soft, sterile dressing. Avoid putting undue pressure on the affected parts.
O. Rewarmed extremities should be kept at a level above the heart, if possible.
P. Protect the rewarmed area from refreezing and other trauma during transport. A frame around the frostbitten area should be constructed to prevent blankets from pressing directly on the injured area.
Q. Do not allow an individual who has frostbitten feet to walk except when the life of the patient or rescuer is in danger. Once frostbitten feet are rewarmed, the patient becomes nonambulatory.

From Department of Health and Social Services, Division of Public Health Section of Community Health and EMS: *State of Alaska Cold Injuries Guidelines*, 2003 version rev 2005. http://www.chems.alaska.gov.

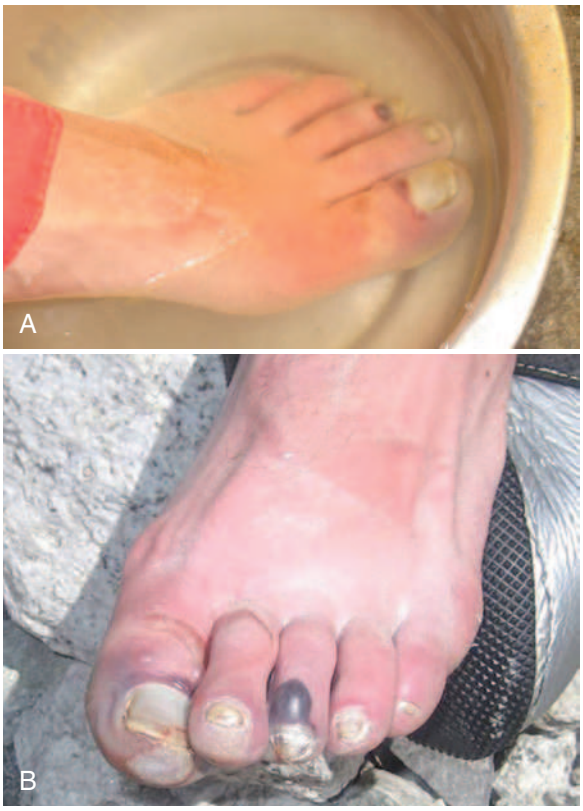



**FIGURE 9-14** **A,** Day 2 after exposure: field rewarming of frostbite injury to Mt Everest summiteer at 6400 m (20,997 feet); **B,** Day 3: field treatment of frostbite injury at 5300 m (17,388 feet). *(Courtesy Christopher H.E. Imray, MD.)*

prevent refreezing, because this creates a much worse outcome than does delayed thawing (Figures 9-14 to 9-16). A patient who must walk through snow should do so before thawing frostbitten feet (see Figure 9-10). During transport, the extremities should be elevated and tobacco smoking prohibited.[130]

The Wilderness Medical Society convened a panel of experts in 2011 and 2014 to review recent literature and ICAR and Alaska State guidelines in order to apply evidence grades based on the quality of supporting evidence and to balance the benefits and risks for each modality according to methodology stipulated by the American College of Chest Physicians.[122,123] Their guidance is in line with that of the Alaska guidelines. The review is a useful evidence-based reference for persons who do not routinely manage frostbite injuries.

## DEFINITIVE TREATMENT (IMMEDIATE TREATMENT)

Once in the emergency department (ED), if tissues are still frozen, rapid rewarming should be started immediately. Any associated traumatic injuries or medical conditions should be identified. Systemic hypothermia should be corrected to a core temperature of at least 34° C (93.2° F) before frostbite management is attempted. Fluid resuscitation is usually not a problem with isolated frostbite injuries, although one case of rhabdomyolysis and acute renal failure has been reported.[165] One must remember that prolonged strenuous exercise or altitude exposure increases the risk for dehydration, so it is advised to encourage oral intake or IV fluids.

Treatment is directed at the specific pathophysiologic effects of the frostbite injury, either blocking direct cellular damage or preventing progressive microvascular thrombosis and tissue loss. Direct cellular damage is treated by rapid thawing of all degrees of frostbite with immersion in gently circulating water warmed

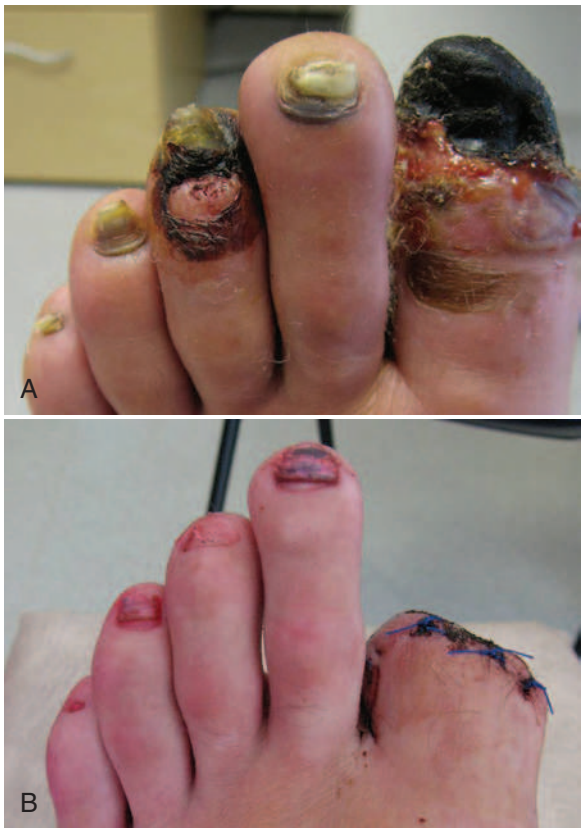



**FIGURE 9-15** **A,** Six weeks after injury: third toe is showing signs of recovery. **B,** Ten weeks after injury: primary closure was achieved with full-thickness skin cover to optimize the functional result. *(Courtesy Christopher H.E. Imray, MD.)*

to 37° to 39° C (98.6° to 102.2° F).[123,137] Adherence to this narrow temperature range (as long as it is easy to monitor in the hospital) is important, because rewarming at lower temperatures is less beneficial for tissue survival, and rewarming at higher temperatures may worsen the injury by producing a burn wound.[57,74,132] Frozen extremities should be rewarmed until the involved skin becomes pliable and erythematous at the most distal parts of the frostbite injury. This usually takes less than 30 minutes. Active motion during rewarming is helpful, but massage may compound the injury. Extreme pain may be experienced during thawing, and unless otherwise contraindicated, parenteral analgesics are administered. Rapid return of skin warmth and sensation with the presence of an erythematous color is a favorable sign, whereas the persistence of cold, anesthetic, and pale skin is unfavorable.

**FIGURE 9-16** Integrated vascular/orthotic assessment in a specialized clinic after surgery (in preparation for a further high-altitude expedition). *(Courtesy Christopher H.E. Imray, MD.)*

Rapid rewarming reverses the direct injury of ice crystal formation in the tissue. However, it does not prevent the progressive phase of the injury. McCauley and associates[119,120] have designed a protocol based on the pathophysiology of progressive dermal ischemia that has been quite successful in minimizing production of local and systemic thromboxane by injured tissues. All patients except those with the most minor frostbite injury should be admitted to the hospital. Patients with minor injuries should be admitted if, after rapid rewarming, a warm environment cannot be ensured for the patient. No patient should ever be discharged into subfreezing weather. Even with a warm car waiting, the patient should be allowed to leave only with proper clothing, such as stocking cap and wool mittens and socks.

Because the majority of frostbite injuries necessitate admission to the hospital, a discussion of the protocol is warranted. White or clear blisters, which represent more superficial injury, are debrided to prevent further contact of $PGF_{2\alpha}$ or $TXA_2$ with the damaged underlying tissues. Unlike the clear blisters, hemorrhagic blisters reflect structural damage to the subdermal plexus. It may be worthwhile to aspirate the thromboxane-containing fluid out of these blisters, but debridement may promote desiccation of the deep dermis and allow conversion to a full-thickness injury. It has been argued that hemorrhagic blisters should be left intact; however, we tend to favor drainage. A specific thromboxane inhibitor, such as *Aloe vera* gel, is placed on the wounds, and dressings should accommodate expected increasing edema.[73] Aspirin was originally recommended to be given systemically to block production of $PGF_{2\alpha}$ and $TXA_2$. The correct dose of aspirin to block $PGF_{2\alpha}$ is difficult to determine, however, so it has been replaced by ibuprofen. Aspirin may still have a useful antiplatelet action if ibuprofen is not available. Ibuprofen not only inhibits the arachidonic acid cascade but has the additional benefit of fibrinolysis. Oxygen should be used to achieve normoxia in a hypoxic patient and is used for frostbite injuries occurring at extreme altitude.

# EVALUATION AND TREATMENT IN THE HOSPITAL

## OVERALL STRATEGY

Frostbite is a thermal injury affecting the vasculature, microvasculature, and tissues of the extremities and, as such, shares many clinical features with both vascular injuries and burn wounds. This section discusses the aspects of definitive patient care, including complete patient assessment, specific evaluation of the frostbite injury regarding perfusion and tissue viability, and optimal medical management, including proper selection of candidates for endoluminal treatments such as catheter-directed thrombolysis or iloprost infusion. Early and late reconstructive surgery, ablative surgery, rehabilitation, and frostbite prevention strategies are also discussed.

## INITIAL ASSESSMENT OF FROSTBITE AND OTHER INJURIES

A rapid and detailed clinical assessment of the patient on arrival in the ED is mandatory. The standard approach of assessing the airway, breathing, and circulation takes precedence over assessment of the frostbite injury. History and examination may reveal coexisting problems, and although the frostbite injuries may be visually distressing and severe, there may be more serious injuries or medical conditions that require treatment first. Particular attention needs to be paid to hypothermia, limb fractures, the peripheral circulation, and coexisting trauma. Medical conditions, such as poor glycemic control and alcohol/drug use, must be considered.

### Principles

Hurley[78] stated in 1957 that frostbite results in three zones of tissue injury: dead tissue, normal living tissue, and an interface zone. If we develop this concept further, immediately after the index frostbite injury, the size of the interface zone is maximal

and potentially salvageable. Weeks after injury, the interface zone will be negligible; as a result, the interface zone has a "dynamic" component.[56,78] The aim of early evaluation of the frostbite injury is to try to determine the exact extent of the three zones so that a subsequent multifaceted management plan may be directed to optimize tissue salvage in the dynamic interface zone.

The initial injury, patient's response, ambient temperature, and time from initial cold injury to presentation at the hospital all contribute to the extent of the intermediate, potentially salvageable interface zone. The patient who is transferred from the mountainside directly to the ED by helicopter will have a relatively large, potentially salvageable interface zone compared with a patient who has undergone a much more lengthy evacuation from a remote climbing region.

## PATIENT CARE

### Specialist Nursing Care

Almost all urban patients with significant frostbite should be admitted to the hospital. Alcohol intoxication, psychiatric illness, and homelessness are common features of the urban frostbite patient, so immediate discharge is rarely prudent.

Overall goals of hospital treatment include keeping the patient calm, well nourished, suitably hydrated, and pain free. Wound care must be meticulous to avoid further trauma. Injured extremities should be elevated above heart level to attempt to minimize edema. Physiotherapy is important, and the patient should be encouraged to mobilize as soon as possible.[206] Extremities should be treated with clean dressings and twice-daily whirlpool baths with an antiseptic such as chlorhexidine or povidone-iodine. Topical *Aloe vera* gel should be applied every 6 to 8 hours through resolution of blisters. This encourages the eschar created by the blisters to separate from underlying healthy tissue. Although patients may be housed anywhere that these objectives can be achieved, vascular surgery or plastic surgery/burns wards (with multidisciplinary input) tend to be most appropriate for more severe injuries.

Frostbite blisters have been shown to contain high concentrations of the vasoconstricting metabolites of arachidonic acid, $PGF_{2\alpha}$ and $TXB_2$, which are known to mediate dermal ischemia in burns and pedicle flaps. It is suggested that these may play a role in the pathogenesis of frostbite.[163] Debate continues about management of such blisters and the risk versus benefit of potential introduction of infection. Current thinking is that clear/cloudy blisters should be drained by needle aspiration (especially if the bullae restrict movement), and that hemorrhagic (presumably deeper) blisters should be left alone.[123] In general, our view is to support aspiration of all blisters. Optimally, large-blister aspiration/deroofing will be carried out in a controlled environment using sterile procedures and anesthetics as needed.

## TECHNIQUES TO EVALUATE TISSUE PERFUSION

Over the years, several diagnostic tests have been used to attempt to predict severity and prognosis of frostbite injury. These include plain radiographs, infrared thermography, angiography,[65] triple-phase bone scanning,[33] laser Doppler, digital plethysmography,[158] and magnetic resonance imaging/magnetic resonance angiography (MRI/MRA). The most promising approaches seem to be triple-phase bone scanning[15,33] and MRI/MRA.[14] Early diagnostic digital subtraction angiography (before administration of tissue plasminogen activator) is an essential first-line investigation for the patient presenting acutely with severe frostbite injury without significant comorbidities, where thrombolysis is an available treatment modality and option.[178]

### Duplex Ultrasonography

Duplex ultrasonography uses B-mode, pulsed-wave Doppler ultrasonography to visualize blood flow within vessels and color flow Doppler imaging to visualize the structure and hemodynamics within vessels. In modern vascular units, there is a move toward using duplex ultrasound examination as the first-line investigative examination, reserving angiograms for situations in which a therapeutic intervention is required. Ease of access, portability, and the ability to make repeat examinations give the technique certain advantages over other imaging modalities. Many remote research stations and even large expeditions may have portable ultrasound machines. Duplex imaging has been used in the field at altitudes as high as 7950 m (26,083 feet) (Figure 9-17). Ultrasound has been used to determine the need for sympathetic blockade after frostbite.[158]

**FIGURE 9-17** Vascular imaging at 7950 m (26,083 feet) using a portable battery-powered SonoSite MicroMaxx duplex ultrasound machine. Caudwell Xtreme Everest Expedition. *(Courtesy Christopher H.E. Imray, MD.)*

### Magnetic Resonance Angiography

The MRI/MRA investigation has a theoretical advantage over $^{99m}$Tc bone scanning because it allows direct visualization of vessels (both patent and occluded), as well as imaging of surrounding tissues. Some suggest that it shows a more clear-cut line of demarcation of ischemic tissue.[14] The other advantage of MRA over angiography is that it is noninvasive. However, there are relatively few accounts of its use in frostbite evaluation in the literature.[14,159]

### Technetium-99m Scanning

The first description of $^{99m}$Tc scanning for assessment of bone viability in patients with frostbite injuries was in 1976.[109] The degree of accretion of the $^{99m}$Tc was found to depend on integrity of the vascular supply. It was successfully used to distinguish viable from nonviable bone. However, Miller and Chasmar[126] found that very early $^{99m}$Tc bone scanning in frostbitten patients was not as accurate an indicator of the ultimate extent of tissue loss as scanning at 5 days after injury. They also noted that lesions appeared to fluctuate in extent over a 3-week period.

Cauchy and colleagues[30,31] recognized that existing frostbite classifications were based on retrospective diagnoses and were not useful for predicting the extent of final tissue loss and prognosis for frostbite patients. The 3- to 6-week waiting period often necessary to determine severity of the lesion and resultant need for amputation often caused considerable distress for patients. The authors suggested a new classification system that begins at day 0 (just after rewarming) and is based mainly on the topography of the lesion and on early bone scan results. This appears to be a very useful classification for the physician and patient, in that it allows accurate determination at a very early stage of the likely extent of subsequent tissue loss (see Tables 9-1 to 9-3).

An interesting insight into some of the possible mechanisms involved in certain frostbite injuries was described by Salimi and co-workers,[171] who designed an experimental model to study pathogenesis and treatment of frostbite. Using $^{99m}$Tc radionuclide imaging, they monitored evolution and extent of tissue damage relative to temperature, rate of freezing, and controlled

rewarming. Characteristic serial changes were demonstrated on sequential scans. Initial nonperfusion was followed by perfusion and finally again by nonperfusion; this occurred in all areas where necrosis subsequently developed. Reappearance of nonperfusion corresponded to vascular injury. Vessel thrombosis was found on pathology examination and may be related to reperfusion injury.

These clinically relevant observations gave evidence to support the concept of temporal "perfusion flux" in blood flow to a frostbitten extremity. Initial reduction is often followed by a temporary hyperperfusion phase before the final infarction phase (probably secondary to endothelial dysfunction and thrombin accumulation). Consequently, measurement of tissue perfusion at a single time point may not be as accurate in predicting outcome as originally believed.

Additional supporting evidence for perfusion flux in frostbite comes from Cauchy and associates,[30,33] who performed a more detailed analysis of two-phase $^{99m}$Tc bone scans. Sensitivity of the technique was enhanced by performing a second scan more than 5 days after rewarming. Comparative analysis of the two scans demonstrated that some of the lesions continued to evolve between day 2 and day 8. Based on this finding, the authors suggested that the outcome of lesions could still be modified during this period. However, in the event of severe sepsis, the results of the first bone scan can be used as an indication for emergency amputation.[31]

Although the large retrospective study of Cauchy and colleagues[30] using two-phase bone scintigraphy suggested that nonuptake (or low uptake) in frostbite lesions had a strong correlation with the subsequent need for amputation, another prospective study has questioned some aspects of the technique.[15] This latter study compared 22 controls with 20 patients with frostbite. Serial scintigraphy using $^{99m}$Tc was performed in some patients. In line with the perfusion flux concept, the study suggests that scintigraphy results are somewhat more variable than previously suggested, and that moderate to severe frostbite lesions can be classified as having infarcted, ischemic, or hibernating (viable) tissue, similar to the classification employed when using myocardial scintigraphy. Absence of uptake of $^{99m}$Tc, even after the initial 10 days in this study, did not necessarily indicate infarction and the need for amputation, because many such lesions retain potential for vasodilation and recovery.

Triple-phase bone scanning (using $^{99m}$Tc) has now become more widely used in specialty units, often within the first few days of presentation. This technique assesses tissue viability in an effort to allow early debridement of soft tissue and early coverage of ischemic bony structures.[67]

There are few prospective data on the efficacy of $^{99m}$Tc scanning in predicting the outcome of frostbite injuries. However, it remains a very useful way of assessing potential tissue loss[79] (Figures 9-18 to 9-21).

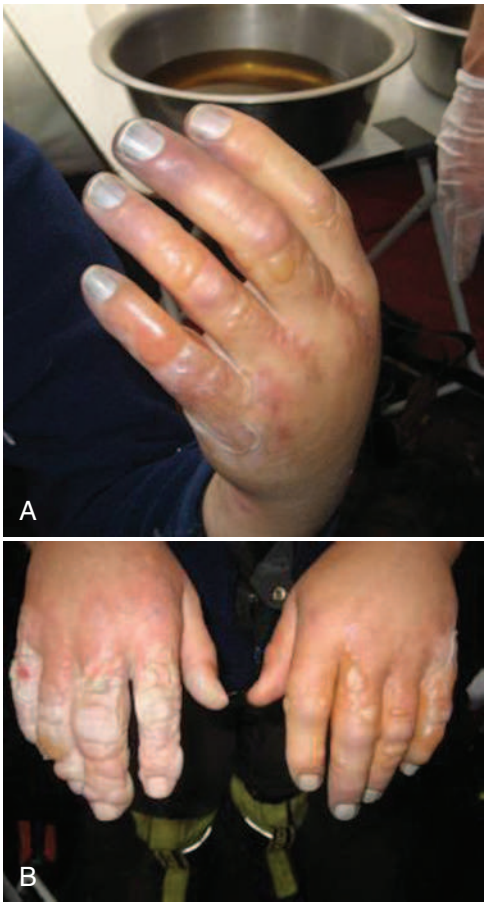



**FIGURE 9-18** Frostbitten left hand of a climber **(A)** taken 36 hours after injury, while climbing in Antarctica **(B)** Note the discoloration and blister formation, iodine warming towels, and aseptic techniques used in tented field hospital. A digital image was reviewed within 6 hours by Dr. Imray in the United Kingdom, and management advice was given over the Internet. *(Courtesy Christopher H.E. Imray, MD. From Imray C, Grieve A, Dhillon S, et al: Cold damage to the extremities: Frostbite and non-freezing cold injuries,* Postgrad Med J *85:481, 2009.)*

## MEDICAL MANAGEMENT

Table 9-4 summarizes the drugs used in the management of frostbite.

### Tetanus Prophylaxis

Frostbite should be considered a high-risk injury. Tetanus prophylaxis status should be completed in all patients according to currently accepted guidelines.[38]

### Heparin

Heparin is a naturally occurring anticoagulant that prevents formation of clots and extension of existing clots within blood vessels. Although true thrombi are not present in dilated, erythrocyte-filled vessels immediately after thawing, they form over the next few days. Heparin has been suggested as a possible treatment for frostbite.[180] Lange and Loewe[104] demonstrated its usefulness in experimental frostbite. Subsequent investigations have been unable to substantiate these findings, and there is no evidence that heparin alters the natural history of frostbite.[21] Deep vein thrombosis (DVT) prophylaxis is indicated in any relatively immobile frostbite patient.

### Indications and Recommendations for Antibiotics

Clinicians have long been aware of the potential for infectious complications in frostbite.[147] The metabolic requirements of infected and healing tissue are increased over those of normal tissue. Consequently, should the marginally perfused interface zone become infected, the resulting tissue loss is likely to be increased. Although scant published evidence exists on their use for frostbite, antibiotics are widely used.

When the skin is edematous, penicillin is administered prophylactically because edema inhibits the skin's inherent antistreptococcal properties.[138] If there are clinical signs of infection, antibiotic use is absolutely indicated.

Wound cultures should be taken from infected tissue to guide therapy. While awaiting identification of species and sensitivities, practitioners should be aware that the common causative organisms include *Staphylococcus aureus*, β-hemolytic streptococci, gram-negative rods, and anaerobes. Empiric use of antibiotics to cover these likely organisms should be considered pending culture results. Although no evidence exists for their prophylactic use, antibiotics should be considered if a large area of infarcted tissue or significant edema is present, or if the patient is immune compromised.

In a 12-year retrospective study, factors found to correlate significantly with amputation after frostbite were duration of exposure, lack of proper attire, remote geographic location, presence of wound infection, and delay in seeking treatment. Prophylactic systemic antibiotics did not decrease the incidence of wound infection.[195]

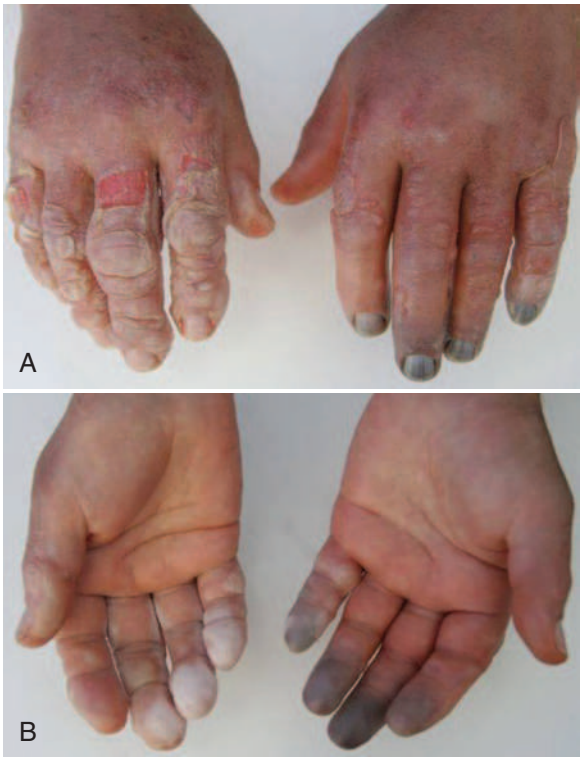



**FIGURE 9-19** Condition of hands of patient in Figure 9-18 on patient's arrival in the United Kingdom, 5 days after initial injury. *(Courtesy Christopher H.E. Imray, MD. From Imray C, Grieve A, Dhillon S, et al: Cold damage to the extremities: Frostbite and non-freezing cold injuries,* Postgrad Med J *85:481, 2009.)*

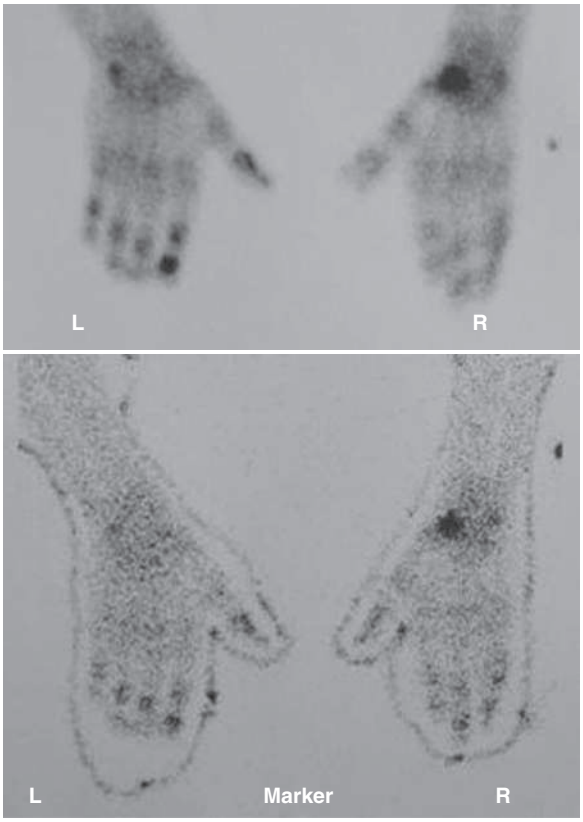



**FIGURE 9-20** Technetium-99m bone scans performed on arrival of patient in Figures 9-18 and 9-19 in the United Kingdom. The scans show minimal perfusion to the terminal phalanges in the left hand, suggesting that amputation of the distal phalanges is likely to be necessary. *(Courtesy Christopher H.E. Imray, MD. From Imray C, Grieve A, Dhillon S, et al: Cold damage to the extremities: Frostbite and non-freezing cold injuries,* Postgrad Med J *85:481, 2009.)*

### Topical *Aloe vera*

Experimental evidence from the frostbite rabbit ear model has suggested a clearly defined role for thromboxane as a mediator of progressive dermal ischemia in frostbite injuries. Rapid rewarming helps preserve tissue by limiting the amount of direct cellular injury. Selective management of blisters helps protect the subdermal plexus, and topical application of *Aloe vera* (e.g., Dermaide Aloe cream or gel) combats the local vasoconstrictive effects of thromboxane (Figure 9-22).

Animal studies suggest thromboxane appears to be a mediator of progressive dermal ischemia in frostbite. In a rabbit ear frostbite model, Heggers and associates[74] compared the effect of (1) the antiprostanoids (methylprednisolone), (2) aspirin combined with *Aloe vera*, (3) methimazole, and (4) a control group that received no therapy.[119] Methimazole treatment gave 34.3% tissue survival; *Aloe vera,* 28.2% survival; aspirin, 22.5% survival; and methylprednisolone, 17.5% survival. In a human study of 154 patients with frostbite, there was significant improvement in outcome and reduction in amputation rates of treated patients compared with controls ($p < 0.001$). It was concluded that morbidity of progressive dermal ischemia in frostbite may be decreased by therapeutic use of inhibitors of the arachidonic acid cascade. *Aloe vera* is the topical agent most often used.

### Antiprostaglandin Agents

Nonsteroidal antiinflammatory drugs (NSAIDs), such as ibuprofen, act as a necessary adjuvant to rewarming because they inhibit inflammatory reactions and pain by decreasing prostaglandin synthesis.[74] Oral ibuprofen decreases systemic levels of thromboxane. Ibuprofen (400 mg) may be given by mouth and should be continued at a dose of 12 mg/kg body weight/day (maximum, 2400 mg/day). This should ideally be commenced in the field.

McCauley and co-workers[121] treated 38 patients with frostbite in a protocol designed to decrease production of thromboxane locally and prostaglandins systemically. All patients recovered without significant tissue loss. Increased tissue survival was demonstrated experimentally with preservation of the dermal microcirculation by using antiprostaglandin agents and thromboxane inhibitors.

### Vasodilators

The equation determining fluid flow within a tube was first described in the 1840s by the French physician and physiologist Jean Poiseuille. He demonstrated that flow was related to perfusion pressure, radius, length, and viscosity. In a frostbite patient, each of these parameters (other than length) can be optimized using appropriate medical interventions.

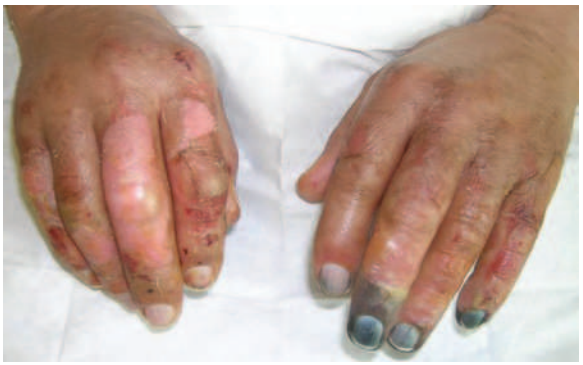


**FIGURE 9-21** Hands of patient in Figures 9-18 to 9-20 after 5 days of intravenous iloprost. *(Courtesy Christopher H.E. Imray, MD. From Imray C, Grieve A, Dhillon S, et al: Cold damage to the extremities: Frostbite and non-freezing cold injuries,* Postgrad Med J *85:481, 2009.)*

**TABLE 9-4** Frostbite Management: Drugs, Doses, and Modes of Action and Rationale*

| Intervention | Dose | Action |
|---|---|---|
| Aspirin | 75-250 mg orally once daily | Antiplatelet agent, improve rheology |
| Ibuprofen | 400 mg bid or tid orally | Antiprostaglandin effect |
| *Aloe vera* gel or cream | With dressing changes every 6 hr | Topical antiprostaglandin effect |
| Oxygen | 2 L/min above 4000 m (13,123 ft) or when $SpO_2$ is below 90% | Improve tissue oxygenation |
| Hyperbaric oxygen therapy | 2-2.5 atm 1-2 hr daily | Improve tissue oxygenation; improve rheology |
| Iloprost | 2-10 mg/hr IV titrated against side effects | Vasodilator; improve rheology |
| Nitroglycerin | 100 mcg IA single dose | Vasodilator |
| Papaverine | 300 mg over 1 hr IA | Vasodilator |
| Reserpine | 0.1 to 0.25 mg once daily | Vasodilator |
| Buflomedil | 400 mg IV *or* 300 mg bid orally | Vasodilator; improve rheology |
| Pentoxifylline | 400 mg tid orally for 2-6 weeks | Vasodilator; improve rheology |
| 10% Dextran 40 | 20-mL bolus, 20 mL/hr IV | Improve rheology |
| t-PA | 1 mg/hr IA or IV | Thrombolytic agent |
| LMW heparin | Prophylactic dosage subcutaneously | DVT prevention; anticoagulant |
| | Therapeutic dosage subcutaneously | Maintain patency of recently thrombolysed vessels |
| Tetanus prophylaxis | | |

*bid,* Twice daily; *DVT,* deep vein thrombosis; *IA,* intraarterially; *IV,* intravenously; *LMW,* low-molecular-weight; *$SpO_2$,* oxygen saturation as measured by pulse oximetry; *tid,* three times daily; *t-PA,* tissue plasminogen activator.
*This table is intended to be used as a potential frostbite formulary reference, not as a protocol for treatment. See text for further discussion.



**Iloprost.** Prostaglandin $E_1$ ($PGE_1$) is a vasoactive drug that dilates arterioles and venules, reduces capillary permeability, suppresses platelet aggregation, and activates fibrinolysis. Its intraarterial use has been effective in treating ischemic peripheral vascular disease.

The potentially beneficial effect in treating frostbite injuries with intraarterial $PGE_1$ was first assessed in an animal model.[209] $PGE_1$ reduced the magnitude of frostbite injury when the injured limb was slowly rewarmed. The data suggested a possible role for the use of $PGE_1$ in frostbite patients who have not undergone rapid rewarming. Since the first description of its use in patients,[68] $PGE_1$ has been used with some success in frostbite injuries.[79,197]

Further experimental evidence implicates an inflammatory process in the underlying mechanism of tissue injury. It has been postulated that progressive ischemic necrosis is secondary to excessive $TXA_2$ production, which upsets the normal balance between prostacyclin (prostaglandin $I_2$) and $TXA_2$.[144]

Cauchy and co-workers[29] showed a promising decrease in the digit amputation rate with the use of IV iloprost in severe frostbite injuries. The clinicians compared results of a controlled trial of 47 frostbite patients who were rapidly rewarmed, received 250 mg of aspirin and 400 mg of IV buflomedil, and who were then randomized to receive 250 mg of aspirin per day, plus buflomedil, iloprost, or recombinant tissue plasminogen activator with iloprost. The iloprost group had the lowest overall amputation rate. Although the ideal dose is undetermined, these encouraging data offer hope to frostbite victims.

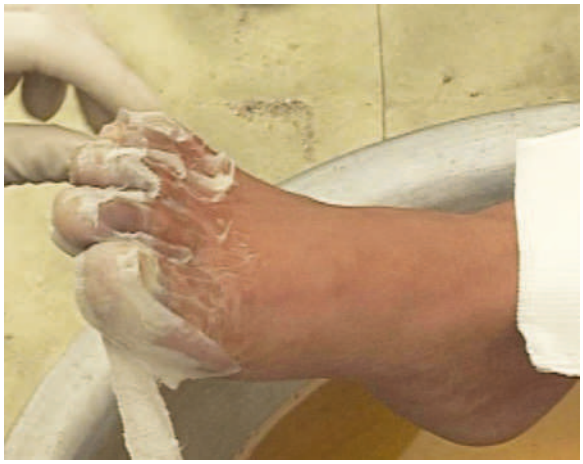


FIGURE 9-22 *Aloe vera* cream being applied at the Everest Base Camp Medical Clinic. Note the care being taken to apply nonconcentric dressings to allow for edema formation. *(Courtesy Suzanne Boyle, MD.)*

Iloprost is best given as an IV infusion through a peripheral or central line in a monitored vascular or general surgical unit. The diluted iloprost should be delivered by an accurate rate delivery system, such as a syringe driver. The infusion is started at a rate of 2 mg/hr and incrementally increased up to 10 mg/hr, titrated against the side effects of facial flushing, headache, nausea, and flulike symptoms. The infusion is usually run for 5 to 8 days for 6 hours a day.[79,81] A practical guide and stepwise algorithm was recently produced to aid clinicians (Figure 9-23).[69]

**Reserpine.** Reserpine is a powerful vasodilator that acts by inhibiting uptake of norepinephrine into storage vesicles.[150] For frostbite, it is used intraarterially. The first description in the treatment of frostbite was by Snider and colleagues.[183] An animal study suggested that a regional "medical sympathectomy" may be beneficial in reducing tissue loss after frostbite, especially when rapid rewarming cannot be performed.[182]

**Pentoxifylline.** Pentoxifylline, a methylxanthine-derived phosphodiesterase inhibitor, has been widely used to treat intermittent claudication, arterial disease, and peripheral vascular disease and has yielded some promising results in human frostbite trials.[72] It increases blood flow to the affected extremity, increases red cell deformability, decreases platelet hyperactivity, helps normalize the prostacyclin/$TXA_2$ ratio, and has been shown to enhance tissue survival. Pentoxifylline is also presumed to lower pathologically increased levels of fibrinogen and may protect against vascular endothelial damage. The drug's efficacy has been demonstrated in animal studies and approaches the effectiveness of *Aloe vera*. The combination of pentoxifylline and *Aloe vera* appears to be synergistic.[128] A similar synergy of aspirin and pentoxifylline was demonstrated in an animal study.[155] Hayes and co-workers[72] have proposed a treatment using pentoxifylline in conjunction with the traditional therapy of rewarming, soaks, pain management, and blister debridement. They recommend pentoxifylline in the controlled-release form of one 400-mg tablet three times daily with meals, continued for 2 to 6 weeks. A controlled study of pentoxifylline in the management of frostbite has yet to be performed.

**Buflomedil.** Buflomedil hydrochloride is a vasoactive drug that may have a number of effects, including inhibition of

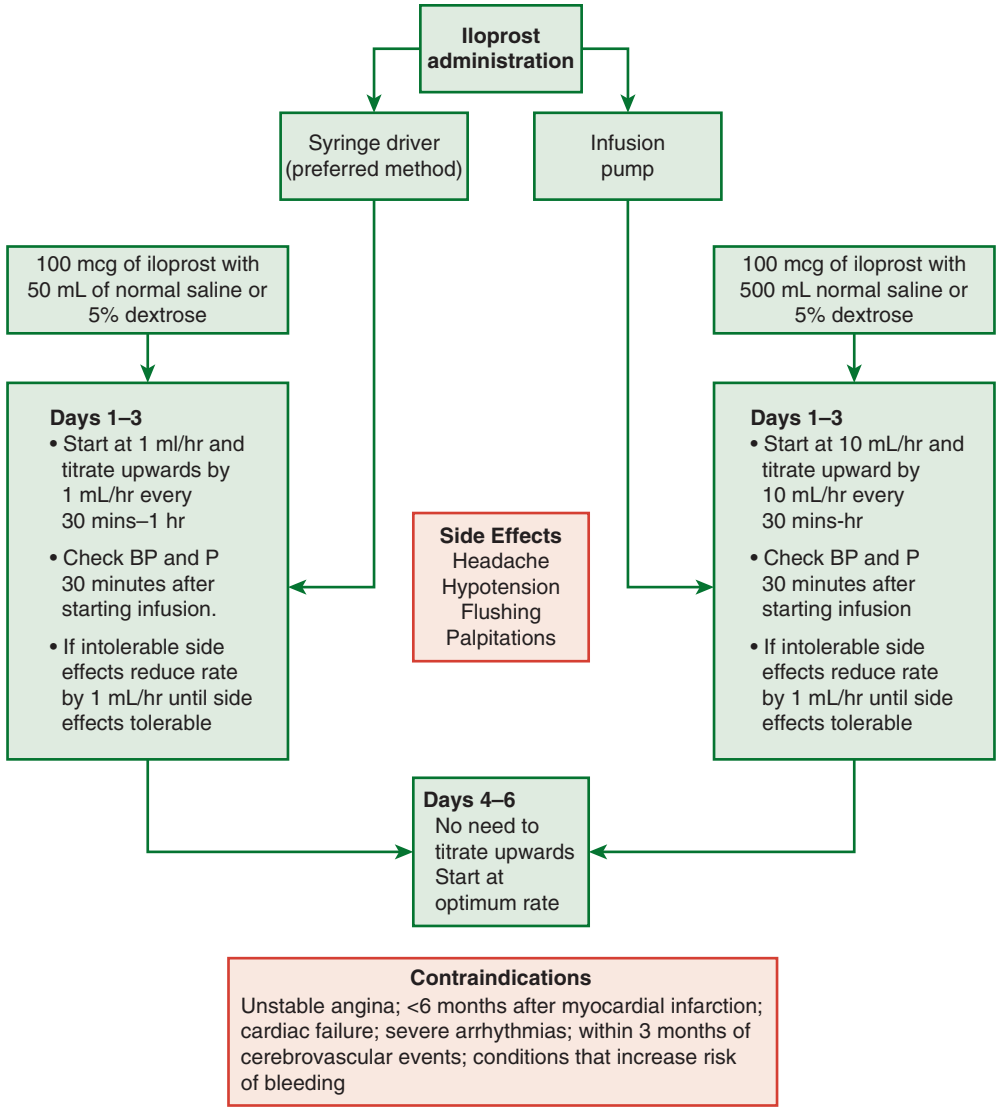



**FIGURE 9-23** Algorithm for the administration of intravenous iloprost for in-hospital thrombolysis of severe frostbite injury. *(From Handford C, Buxton P, Russell K, et al. Frostbite: a practical approach to hospital management.* Extrem Physiol Med *3:7, 2014.)*

α-receptors, inhibition of platelet aggregation, improved erythrocyte deformability, nonspecific and weak calcium antagonistic effects, and oxygen-sparing activity.[35,115,117] A case series of 20 patients reported that early administration of IV buflomedil appeared to reduce the risk for subsequent amputation.[54] However, buflomedil has not been shown to reduce microcirculatory damage from acute, experimentally induced freeze injury.[45] Although buflomedil does not have U.S. Food and Drug Administration (FDA) approval, it has been used extensively in France to treat frostbite, with considerable beneficial effect.[31]

### Blood Viscosity: Low-Molecular-Weight Dextran

It has been observed that shortly after thawing, cold-injured vessels become dilated and filled with clumps of erythrocytes. These clumps can be easily dislodged by gentle manipulation and do not represent true thrombosis. Although the mechanism that leads to erythrocyte clumping is not completely understood, it may reflect cold-induced increase in blood viscosity. This suggests that use of low-molecular-weight (LMW) dextran may be beneficial for early treatment of frostbite. Although no controlled clinical trial of LMW dextran has been reported, experimental evidence supports its use. Weatherly-White and colleagues[204] demonstrated that LMW dextran, 1 g/kg/day, protected against tissue loss in the rabbit ear model. This led to the suggestion that the use of 1 L of IV 6% dextran on the day of injury, followed by 500 mL on each of 5 successive days, might be of benefit.[164] The extent of tissue necrosis was also found to be significantly less than in controls, when hemodilution with dextran was combined with water bath rewarming.

With our present understanding of the etiology of frostbite and introduction of newer interventions (e.g., iloprost, t-PA), there appear to be fewer cases when LMW dextran may have benefit.

## ENDOVASCULAR INTERVENTIONS

### Thrombolysis with Tissue Plasminogen Activator

In 1963, Fogarty and co-workers[52] reported treating acute occlusion of a peripheral vessel with an embolectomy catheter technique. More recently, catheter-directed thrombolysis has been used to clear distal arteries and the microvasculature using a thrombolytic agent such as tissue plasminogen activator (t-PA). Found in vascular endothelial cells, t-PA has fibrinolytic action and plays an important role in the dynamic balance between clot formation and lysis. Plasminogen and t-PA bind to the fibrin surface of the thrombus, resulting in production of plasmin and subsequent dissolution of the thrombus. t-PA has been used extensively in coronary, cerebrovascular, and peripheral arterial disease.[143]

A small retrospective study reported successful use of catheter-directed intraarterial t-PA to reduce amputation rates in frostbite.[22] Among the six patients who received t-PA within 24 hours of injury, 6 of 59 (10%) affected fingers or toes were amputated, compared with 97 of 234 (41%) of those who did not receive t-PA. It was postulated that rapid clearance of the microvasculature improves tissue salvage. The protocol in this study employed a 2- to 4-mg bolus of t-PA after the catheter was secured and total maximum dose of 1 mg/hr run continuously while simultaneous heparin was given at 500 units/hr through the access sheath and continued for 72 to 96 hours. When there was evidence of digital flow by angiography, t-PA was discontinued. The clinicians noted that there was limited benefit for administration of t-PA when treatment was started more than 24 hours after the initial injury.

Twomey and associates[191] reported another series using 0.15-mg/kg IV t-PA bolus, followed by 0.15-mg/kg/hr infusion over the next 6 hours, to a total dose of 100 mg.[191] Heparin was started after completion of the t-PA infusion, and the partial thromboplastin time was adjusted to twice that of normal control. Warfarin was initiated 3 to 5 days after t-PA and continued for 4 weeks in this study, which found decreased amputation rates similar to those in the study by Bruen and colleagues.[22] Both these studies demonstrated excellent and similar amputation rates when using t-PA. However, Johnson et al.[84] retrospectively reviewed their experience with t-PA and found less promising results (compared to Twomey et al.[191]),with 43 out of 73 at-risk digits (by $^{99m}$Tc triple-phase bone scintiscan) requiring amputation, representing an amputation rate of 59%.

Successful use of the combination of intraarterial (IA) t-PA (previous series were IV) and vasodilators infused coaxially has recently been described in various studies.[29,44,170,178] After proper rewarming, the patient undergoes an arteriogram to assess perfusion and document vascular flow cutoff if present. A recent case report study describes successful use of a combination of endoluminal approaches in a patient with frostbite affecting both hands. Upper-extremity and hand angiography performed within 16 hours of the frostbite injury demonstrated thrombotic occlusive disease and vasospasm. Bilateral brachial artery catheters were placed and a papaverine infusion initiated, followed by IA t-PA thrombolysis.[170] In a second case report, a 16-year-old boy was treated for hypothermia and concomitant frostbite of the right foot and both hands.[178] The patient was rewarmed and then treated with selective angiography and an IA vasodilator (nitroglycerin), followed by IA t-PA thrombolysis, which resulted in salvage of the limbs, but loss of the right great toe (Figures 9-24 to 9-27). A proposed screening and treatment tool was included in the case report (Box 9-3).

Currently, IV administration of t-PA for frostbite injury is more common; however, the previous case reports warrant future comparison between IA and IV delivery. The variable response to thrombolytic therapy has been reported.[39]

## Current Strategy for Imaging and Thrombolysis in Acute Phase of Frostbite

The role of thrombolytic therapy in the treatment of frostbite is evolving rapidly. The aim of t-PA treatment is to attempt to clear the microvascular thrombosis. However, there are both risks and benefits to t-PA therapy, and an appropriate balance needs to be struck.

**The Patient.** t-PA should be considered for patients with a "significant" deep frostbite injury presenting to an appropriately equipped unit within 24 hours of the injury. A significant frostbite injury will vary from individual to individual, dominant versus nondominant hand, occupation, hands versus feet, and existing comorbidities. The injury will usually extend proximal to the proximal interphalangeal joints. Experienced clinicians familiar with the techniques need to evaluate each injury to determine whether intervention with t-PA is justified.

**Tissue Plasminogen Activator in the Field.** If a frostbite patient is being cared for in a remote area, transfer to a facility with t-PA administration and monitoring capabilities should be considered if the patient will arrive in the specialist unit within the first 24 hours after the injury. Use of t-PA in the field setting

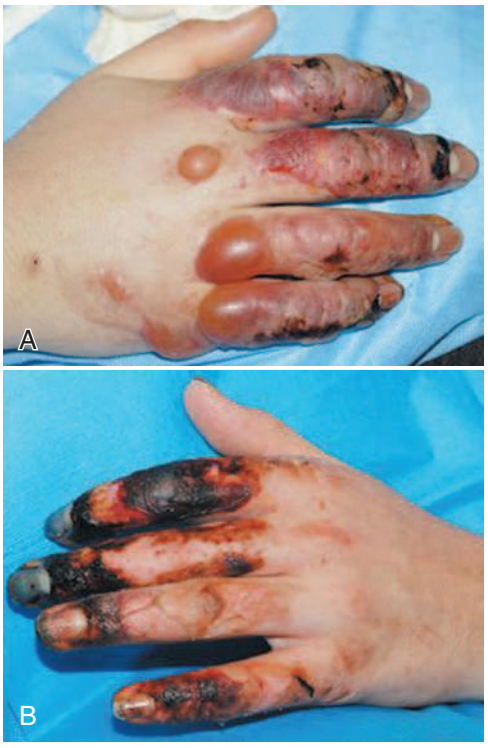



**FIGURE 9-24** Early appearance of hands. *(From Sheridan RL, Goldstein MA, Stoddard FJ, et al: Case 41-2009: A 16-year-old boy with hypothermia and frostbite,* N Engl J Med *361:2654, 2009.)*

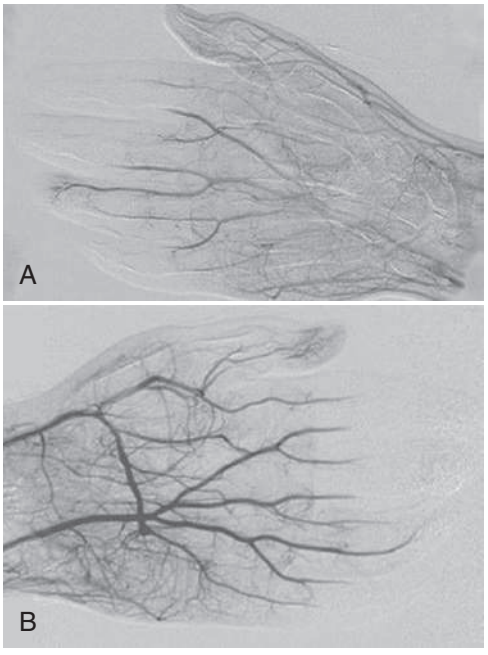



**FIGURE 9-25** Initial angiographic images of the hands of the patient in Figure 9-24. After the infusion of vasodilators, diagnostic angiographic images of the hands show relatively preserved perfusion of the thumbs and ring fingers, but abrupt termination of the proper digital arteries of each of the remaining fingers at the midphalangeal level. *(From Sheridan RL, Goldstein MA, Stoddard FJ, et al: Case 41-2009: A 16-year-old boy with hypothermia and frostbite,* N Engl J Med *361:2654, 2009.)*

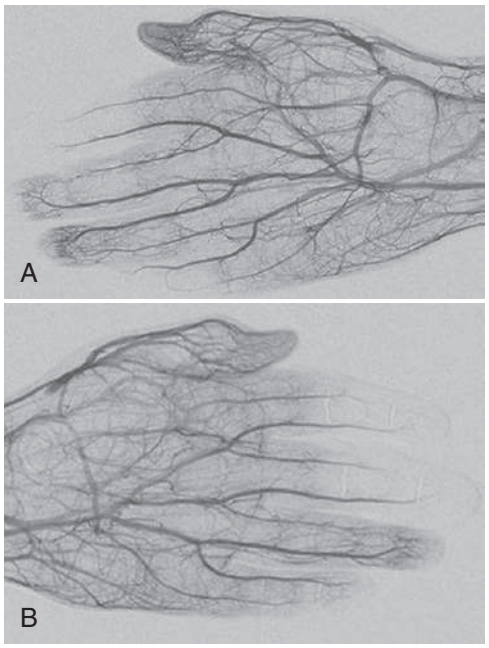



**FIGURE 9-26** Repeat images of the hands of the patient in Figures 9-24 and 9-25 after 24 hours of intraarterial catheter-directed thrombolytic therapy with tissue plasminogen activator show greatly improved perfusion at all levels. *(From Sheridan RL, Goldstein MA, Stoddard FJ, et al: Case 41-2009: A 16-year-old boy with hypothermia and frostbite,* N Engl J Med *361:2654, 2009.)*

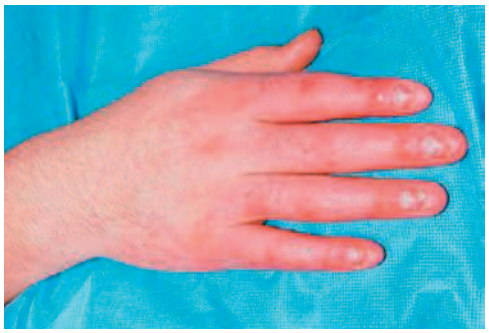


**FIGURE 9-27** Appearance of right hand of the patient in Figures 9-24 to 9-26 at approximately 30 days. *(From Sheridan RL, Goldstein MA, Stoddard FJ, et al: Case 41-2009: A 16-year-old boy with hypothermia and frostbite,* N Engl J Med *361:2654, 2009.)*

is not recommended because it may not be possible to detect and treat bleeding complications.

**The Hospital Unit.** The hospital unit needs intensive care monitoring capabilities, and clinicians should be familiar with IA angiography and t-PA. A review of absolute and relative contraindications of t-PA should be undertaken. The Massachusetts General Hospital group has proposed a screening and treatment tool for thrombolytic management of frostbite, including a protocol (see Box 9-3).[178]

**Choice of Imaging in the Patient Presenting within 24 Hours of Injury.** Angiography or $^{99m}$Tc scanning should be used to evaluate the initial injury and monitor progress after t-PA administration per local protocol and resources. Angiography is an invasive procedure that allows both diagnostic and therapeutic measures to be carried out, unlike $^{99m}$Tc scanning, which is only diagnostic. Logical practice dictates that angiography be used to monitor IA t-PA and $^{99m}$Tc scanning used to monitor IV administration of t-PA. No evidence demonstrates superiority of one imaging modality over the other.

**Choice of Imaging in the Patient Presenting after 24 Hours of Injury.** In patients with delayed presentation (>24 hours from time of injury), $^{99m}$Tc or MRA can be used to predict at a very early stage the likely levels of tissue viability and amputation when t-PA would not be considered.[30,31,33]

### Papaverine

Papaverine is a powerful topical and intravascular vasodilator that is used clinically as a smooth muscle relaxant in microvascular surgery and that has been used to treat cerebral vasospasm.[89] The exact mechanism of action remains to be determined. It appears that inhibition of the enzyme phosphodiesterase causes elevation of intracellular cyclic adenosine monophosphate levels. Papaverine might improve outcomes in early frostbite. When used in conjunction with IA t-PA in older patients, papaverine appears to cause a less pronounced decrease in systemic blood pressure than IA nitroglycerin in older adults.[43]

### Iloprost versus Tissue Plasminogen Activator

Groechenig[68] first reported his experiences with iloprost in 1994. Despite the promising results of no amputations after iloprost infusion, focus shifted away from iloprost toward t-PA. Cauchy et al.[29] published a randomized controlled trial to compare iloprost and t-PA; 47 patients were included (407 at-risk digits), each randomized into three arms: buflomedil, iloprost, or iloprost and IV t-PA. All other treatments were the same. The highest amputation rate was observed in the buflomedil group, at 39.9%. No amputations were observed in the iloprost group, whereas those treated with iloprost/IV t-PA had an amputation rate of 3.1%.

Iloprost has some advantages compared with t-PA. Radiologic intervention is not needed during its administration, which can be carried out on a vascular or general surgery ward. In contrast, with t-PA, it is advisable to be in an intensive care unit. Iloprost is also safe to use in patients with is a history of trauma, as well as for a delayed presentation, because there is some evidence for its effectiveness 24 hours after injury. We have used it as late as 5 days after injury; however, the longer the delay, the less effective iloprost is likely to be.

Experts may prefer iloprost to t-PA because of its comparative safety, ease of administration, and efficacy. However, iloprost is not approved for use in frostbite in the United States. Either treatment should be commenced as rapidly as possible. Figures 9-28 and 9-29 provide algorithms for the administration of recombinant t-PA (rt-PA)and iloprost and rt-PA and heparin, respectively, for severe frostbite (see also Figure 9-23).[69]

**BOX 9-3 Proposed Screening and Treatment Tool for Use of Thrombolysis in Frostbite Patients**

**Treatment Screen (Four "Yes" Answers Required to Proceed to Angiography)**

Are the patient's gas exchange and hemodynamics stable?
Is flow absent after rewarming (no capillary refill or Doppler signals)?
Was the cold exposure time less than 24 hr?
Is the warm ischemia time less than 24 hr?

**Treatment Protocol**

Perform angiography with intraarterial vasodilators.
If there is still no flow after angiography with vasodilators, infuse tissue plasminogen activator (t-PA) with systemic heparinization, with priority to the hands—other sites receive a systemic dose.
Repeat angiography every 24 hr.

**Indications for Stopping the Infusion of t-PA**

When restored flow has been confirmed by angiography or clinical examination
If a major bleeding complication occurs
After 72 hr of treatment

**Postlysis Anticoagulation**

One month of subcutaneous low-molecular-weight heparin at a prophylactic dose

From Sheridan RL, Goldstein MA, Stoddard FJ, et al: Case 41-2009: A 16-year-old boy with hypothermia and frostbite, *N Engl J Med* 361:2654, 2009.

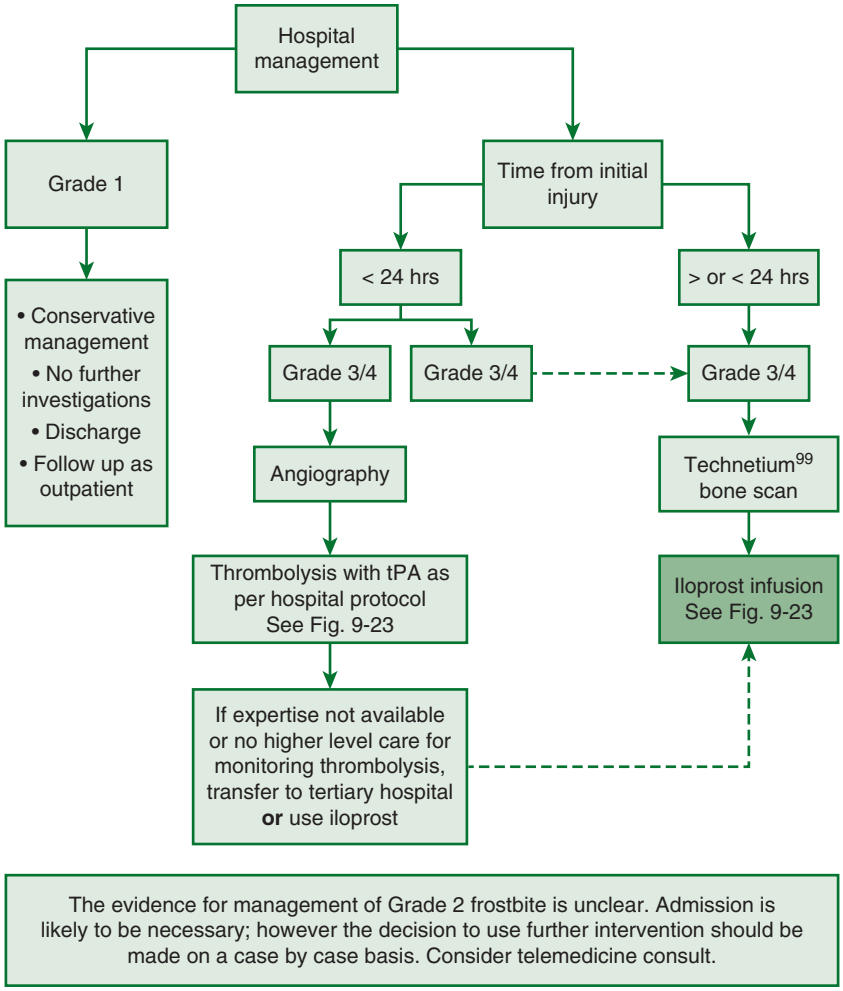



**FIGURE 9-28** Algorithm for the use of recombinant tissue plasminogen activator (rt-PA, rTPA) and iloprost in the management of frostbite injuries. *(From Handford C, Buxton P, Russell K, et al: Frostbite: A practical approach to hospital management.* Extrem Physiol Med *3:7, 2014.)*

## ADJUNCTIVE TREATMENTS

### Sympathectomy

Cutaneous vessels are controlled by sympathetic adrenergic vasoconstrictor fibers, and vascular smooth muscles have both α-adrenergic and β-adrenergic receptors. Because vasodilation of extremities is passive, maximal reflex vasodilation occurs after sympathectomy.

The use of sympathectomy (open or minimally invasive surgery) has yielded mixed results. Surgical sympathectomy performed within the first few hours of injury increases edema formation and leads to increased tissue destruction. However, if performed 24 to 48 hours after thawing, sympathectomy is believed to hasten resolution of edema and decrease tissue loss. Surgical sympathectomy may have a role in preventing certain long-term sequelae of frostbite, such as pain (often caused by vasospasm), paresthesias, and hyperhidrosis.[188]

In a study of 66 patients with frostbite, 15 patients with acute, bilaterally equal, severe injuries were treated with immediate IA reserpine in one limb and ipsilateral surgical sympathectomy. Efficacy of therapy was assessed by comparison of the sympathectomized limb with the contralateral untreated limb. There was no conservation of tissue, resolution of edema, pain reduction, or improved function in sympathectomized limbs compared with those treated with IA reserpine. One patient demarcated more rapidly, and another patient appeared to be protected from recurrent injury. Sympathectomy was not effective therapy for acute frostbite, even when achieved early with IA reserpine. Late protection against subsequent cold injury appears to be the only benefit of surgical sympathectomy for frostbite.[19]

Because surgical sympathectomy is irreversible, great caution should be exercised when considering its use, particularly with the advent of alternative IV vasodilators. Many would argue there is now no role for its use in the early management of frostbite. However, some interest in a potential role for more selective chemical sympathectomy remains.[34,145]

### Hyperbaric Oxygen Therapy

Evaluating the effectiveness of use of hyperbaric oxygen therapy (HBOT) in the management of frostbite is difficult. Although several animal studies have demonstrated no benefit,[138] two recent human studies have yielded excellent results.[50,199] Multiple mechanisms of action are proposed, but the major changes are postulated to occur in the microcirculation. HBOT reportedly increases erythrocyte flexibility, decreases edema formation in postischemic tissues, and is bacteriostatic. Such actions may counteract vascular congestion, platelet aggregation, and infiltration of leukocytes seen in the microcirculation of frostbite patients. Finderle and Cankar[50] report successful HBOT of a patient at 2.5 atm for 90 minutes daily for 28 sessions in a multiplace chamber, without significant tissue loss; this treatment started 12 days after injury. HBOT may also act as an antioxidant. A series of case reports suggests significant beneficial effects from HBOT.[11,53,140,199,201]

Cauchy and colleagues[32] have recently suggested a novel use for hyperbaric oxygenation. Most high-altitude expeditions have

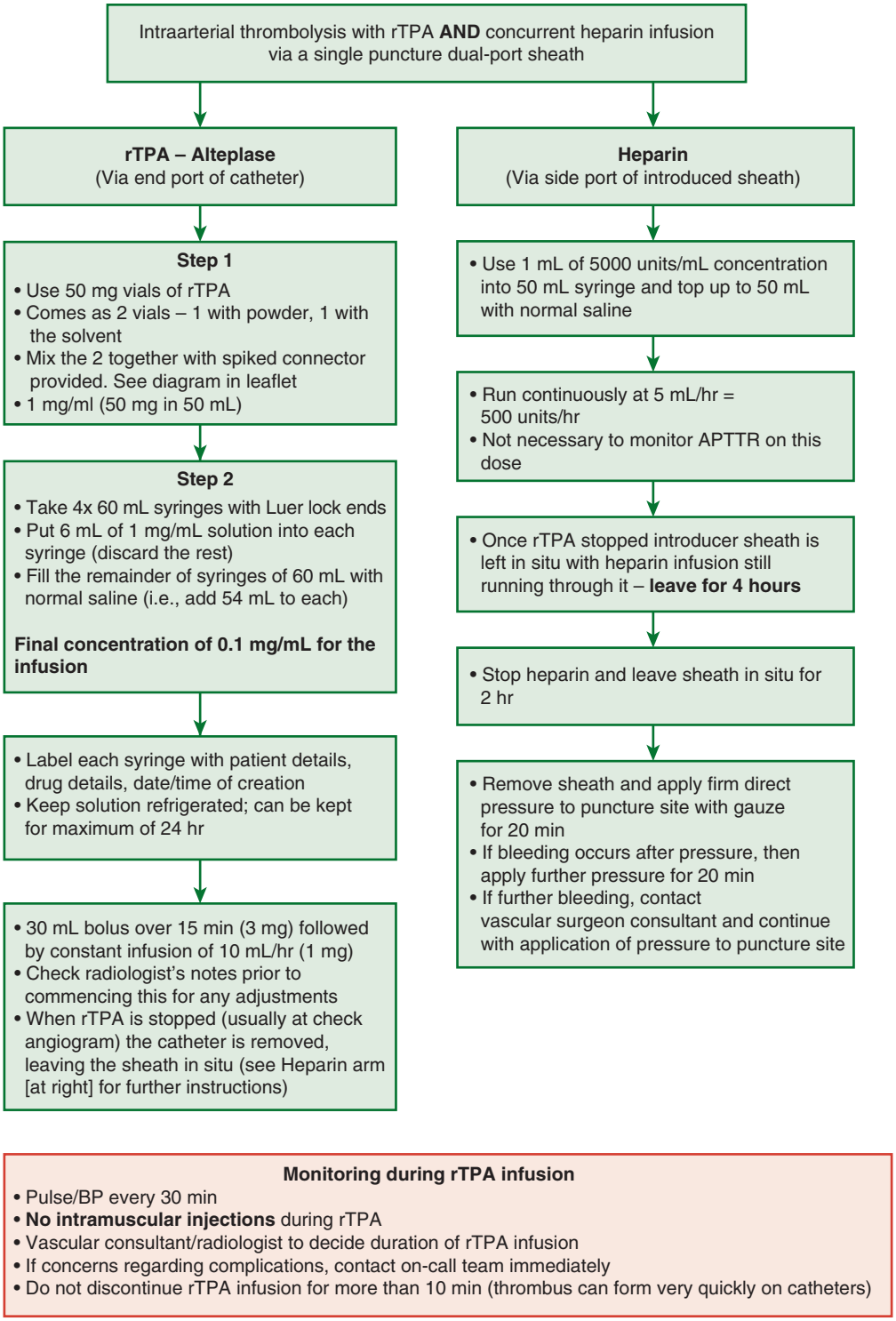



**FIGURE 9-29** Algorithm for the intraarterial administration of rt-PA (rTPA) and heparin for in-hospital thrombolysis of severe frostbite injury. *(From Handford C, Buxton P, Russell K, et al: Frostbite: A practical approach to hospital management.* Extrem Physiol Med *3:7, 2014.)*

access to a portable hyperbaric chamber to replicate low-altitude conditions in acute mountain sickness when true descent is not possible. The authors note that altitude itself exaggerates cold-induced vasospasm and hypothesize that placing a frostbite patient in a field hyperbaric chamber may dampen this response and improve tissue perfusion. Although there is no evidence for HBOT at altitude for frostbite, it warrants further investigation because of its simplicity and likely availability during high-altitude expeditions.

The role of HBOT in all stages of frostbite therapy warrants further investigation because it is a relatively safe and inexpensive treatment.[90,202]

## Epidural Spinal Cord Stimulation

An anecdotal case series that described epidural spinal cord stimulation versus conventional treatment reported good therapeutic effects in four young patients with frostbite of the lower limbs. The authors state the mechanism of action is unknown,

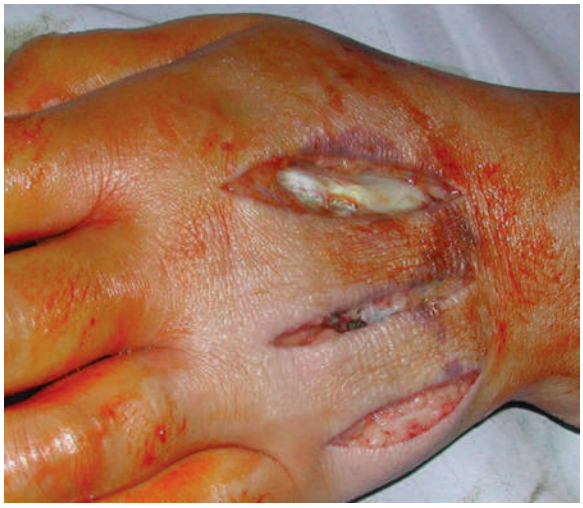


**FIGURE 9-30** Axial fasciotomies on the dorsum of the left hand. *(Courtesy Christopher H.E. Imray, MD.)*

but the treatment is reported to have resulted in rapid recovery, reduced pain, and more peripheral level of amputation.[7]

## SURGICAL TREATMENT

The conventional teaching is that early surgical intervention has no role in the acute care of frostbite. However, early surgical intervention in the form of fasciotomy is required for compartment syndrome in the immediate post-thaw scenario or for ischemia from a constricting eschar or subeschar infection.[62] Decompressing escharotomy incisions are rarely necessary to increase distal circulation. If such escharotomies are necessary to decompress digits and facilitate joint motion, incisions along the transaxial line may be the most appropriate.[121] However, many plastic and vascular surgeons would consider using transaxial with axial incisions on the trunk and axial fasciotomy incisions on the limbs (Figure 9-30). It is important that incisions avoid injury to underlying structures.

Occasionally, early amputation is indicated if liquefaction, moist gangrene, or overwhelming infection and sepsis develop.[5] There is rarely any urgency to surgically intervene, so amputation should be undertaken by a surgeon with appropriate experience, usually 4 to 8 weeks after the injury. In the vast majority of patients, it is a failure to delay surgery when it is the major source of avoidable morbidity. The functional end result of any surgery needs to be considered. Ideally, when major limb loss is foreseen, early involvement of a multidisciplinary rehabilitation team will result in better long-term function.[80]

Surgical intervention is normally reserved for late treatment of frostbite. This is most often necessary if frostbite is severe or treatment has been delayed. Aggressive therapeutic measures can often prevent or reduce progressive injury and gangrene. If gangrene ensues, amputation or debridement with resurfacing may be necessary (Figure 9-31).

Surgery should be accomplished only after the area is well demarcated, which generally requires 4 to 8 weeks. Historically, aggressive early debridement and attempted salvage have been thought to jeopardize recovering tissue and add to tissue loss. Gottlieb and associates[63] and Greenwald and colleagues[67] have taken a much more aggressive approach to coverage of severe frostbite injury. Using $^{99m}$Tc phosphate bone scans, they identify nonperfused tissue by 10 days after injury and surgically remove necrotic tissue. The remaining nonvascularized and nonviable, yet non-necrotic and noninfected, tissue is salvaged by early coverage with well-vascularized tissue. Theoretically, if nonvascularized tissue has not undergone autolysis and is not infected, it should behave like a composite graft. Preliminary reports are promising, because with better imaging, more accurate prediction of viable tissue is possible. Anecdotal reports suggest that there may be increased risk for infection when complex reconstructions are undertaken at an early stage.[81]

A conservative approach remains reasonable. In one of the largest number of frostbite patients (847) treated simultaneously (2-week period), during the Indo-Pakistan conflict in 1971, a combination of LMW dextran, an antiinflammatory agent (oxyphenbutazone), and a vasodilator (isoxsuprine) was used for the third-degree and fourth-degree injuries, improving limb salvage compared with historical controls.[12] A conservative approach remains reasonable.

## AMPUTATION

Surgery should usually be delayed unless there is evidence of overwhelming sepsis.[5] Because there is rarely a reason for rushing to operate, a suitably experienced multidisciplinary surgical team familiar with performing a range of amputations should undertake the procedure(s). Careful preoperative planning involving the relevant medical, surgical, physiotherapy, and occupational therapy teams should take place.[79,80] The level and type of tissue excised during the amputation will be determined by the specific injury or injuries.

Following amputation, primary skin cover is usually preferred. The temptation to preserve bone length by accepting closure by secondary intention or skin grafting needs to be balanced against the problems associated with a dysfunctional, neuropathic, and weight-bearing stump. Split grafts inserted directly onto bone tend to ulcerate as a result of shear forces on insensate grafted skin as soon as the patient mobilizes and becomes weight bearing, so a delayed revision then becomes necessary. Inappropriate attempts at preserving long bone length restrict use of modern "intelligent" prosthetic limbs; preoperative consultation with the rehabilitation/prosthetic team is strongly advised.

The patellar tendon–bearing orthosis technique was originally designed to support body weight for treatment of the below-knee segment that is structurally inadequate or causes severe pain.[168,189] The technique allows unloading of the leg at the below-knee level while retaining full knee movement. It is beneficial in

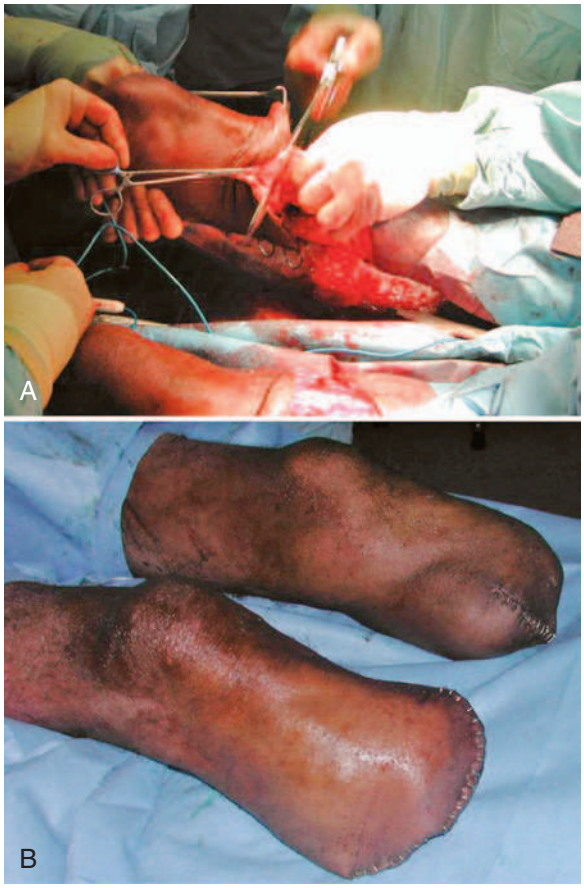



**FIGURE 9-31** Bilateral below-knee amputation for frostbite in a homeless patient. *(Courtesy Christopher H.E. Imray, MD.)*

treatment of plantar neuropathic ulcers of the feet, allowing the patient to mobilize while minimizing further damage from vertical and horizontal shear forces. Using this approach, with early bedside interventions as part of an integrated approach (including aggressive vascular/endovascular surgery), the major lower-limb amputation rate and length of stay have both been significantly reduced.[91]

### TELEMEDICINE

Use of the Internet to access expert advice has been driven by patients and clinicians with more limited experience in treatment of frostbite, permitting a virtual opinion from anywhere in the world.[82] The United Kingdom–based service can be accessed through the Diploma in Mountain Medicine or the British Mountaineering Council website (http://www.thebmc.co.uk/Category.aspx?category=19). The service is run by diploma faculty members and serves climbers and physicians worldwide, often to obtain a second opinion or to seek specialized advice. It is also possible to follow patients in a "virtual clinic," reviewing digital images and discussing management options by telephone or e-mail (see Figures 9-18 to 9-21).[79,169] Digital images have been used to assess wound healing in conjunction with HBOT.[53,]

## LONG-TERM SEQUELAE OF FROSTBITE

Until 1957, minimal information was recorded about the long-term sequelae of frostbite injuries. Blair and colleagues[16] studied 100 veterans of the Korean conflict 4 years after their injuries. In order of decreasing frequency, the patients reported excessive sweating, pain, coldness, numbness, abnormal skin color, and joint stiffness. The investigators noted frequent asymptomatic abnormalities of the nails, including ridges and inward curving of the edges. In general, the degree of long-term disability was related to severity of the original injury. Symptoms were worse in cold than in warm weather. This is attributed to blood vessels that do not react as well to stress.[180] Previously injured vessels do not constrict when exposed to cold as effectively as do normal vessels, and they do not dilate as effectively when vasoconstriction is blocked.

Hyperhidrosis is probably both a cause and a result of frostbite. Hyperhidrosis suggests presence of an abnormal sympathetic nervous response induced by cold injury and is abolished by sympathetic denervation. Sensitivity to cold and predisposition to recurrent cold injury should suggest hyperhidrosis. Blanching and pain on subsequent cold exposure may be a nuisance or may be dramatic enough to suggest a diagnosis of Raynaud's phenomenon (see Figure 9-12). Almost without exception, after sympathetic interruption, a painful, shiny, cyanotic, and sweaty limb becomes warm, dry, and useful.[176,177] Schoning[175] examined changes in the sweat glands of Hanford miniature swine after experimental frostbite injury to determine the etiology of hyperhidrosis. She noted that severe sweat gland changes were of two types: degeneration with necrosis and squamous metaplasia. Clearly, if hypohidrosis was a sequela of frostbite injury, morphologically normal and active sweat glands would be an expected finding. One can conclude that hyperhidrosis lacks histologic documentation.

A beneficial effect of open cervicothoracic sympathectomy for frostbite sequelae was described in 48 patients.[93] The minimally invasive endoscopic transthoracic sympathectomy approach reduces surgical trauma, allows more rapid recovery (Figure 9-32), and may have a limited role in late, persisting palmar hyperhidrosis. Iontophoresis may be of benefit in plantar hyperhidrosis.

The late abnormalities of change in skin color, including depigmentation of dark skin and an appearance resembling erythrocyanosis in light skin, are most likely the result of ischemia.[16] Similarly, the nail abnormality is comparable to that seen with ischemia. Usually, neither of these sequelae requires treatment.

Late symptoms of joint stiffness and pain on motion are relatively common and are undoubtedly related to the underlying scars and mechanical problems occasioned by the variety of amputations. "Punched-out" defects in subchondral bone of involved limbs have been noted. These localized areas of bone resorption generally appear within 5 to 10 months after injury and may heal spontaneously. Vascular occlusion is the probable cause of these lesions. Such bone involvement close to joint surfaces may help explain joint symptoms.

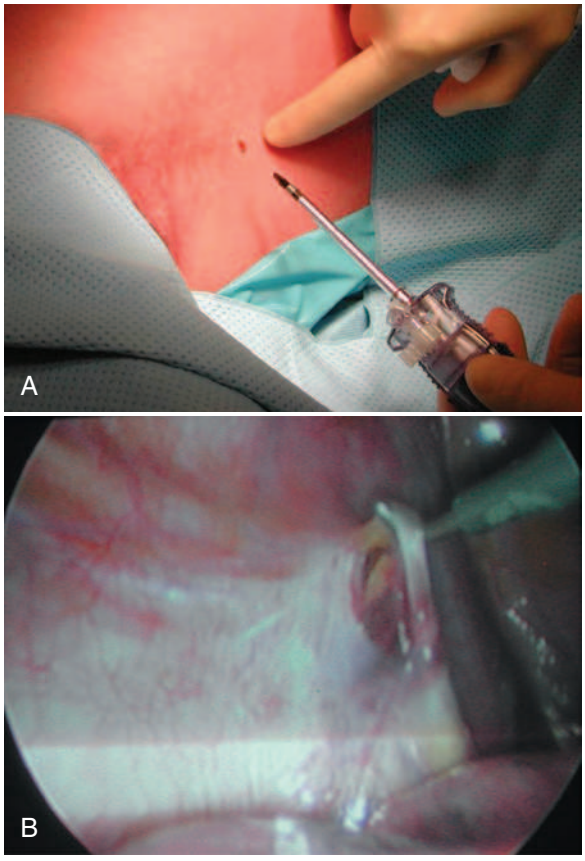



**FIGURE 9-32** **A,** One of the two 3-mm thoracoscopic port insertions into the axilla for a right endoscopic transthoracic sympathectomy (ETS) performed under general anesthesia. **B,** View of right sympathetic chain during ETS. *(Courtesy Christopher H.E. Imray, MD.)*

The effects of frostbite on premature closure of epiphyses in the growing hand have been emphasized.[205] Extent of premature closure has been correlated with severity of frostbite and noted in partial-thickness injuries. In the digits, premature closure is more frequently from a distal to proximal direction (distal interphalangeal > proximal interphalangeal > metacarpophalangeal). The thumb is less often involved. In only 2% of cases does partial epiphyseal closure cause angular deformity.

Cold-induced neuropathy may play an important role in the long-term sequelae of cold sensitivity after local cold injury. Alteration in somatosensory function was found to be more pronounced in lower-limb injuries.[8] Changes in nerve conduction velocity measurements may provide objective findings in cold-injured patients and in those with few or no conspicuous clinical signs. Tissue that has recovered from frostbite is more susceptible to further injury. This needs to be recognized when advising individuals about a return to environments where they may be at risk. Preventive measures remain the mainstay of primary and secondary treatment.[79]

Malignant transformation of old frostbite scars is a rare but well-recognized condition.[190] The lesions are sometimes described as "Marjolin's ulcer,"[194] but more often as squamous cell carcinomas.[48] One of the largest series of patients found that the tumors tended to be low grade and unlikely to metastasize; the physicians advocated surgical excision.[166]

## PREDICTION OF INDIVIDUALS AT RISK

Recent experimental techniques have been studied to predict which individuals are susceptible to frostbite injury. Predicting

those at risk would be helpful to assess risk for people planning to work or travel to high altitude or into extreme cold, as well as those who may be particularly valuable to military recruiting and planning. It would also be especially helpful when trying to advise persons who have sustained previous cold injury.

The RIF finger skin temperature response, determined in a simple laboratory test, may be related to the risk for cold injuries during operations in the field.[36] The reproducibility of the time course of CIVD suggests this methodology may be of value for further studies examining the mechanism of the response.[139] Kamikomaki[88] proposed that a case of frostbite in a climber with ACE DD allele was caused by genetic propensity for vasoconstriction. Perhaps we will see the evolution of testing for genetic predisposition to frostbite as a screening tool.

Thermography is an easy, noninvasive method for monitoring thermal changes after experimental frostbite, but its clinical value is as yet unknown.[45,86,173] Laser Doppler techniques have been used to assess efficacy of HBOT of frostbite. The number of visible nutritive capillaries in frostbitten areas was shown to increase.[50]

# PREVENTION

In 1950, Herzog and Lachenal made a successful lightweight bid without oxygen for the summit of Annapurna, the first 8000-m (26,247-foot) peak to be climbed. Herzog[77] lost his gloves near the summit, and the summit team spent a night in a crevasse. Both climbers suffered severe frostbite to their hands and feet. In a heroic retreat, Dr. Jacques Oudot first gave intraarterial vasodilators and then performed field amputations without anesthetic.

Eleven of the 210 deaths on Mt Everest between 1921 and 2006 were attributable to hypothermia,[51] and a significant proportion of climbers attempting to climb to extreme altitude develop frostbite,[56] suggesting that climbing above 8000 m (26,247 feet) carries significant risk for permanent cold injury (see Figure 9-7).

## STRATEGY TO PREVENT FROSTBITE

Prevention of frostbite is one key to safe and successful travel and work in cold environments. Box 9-4 summarizes general prevention strategies. Sound pre-participation education, selection of proper clothing, optimal nutrition, and hydration are all advised. Washburn's recommendations, originally published in 1962, remain relevant[203]:

- Dress to maintain general body warmth. In cold, windy weather, the face, head, and neck must be protected, because enormous amounts of body heat can be lost through these parts.
- Eat plenty of appetizing food to produce maximal output of body heat. Diet in cold weather at low altitude should tend toward fats, with carbohydrates of intermediate importance and proteins least important. As altitude increases above 3048 m (10,000 feet), carbohydrates become most important and proteins remain least important.
- Do not climb under extreme weather conditions, particularly at high altitudes on exposed terrain, or start too early in cold weather. The configuration of a mountain can help a climber find maximal shelter and solar warmth.
- Avoid tight, snug-fitting clothing, particularly on the hands and feet. Socks and boots should fit closely, with no points of tightness or pressure. When donning socks and boots, a person should carefully eliminate all wrinkles in socks. Old, matted insoles should be avoided.
- Avoid perspiration under conditions of extreme cold; wear adequately ventilated clothing. If perspiring, remove some clothing or slow down.
- Keep the feet and hands dry. Even with vapor-barrier boots, socks must not become wet. All types of boots must be worn with great care during periods of inactivity, especially after exercise has resulted in damp socks or insoles. Wet socks in any type of boot soften the feet and make the skin more tender, greatly lowering resistance to cold and simultaneously increasing the danger of other foot injuries, such as blistering. Extra socks and insoles should always be carried. Light, smooth, dry, and clean socks should be worn next to the skin, followed by one or two heavier outer pairs.
- Wear mittens instead of gloves in extreme cold, although gloves can be worn for short intervals when great manual dexterity is required for specialized work such as photography or surveying. In these situations, a mitten should be worn on one hand and a glove temporarily on the other. If bare-finger dexterity is required, silk or rayon gloves should be worn, or metal parts that must be touched frequently should be covered with adhesive tape. Occasionally, the thumbs should be pulled into the fists and held in the palms of the mittens to regain warmth of the entire hand.
- Be careful while loading cameras, taking pictures, or handling stoves and fuel. The freezing point of gasoline (−57°C [−70.6°F]) and its rapid rate of evaporation make it very dangerous. Metal objects should never be touched with bare hands in extreme cold, or in moderate cold if the hands are moist.
- Mitten shells and gloves worn in extreme cold should be made of soft, flexible, and dry-tanned deerskin, or moose, elk, or caribou hide. Horsehide is less favorable because it dries stiffly after wetting. Removable mitten inserts or glove linings should be of soft wool.
- Mittens should be tied together on a string hung around the neck or tied to the ends of parka sleeves. Oiled or greased leather gloves, boots, or clothing should never be used in cold-weather operations.
- Keep toenails and fingernails trimmed.
- Hands, face, and feet should not be washed too thoroughly or too frequently under rough weather conditions. Tough, weather-beaten face and hands resist frostbite most effectively.
- Wind and high altitude should be approached with respect. They can produce dramatic results when combined with cold. Exercise should not be too strenuous in extreme cold, particularly at high altitude, where undue exertion results in panting or very deep breathing. Cold inspired air will chill the whole body and under extreme conditions may damage lung tissue and cause internal hemorrhage.
- When a person becomes thoroughly chilled, it takes several hours of warmth and rest to return to normal, regardless of superficial feelings of comfort. A person recovering from an emergency cold situation should not venture out into extreme cold too soon.
- Avoid tobacco or alcohol at high altitudes and under conditions of frostbite danger.
- A person who is frostbitten or otherwise injured in the field must remain calm. Panic or fear results in perspiration, which evaporates and causes further chilling.
- Tetanus immunity should be current.

**BOX 9-4 Strategies for Prevention of Frostbite**

Good experience is the base of core survival skills.
- Wear protective clothing—layers, loose, heat insulating
- Avoid constriction of body parts with clothing
- Stay dry
- Wear wind protection

Hands:
- Wear mittens instead of gloves
- Use chemical hand warmers

Feet:
- Avoid tight-fitting boots
- Wear suitably warm boots such as triple-layer extreme-altitude boots

- Use electric-heated insoles
- Ensure adequate nutrition
- Maintain hydration
- Take aspirin (if not contraindicated)
- Use supplemental oxygen at extreme altitude

FIGURE 9-33 Selection of gloves and mittens used on a frostbite-free summit day on Mt Everest. *(Courtesy Christopher H.E. Imray, MD.)*


FIGURE 9-34 Chemical hand warmers for use in extreme cold used on a frostbite-free summit day on Mt Everest. *(Courtesy Christopher H.E. Imray, MD.)*

## CHEMICAL OR OTHER WARMERS

The well-equipped sojourner at extreme altitude or in cold environs should have a wide selection of gloves and mittens, including spares (Figure 9-33). In addition to protective clothing and insulation, external heat sources are advisable. A recent paper by Sands and co-workers[172] assessed the efficacy of commercially available, disposable, chemical hand and foot warmers. They found variations between the devices, but a strong relationship between the mass of the devices and duration of the heat production. Despite concerns about whether the chemical hand warmers function at the low levels of oxygen found at extreme altitude, anecdotally these warmers function well (Figure 9-34).[81]

Electric foot warmers are probably more useful than chemical foot warmers in extreme cold and at high altitude (Figure 9-35), where removing boots to insert warmers may be not only impractical but unwise. New lithium batteries opened on summit day are probably superior to rechargeable units. Chemical warmers also occupy a significant volume, resulting in pressure points that can either overheat and burn or lead to blistering.[81]

# POTENTIAL FUTURE DEVELOPMENTS: PREVENTIVE STRATEGIES

Over the past decade there has been substantial improvement in available equipment; in part because of the increased number of climbers attempting 8000-m (26,247-foot) peaks. Consequently, there is considerable financial incentive for developing state-of-the-art equipment. Current 8000-m boots are rated down to −50° to −60° C (−58° to −76° F) (see Figure 9-35). As new technologies are developed, such as "intelligent fabrics" and temperature-responsive fibers, numerous outdoor applications will likely occur. Newer insulating materials have already given rise to significantly better boots, gloves, and mittens (see Figures 9-33 to 9-35). Climbing equipment has also improved. For example, newer step-in crampons greatly reduce the time involved in fitting the crampons and the likelihood of having to adjust them while climbing, which substantially reduces the risk for cold exposure.

# POSSIBLE FUTURE TREATMENTS

## TIMING OF INTRAARTERIAL THROMBOLYSIS FOR FROSTBITE

Current opinion suggests that t-PA for acute frostbite may be beneficial and thus should be used if it can be started within 24 hours of the initial injury. However, considerable evidence from the treatment of both acute coronary syndrome[26] and acute stroke[94] indicates a variable window of opportunity for successful t-PA treatment. The timing of intervention for frostbite is yet to be determined, but longer delays are likely to be associated with

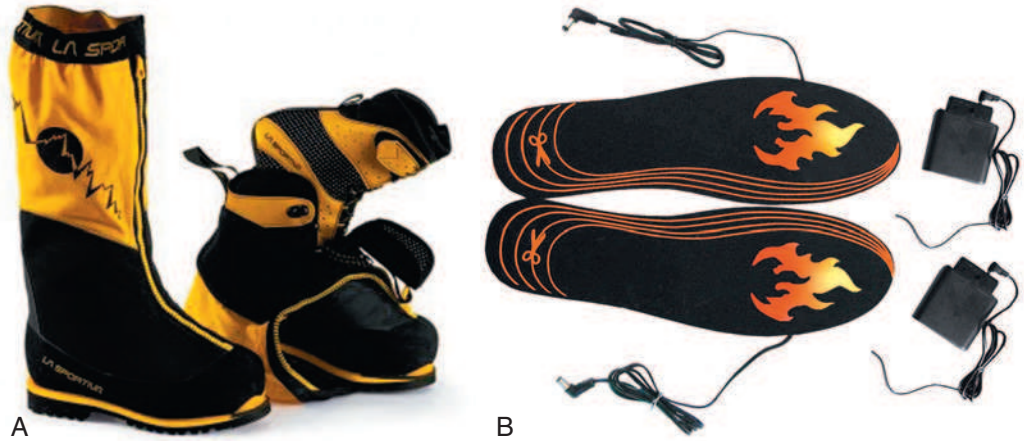



FIGURE 9-35 Triple-layer, 8000-m mountaineering boots **(A)** rated to −55° C (−67° F) and electric boot warmers **(B)** used on a frostbite-free summit day on Mt Everest. *(Courtesy Christopher H.E. Imray, MD.)*

less benefit[44] and thus to increase the need for secondary interventions, such as fasciotomies for reperfusion injuries, or subsequent amputations.[81]

### ULTRASOUND-ACCELERATED THROMBOLYSIS

In vitro work has shown that ultrasound accelerates transport of recombinant t-PA into clots.[55] Ultrasound is believed to reversibly loosen fibrin strands and reduce their diameter, exposing more individual strands, increasing thrombus permeability, and exposing more plasminogen receptor sites for binding.[20] More rapid and complete thrombolysis has been reported with the use of this technique than with standard catheter-directed thrombolysis. Results of one study suggest that percutaneous ultrasound-accelerated thrombolysis is more effective at clearing clots than is catheter-directed thrombolysis in patients with acute massive pulmonary embolism.[108]

### ANTIPLATELET AGENTS

There have been significant advances in the understanding, management, and outcomes of patients with acute coronary syndrome with the introduction of IV antiplatelet agents, such as glycoprotein IIb/IIIa inhibitors. Inhibiting platelet aggregation is a vital link in optimizing outcome.[2] In a pilot study, outcomes in unstable, symptomatic carotid endarterectomy patients appeared to improve after using a glycoprotein IIb/IIIa inhibitor.[196] There likely will be a role in frostbite treatment for the use of combination oral (aspirin and clopidogrel) and IV antiplatelet agents to improve vessel patency after t-PA clearance of thrombus.

### TUMOR NECROSIS FACTOR-α

Evidence indicates that tumor necrosis factor (TNF)-α–induced reactive oxygen species have a role in endothelial dysfunction during reperfusion injury.[58] Investigation into the effects of inhibition of phosphodiesterase type 4 and TNF-α on local and remote injuries after ischemia and reperfusion injury suggests that these processes may be modified.[184] This particular approach might offer improved outcome in early frostbite.

### VACUUM-ASSISTED CLOSURE THERAPY

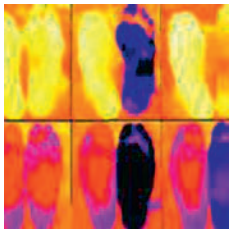
Vacuum-assisted closure therapy has been shown to be beneficial in accelerating wound healing in partial diabetic foot amputations.[6] This therapy can be used in community and specialty hospitals, and in many tertiary care hospitals it is being administered through specialist tissue-viability nurses. One report has shown a good outcome with frostbite.[152]

### FROSTBITE MANAGEMENT REGISTRY AND THE INTERNET

One of the persisting characteristics of frostbite research is the lack of good evidence to support newer treatments. An international frostbite management registry would allow pooling of data, accelerating the learning process.

## REFERENCES

***Complete references used in this text are available online at expertconsult.inkling.com.***



CHAPTER 10

# Nonfreezing Cold-Induced Injuries

CHRISTOPHER H.E. IMRAY, CHARLES HANDFORD, OWEN D. THOMAS, AND JOHN W. CASTELLANI

Nonfreezing cold-induced injury (NFCI) is a clinical syndrome that results from the damage caused to tissues exposed to cold temperatures at or above freezing point (0° to 15°C [32° to 59°F). NFCI does not involve tissue freezing, which distinguishes it both clinically and pathologically from frostbite.[45] The earliest descriptions of this syndrome originated in the military. Baron Dominique Jean Larrey, Napoleon's chief surgeon, used the word "congelation" to describe the nonfreezing injuries together with frostbite casualties that occurred during the 1812 assault on Russia.[115] Historically, infantry regiments have been decimated by cold and wet conditions, and many medical advances in understanding the pathophysiology and clinical course of NFCI have occurred after wars.[1,44,] However, the continuity of research tends to lag during the periods between major military campaigns.[123] Developments in the prevention of cold injury have flourished as new clothing and footwear are designed, but little progress has been made in the treatment of NFCI.

An increasing number of people are pursuing recreational activities in harsh environments, and as a consequence, civilian NFCIs are becoming more prevalent. However, because many physicians are unfamiliar with these injuries, they may go undiagnosed during assessment of the cold-exposed patient.[123] This results in unnecessary hospital admissions and potentially harmful and expensive therapy.[49] Proper education and awareness of the hazards innate to the cold environment should mean that NFCI is preventable in most circumstances.

This chapter explores the history, epidemiology, pathophysiology, and current prevention and treatment of NFCI and specifically discusses pernio (chilblains), cryoglobulinemia, cold urticaria, and Raynaud's phenomenon.

## EPIDEMIOLOGY

Individuals with cold and wet extremities for extended periods are at risk for nonfreezing cold injuries. During the 1800s, NFCI was observed more frequently when the temperature hovered around the freezing point—when the ground was muddy rather than frozen.[54,114] Standing or sitting for long periods, wearing constrictive footwear, malnutrition, fatigue, or the blunt trauma of marching on cold, wet feet all added to the severity of injury.[115] Original animal studies that modeled NFCI demonstrated that cold temperatures near the freezing point were more likely to cause injury when the extremities were wet than when they were dry.[13,114] Ambient temperature and wind speed can both influence cooling.[39,140]

In "shelter limb" (dependency without cold) and "paddy foot" (wet but not cold), there is an injury that has no apparent distinguishing differential features from NFCI. This would suggest

## REFERENCES


1. Department of Health and Social Services Division of Public Health. Section of Community Health and EMS. State of Alaska Cold Injuries Guidelines. 2003 (revised 2005).
2. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. N Engl J Med 1998;338(21):1488–97.
3. U.S. Army survival manual: FM21-76. Washington, DC: US Department of the Army; 1970.
4. Adams-ray J, Bellman S. Vascular reactions after experimental cold injury: A microangiographic study of rabbit ears. Angiology 1956;7(4): 339–67.
5. Andrew J. Life and limb: A true story of tragedy and survival. London: Portrait; 2005. p. 2003.
6. Armstrong DG, Lavery LA, Consortium DFS. Negative pressure wound therapy after partial diabetic foot amputation: A multicentre, randomised controlled trial. Lancet 2005;366(9498):1704–10.
7. Arregui R, Morandeira JR, Martinez G, et al. Epidural neurostimulation in the treatment of frostbite. Pacing Clin Electrophysiol 1989;12(4 Pt 2):713–17.
8. Arvesen A, Wilson J, Rosén L. Nerve conduction velocity in human limbs with late sequelae after local cold injury. Eur J Clin Invest 1996;26(6):443–50.
9. Auerbach LJ, DeClerk BK, Fathman CG, et al. Poly-L-arginine topical lotion tested in a mouse model for frostbite injury. Wilderness Environ Med 2014;25(2):160–5.
10. Auerbach LJ, Galvez MG, De Clerck BK, et al. A novel mouse model for frostbite injury. Wilderness Environ Med 2013;24(2):94–104.
11. Ay H, Yildiz S, Uzun G, et al. The treatment of deep frostbite with hyperbaric oxygen. Injury Extra 2005;36:499.
12. Barat AK, Puri HC, Ray N. Cold injuries in Kashmir, December 1971. Ann R Coll Surg Engl 1978;60(4):332–5.
13. Barillo DJ, Spillert CR, LoVerme PJ, Lazaro EJ. Detrimental effects of ethanol on murine frostbite. Am Surg 1984;50(12):649–52.
14. Barker JR, Haws MJ, Brown RE, et al. Magnetic resonance imaging of severe frostbite injuries. Ann Plast Surg 1997;38(3):275–9.
15. Bhatnagar A, Sarker BB, Sawroop K, et al. Diagnosis, characterisation and evaluation of treatment response of frostbite using pertechnetate scintigraphy: A prospective study. Eur J Nucl Med Mol Imaging 2002;29(2):170–5.
16. Blair JR, Schatzki R, Orr KD. Sequelae to cold injury in one hundred patients: Follow-up study four years after occurrence of cold injury. JAMA 1957;163(14):1203–8.
17. Boswick JA, Thompson JD, Jonas RA. The epidemiology of cold injuries. Surg Gynecol Obstet 1979;149(3):326–32.
18. Bourne MH, Piepkorn MW, Clayton F, Leonard LG. Analysis of microvascular changes in frostbite injury. J Surg Res 1986;40(1):26–35.
19. Bouwman DL, Morrison S, Lucas CE, Ledgerwood AM. Early sympathetic blockade for frostbite—is it of value? J Trauma 1980;20(9): 744–9.
20. Braaten JV, Goss RA, Francis CW. Ultrasound reversibly disaggregates fibrin fibers. Thromb Haemost 1997;78(3):1063–8.
21. Brown FE, Spiegel PK, Boyle WE. Digital deformity: An effect of frostbite in children. Pediatrics 1983;71(6):955–9.
22. Bruen KJ, Ballard JR, Morris SE, et al. Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy. Arch Surg 2007;142(6):546–51.
23. Buikema H, Pinto YM, Rooks G, et al. The deletion polymorphism of the angiotensin-converting enzyme gene is related to phenotypic differences in human arteries. Eur Heart J 1996;17(5):787–94.
24. Bulkley GB. The role of oxygen free radicals in human disease processes. Surgery 1983;94(3):407–11.
25. Campbell R. General cooling and local frostbite. In: Proceedings of Symposium on Arctic Biology and Medicine. Fort Wainwright, Alaska: Artic Aeromedical Laboratory; 1964.
26. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001;344(25):1879–87.
27. Carrera GF, Kozin F, Flaherty L, McCarty DJ. Radiographic changes in the hands following childhood frostbite injury. Skeletal Radiol 1981;6(1):33–7.
28. Cattermole TJ. The epidemiology of cold injury in Antarctica. Aviat Space Environ Med 1999;70(2):135–40.
29. Cauchy E, Cheguillaume B, Chetaille E. A controlled trial of a prostacyclin and rt-PA in the treatment of severe frostbite. N Engl J Med 2011;364(2):189–90.
30. Cauchy E, Chetaille E, Lefevre M, et al. The role of bone scanning in severe frostbite of the extremities: A retrospective study of 88 cases. Eur J Nucl Med 2000;27(5):497–502.
31. Cauchy E, Chetaille E, Marchand V. Marsigny B. Retrospective study of 70 cases of severe frostbite lesions: A proposed new classification scheme. Wilderness Environ Med 2001;12(4):248–55.
32. Cauchy E, Leal S, Magnan MA. Nespoulet H. Portable hyperbaric chamber and management of hypothermia and frostbite: an evident utilization. High Alt Med Biol 2014;15(1):95–6.
33. Cauchy E, Marsigny B, Allamel G, et al. The value of technetium 99 scintigraphy in the prognosis of amputation in severe frostbite injuries of the extremities: A retrospective study of 92 severe frostbite injuries. J Hand Surg [Am] 2000;25(5):969–78.
34. Chandran GJ, Chung B, Lalonde J, Lalonde DH. The hyperthermic effect of a distal volar forearm nerve block: A possible treatment of acute digital frostbite injuries? Plast Reconstr Surg 2010;126(3): 946–50.
35. Clissold SP, Lynch S, Sorkin EM. Buflomedil. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in peripheral and cerebral vascular diseases. Drugs 1987;33(5): 430–60.
36. Daanen HA, van der Struijs NR. Resistance Index of Frostbite as a predictor of cold injury in arctic operations. Aviat Space Environ Med 2005;76(12):1119–22.
37. DeGroot DW, Castellani JW, Williams JO, Amoroso PJ. Epidemiology of U.S. Army cold weather injuries, 1980-1999. Aviat Space Environ Med 2003;74(5):564–70.
38. Didlake RH. Kukora JS. Tetanus following frostbite injury. Contemp Orthop 1985;10:69.
39. Dolbec KW, Higgins GL, Riedesel EL. Images in emergency medicine: Two patients with frostbite. Ann Emerg Med 2013;62(2): 194–200.
40. Donaldson GC, Rintamäki H, Näyhä S. Outdoor clothing: its relationship to geography, climate, behaviour and cold-related mortality in Europe. Int J Biometeorol 2001;45(1):45–51.
41. Ducuing J. Les troubles trophiques des produits par de froid sec en pathologic de guerre. J Chir 1940;55:385.
42. Lovelock JE. Physical instability and thermal shock in red cells. Nature 1954;173(4406):659–61.
43. Edmonson G. Personal comminication, 2010.
44. Edmonson G, Bretzman P, Mohr D. et al. Intra-arterial thrombolytic therapy for limb salvage in severe frostbite. J Vasc Interv Radiol 2008;19:Abstract 52.
45. Eglin C, Golden F, Tipton M. The effect of gentle exercise prior to a cold sensitivity test used to classify non-freezing cold injury. In: Prevention of cold injuries, Meeting Proceedings RTO-MP-HFM-126, Neuilly-sur-Seine. France: RTO; 2005. p. 11-1–11-6.
46. Eleftheriou-Smith L. Himalayas avalanches: Rescue teams to make final search for survivors. The Independent. 2014.
47. Ervasti O, Juopperi K, Kettunen P, et al. The occurrence of frostbite and its risk factors in young men. Int J Circumpolar Health 2004; 63(1):71–80.
48. Eun HC, Kim JA, Lee YS. Squamous cell carcinoma in a frost-bite scar. Clin Exp Dermatol 1986;11(5):517–20.
49. Farnell GS, Pierce KE, Collinsworth TA, et al. The influence of ethnicity on thermoregulation after acute cold exposure. Wilderness Environ Med 2008;19(4):238–44.
50. Finderle Z, Cankar K. Delayed treatment of frostbite injury with hyperbaric oxygen therapy: A case report. Aviat Space Environ Med 2002;73(4):392–4.
51. Firth PG, Zheng H, Windsor JS, et al. Mortality on Mount Everest, 1921-2006: Descriptive study. BMJ 2008;337:a2654.
52. Fogarty TJ, Cranley JJ, Krause RJ, et al. A method for extraction of arterial emboli and thrombi. Surg Gynecol Obstet 1963;116: 241–4.
53. Folio LR, Arkin K, Butler WP. Frostbite in a mountain climber treated with hyperbaric oxygen: Case report. Mil Med 2007;172(5):560–3.
54. Foray J, Baisse PE, Mont JP, Cahen C. Treatment of frostbites: Analysis of results in twenty patients with buflomedil chlorhydrate (author's transl). Sem Hop 1980;(9–10).
55. Francis CW, Blinc A, Lee S, Cox C. Ultrasound accelerates transport of recombinant tissue plasminogen activator into clots. Ultrasound Med Biol 1995;21(3):419–24.
56. Freer L. Personal communication, 2009.
57. Fuhrman FA, Crismon JM. Studies on gangrene following cold injury: treatment of cold injury by means of immediate rapid warming. J Clin Invest 1947;26(3):476–85.
58. Gao X, Zhang H, Belmadani S, et al. Role of TNF-alpha-induced reactive oxygen species in endothelial dysfunction during reperfusion injury. Am J Physiol Heart Circ Physiol 2008;295(6):H2242–9.
59. Garvey MB, Dennis LH, Hildebrandt PK, Conrad ME. Hypobaric erythraemia: Pathology and coagulation studies. Br J Haematol 1969; 17(3):275–81.
60. Geng Q, Holmér I, Hartog DE, et al. Temperature limit values for touching cold surfaces with the fingertip. Ann Occup Hyg 2006;50(8): 851–62.

61. Giesbrecht GG. Hypothermia, frostbite, and other cold injuries: Prevention, survival, rescue and treatment. 2nd ed. Seattle, WA: Mountaineers Books; 2006.
62. Golant A, Nord RM, Paksima N, Posner MA. Cold exposure injuries to the extremities. J Am Acad Orthop Surg 2008;16(12):704–15.
63. Gottlieb LJ, Zachary LS, Krizek TJ. Aggressive surgical treatment of frostbite injuries. Presented at Midwestern Association of Plastic Surgeons meeting. 1987.
64. Graham CA, Stevenson J. Frozen chips: an unusual cause of severe frostbite injury. Br J Sports Med 2000;34(5):382–3.
65. Gralino BJ, Porter JM, Rosch J. Angiography in the diagnosis and therapy of frostbite. Radiology 1976;119(2):301–5.
66. Greenfield AD, Shepherd JT, Whelan RF. Cold vasoconstriction and vasodilatation. Ir J Med Sci 1951;309:415–19.
67. Greenwald D, Cooper B, Gottlieb L. An algorithm for early aggressive treatment of frostbite with limb salvage directed by triple-phase scanning. Plast Reconstr Surg 1998;102(4):1069–74.
68. Groechenig E. Treatment of frostbite with iloprost. Lancet 1994; 344(8930):1152–3.
69. Handford C, Buxton P, Russell K, et al. Frostbite: a practical approach to hospital management. Extrem Physiol Med 2014;3:7.
70. Harirchi I, Arvin A, Vash JH, Zafarmand V. Frostbite: incidence and predisposing factors in mountaineers. Br J Sports Med 2005;39(12):898–901, discussion.
71. Hashmi MA, Rashid M, Haleem A, et al. Frostbite: epidemiology at high altitude in the Karakoram mountains. Ann R Coll Surg Engl 1998;80(2):91–5.
72. Hayes DW Jr, Mandracchia VJ, Considine C, Webb GE. Pentoxifylline: Adjunctive therapy in the treatment of pedal frostbite. Clin Podiatr Med Surg 2000;17(4):715–22.
73. Heggers JP, Pelley RP, Robson MC. Beneficial effects of *Aloe* in wound healing. Phytother Res 1993;7:48–52.
74. Heggers JP, Robson MC, Manavalen K, et al. Experimental and clinical observations on frostbite. Ann Emerg Med 1987;16(9):1056–62.
75. Henrion D, Benessiano J, Philip I, et al. The deletion genotype of the angiotensin I-converting enzyme is associated with an increased vascular reactivity in vivo and in vitro. J Am Coll Cardiol 1999; 34(3):830–6.
76. Hershkowitz M. Penile frostbite, an unforeseen hazard of jogging. N Engl J Med 1977;296(3):178.
77. Herzog M. Annapurna, first conquest of an 8000-meter peak (26,493 feet). 1st American ed. New York: Dutton; 1953.
78. Hurley LA. Angioarchitectural changes associated with rapid rewarming subsequent to freezing injury. Angiology 1957;8(1):19–28.
79. Imray C, Grieve A, Dhillon S, Caudwell Xtreme Everest Research G. Cold damage to the extremities: Frostbite and non-freezing cold injuries. Postgrad Med J 2009;85(1007):481–8.
80. Imray CH, Oakley EH. Cold still kills: Cold-related illnesses in military practice freezing and non-freezing cold injury. J R Army Medical Corps 2005;151(4):218–22.
81. Imray CHE Personal communication, 2010.
82. Imray CHE, Hillebrandt D. Telemedicine and frostbite injuries. BMJ 2004;328:1210.
83. Ince C, Sinaasappel M. Microcirculatory oxygenation and shunting in sepsis and shock. Crit Care Med 1999;27(7):1369–77.
84. Johnson AR, Jensen HL, Peltier G, DelaCruz E. Efficacy of intravenous tissue plasminogen activator in frostbite patients and presentation of a treatment protocol for frostbite patients. Foot Ankle Spec 2011;4(6):344–8.
85. Johnson BE, Daniels F. Enzyme studies in experimental cryosurgery of the skin. Cryobiology 1974;11(3):222–32.
86. Junila J, Kaarela O, Mäkäräinen H, Waris T. Assessment of tissue viability by thermography after experimentally produced frostbite of the rabbit ear. Acta Radiol 1993;34(6):622–4.
87. Juopperi K, Hassi J, Ervasti O, et al. Incidence of frostbite and ambient temperature in Finland, 1986-1995. A national study based on hospital admissions. Int J Circumpolar Health 2002;61(4): 352–62.
88. Kamikomaki N. A climber with the DD ACE allele developed frostbite despite taking more than adequate measures against cold on Mount Everest. High Alt Med Biol 2007;8(2):167–8.
89. Kassell NF, Helm G, Simmons N, et al. Treatment of cerebral vasospasm with intra-arterial papaverine. J Neurosurg 1992;77(6): 848–52.
90. Kemper TC, de Jong VM, Anema HA, et al. Frostbite of both first digits of the foot treated with delayed hyperbaric oxygen: A case report and review of literature. Undersea Hyperb Med 2014;41(1): 65–70.
91. Khaira HS, Coddington T, Drew A, et al. Patellar tendon bearing orthosis: Application as adjunctive treatment in healing of lower-limb tissue loss. Eur J Vasc Endovasc Surg 1998;16(6):485–8.
92. Khan M, Wyne A, Khan N, et al. Frostbite during the Kashmir conflict. Pak Arm Forc Med J 2005.
93. Khan MI, Tariq M, Rehman A, et al. Efficacy of cervicothoracic sympathectomy versus conservative management in patients suffering from incapacitating Raynaud's syndrome after frostbite. J Ayub Med Coll Abbottabad 2008;20(2):21–4.
94. Khatri P, Abruzzo T, Yeatts SD, et al. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. Neurology 2009;73(13):1066–72.
95. Kinmouth JB, Rob CG, Simeone FA. The cryopathies in vascular surgery. London: E Arnold; 1962.
96. Knize DM. Cold injury in reconstructive plastic surgery: General Principles. 2nd ed. Philadelphia: WB Saunders; 1977.
97. Knize DM, Weatherley-White RC, Paton BC, Owens JC. Prognostic factors in the management of frostbite. J Trauma 1969;9(9): 749–59.
98. Kroeger K, Janssen S, Niebel W. Frostbite in a mountaineer. Vasa 2004;33(3):173–6.
99. Kulka JP. Histopathologic studies in frostbitten rabbits. Conferences in Cold Injury. New York: Josiah Macy Jr Foundation; 1956.
100. Kulka JP. Microcirculatory impairment as a factor in inflammatory tissue damage. Ann N Y Acad Sci 1964;116:1018–44.
101. Küpper T, Steffgen J, Jansing P. Cold exposure during helicopter rescue operations in the Western Alps. Ann Occup Hyg 2003;47(1): 7–16.
102. Kyösola K. Clinical experiences in the management of cold injuries: A study of 110 cases. J Trauma 1974;14(1):32–6.
103. Lacour M, Le Coultre C. Spray-induced frostbite in a child: A new hazard with novel aerosol propellants. Pediatr Dermatol 1991;8(3): 207–9.
104. Lange K, Loewe L. Subcutaneous heparin in the Pitkin menstruum for the treatment of experimental human frostbite. Surg Gynecol Obstet 1946;82:256–60.
105. Larrey DJ, Hall RW. Memoirs of military surgery. 1st American from 2nd Paris ed. Baltimore Published by Joseph Cushing; 1814. p. 6.
106. Lawrence WT, Murphy RC, Robson MC, Heggers JP. The detrimental effect of cigarette smoking on flap survival: An experimental study in the rat. Br J Plast Surg 1984;37(2):216–19.
107. Lewis T. Observations on some normal and injurious effects of cold upon the skin and underlying tissues: III. Frost-bite. Br Med J 1941; 2(4224):869–71.
108. Lin PH, Annambhotla S, Bechara CF, et al. Comparison of percutaneous ultrasound-accelerated thrombolysis versus catheter-directed thrombolysis in patients with acute massive pulmonary embolism. Vascular 2009;17(Suppl. 3):S137–47.
109. Lisbona R, Rosenthall L. Assessment of bone viability by scintiscanning in frostbite injuries. J Trauma 1976;16(12):989–92.
110. Lovelock JE. The denaturation of lipid-protein complexes as a cause of damage by freezing. Proc R Soc Lond B Biol Sci 1957;147(929): 427–33.
111. Manson PN, Jesudass R, Marzella L, et al. Evidence for an early free radical-mediated reperfusion injury in frostbite. Free Radic Biol Med 1991;10(1):7–11.
112. Markert CL. Lactate dehydrogenase isozymes: dissociation and recombination of subunits. Science 1963;140(3573):1329–30.
113. Martin DS, Ince C, Goedhart P, et al. Caudwell Xtreme Everest Research Group. Abnormal blood flow in the sublingual microcirculation at high altitude. Eur J Appl Physiol 2009;106(3):473–8.
114. Marzella L, Jesudass RR, Manson PN, et al. Morphologic characterization of acute injury to vascular endothelium of skin after frostbite. Plast Reconstr Surg 1989;83(1):67–76.
115. Maurel A, Betrancourt JC, Van Frenkel R, Thuillez C. Action of Buflomedil on the cutaneous microcirculation studies by a cold provocation test: Multicenter, double-blind, placebo controlled trial. J Mal Vasc 1995;20(2):127–33.
116. Mazur P. Causes of injury in frozen and thawed cells. Fed Proc 1965;24:S175–82.
117. Mazur P. Freezing of living cells: mechanisms and implications. Am J Physiol 1984;247(3 Pt 1):C125–42.
118. Mazur P. Studies on rapidly frozen suspensions of yeast cells by differential thermal analysis and conductometry. Biophys J 1963;3: 323–53.
119. McCauley RL, Heggers JP, Robson MC. Frostbite: Methods to minimize tissue loss. Postgrad Med 1990;88(8):67–8, 73–7.
120. McCauley RL, Hing DN, Robson MC, Heggers JP. Frostbite injuries: A rational approach based on the pathophysiology. J Trauma 1983; 23(2):143–7.
121. McCauley RL, Killyon GW, Smith DJ, et al. Frostbite. In: Auerbach PS: Wilderness medicine. 5th ed. Philadelphia: Mosby Elsevier; 2007.
122. McIntosh SE, Hamonko M, Freer L, et al. Wilderness Medical Society Practice Guidelines for the Prevention and Treatment of Frostbite. Wilderness Environ Med 2011;22(2):156–66.
123. McIntosh SE, Opacic M, Freer L, et al. Wilderness Medical Society Practice Guidelines for the Prevention and Treatment of Frostbite: 2014 update. Wilderness Environ Med 2014;25(4 Suppl.):S43–54.

124. Meryman HT. The exceeding of a minimum tolerable cell volume in hypertonic suspension as a cause of freezing injury. In: CIBA Foundation Symposium: The Frozen Cell. London: Churchill; 1970.
125. Meryman HT. Mechanics of freezing in living cells and tissues. Science 1956;124(3221):515–21.
126. Miller BJ, Chasmar LR. Frostbite in Saskatoon: a review of 10 winters. Can J Surg 1980;23(5):423–6.
127. Miller JW, Danzl DF, Thomas DM. Urban accidental hypothermia: 135 cases. Ann Emerg Med 1980;9(9):456–61.
128. Miller MB, Koltai PJ. Treatment of experimental frostbite with pentoxifylline and aloe vera cream. Arch Otolaryngol Head Neck Surg 1995;121(6):678–80.
129. Mills WJ. Clinical aspects of frostbite injury. In: Proceedings of the Symposium on Arctic Medicine and Biology. IV. Frostbite. Fort Wainwright, Alaska: Arctic Aeromedical Laboratory; 1964. p. 1964.
130. Mills WJ. Out in the cold. Emerg Med 1975;8:134.
131. Mills WJ. Summary of treatment of the cold injured patient. Alaska Med 1973;15(2):56–9.
132. Mills WJ, Whaley R. Frostbite: experience with rapid rewarming and ultrasonic therapy. 1960-1. Wilderness Environ Med 1998;9(4):226–47.
133. Mitchell HH, Edman M Nutrition and climatic stress. Springfield, Ill.: Thomas; 1951.
134. Mohr WJ, Jenabzadeh K, Ahrenholz DH. Cold injury. Hand Clin 2009;25(4):481–96.
135. Molnar GW, Hughes AL, Wilson O, Goldman RF. Effect of skin wetting on finger cooling and freezing. J Appl Physiol 1973;35(2):205–7.
136. Moran T. Critical temperature of freezing living muscle. Proceedings of the Royal Society of London 1929;105(736):177–97.
137. Murkowski FG, Mandsager J, Choromanski Hull-Jilly R, D. State of Alaska Cold Injuries Guidelines. 2003 (Revised 01/2005). pp 36–41.
138. Murphy JV, Banwell PE, Roberts AH, McGrouther DA. Frostbite: pathogenesis and treatment. J Trauma 2000;48(1):171–8.
139. O'Brien C. Reproducibility of the cold-induced vasodilation response in the human finger. J Appl Physiol 2005;98(4):1334–40.
140. Okuboye JA, Ferguson CC. The use of hyperbaric oxygen in the treatment of experimental frostbite. Can J Surg 1968;11(1):78–84.
141. Olsen N. Diagnostic aspects of vibration-induced white finger. Int Arch Occup Environ Health 2002;75(1–2):6–13.
142. Orr KD, Fainer DC. Cold injuries in Korea during winter of 1950-51. Medicine (Baltimore) 1952;31(2):177–220.
143. Ouriel K. A history of thrombolytic therapy. J Endovasc Ther 2004;11(Suppl. 2):II128–33.
144. Ozyazgan I, Tercan M, Melli M, et al. Eicosanoids and inflammatory cells in frostbitten tissue: Prostacyclin, thromboxane, polymorphonuclear leukocytes, and mast cells. Plast Reconstr Surg 1998;101(7):1881–6.
145. Pasquier M, Ruffinen GZ, Brugger H, Paal P. Pre-hospital wrist block for digital frostbite injuries. High Alt Med Biol 2012;13(1):65–6.
146. Petrone P, Kuncir EJ, Asensio JA. Surgical management and strategies in the treatment of hypothermia and cold injury. Emerg Med Clin North Am 2003;21(4):1165–78.
147. Pichotka J, Lewis RB. Prevention of secondary infection due to *Pseudomonas aeruginosa* in frostbitten tissue. Proc Soc Exp Biol Med 1949;72(1):127–30.
148. Pinzur MS, Weaver FM. Is urban frostbite a psychiatric disorder? Orthopedics 1997;20(1):43–5.
149. Reference deleted in proofs.
150. Porter JM, Wesche DH, Rösch J, Baur GM. Intra-arterial sympathetic blockade in the treatment of clinical frostbite. Am J Surg 1976;132(5):625–30.
151. Post PW, Donner DD. Frostbite in a pre-Columbian mummy. Am J Phys Anthropol 1972;37(2):187–91.
152. Poulakidas S, Cologne K, Kowal-Vern A. Treatment of frostbite with subatmospheric pressure therapy. J Burn Care Res 2008;29(6):1012–14.
153. Pretorius T, Bristow GK, Steinman AM, Giesbrecht GG. Thermal effects of whole head submersion in cold water on nonshivering humans. J Appl Physiol (1985) 2006;101(2):669–75.
154. Pugh G. Expedition to Cho-Oyo. Geogr J 1953;119:137.
155. Purkayastha SS, Roy A, Chauhan SK, et al. Efficacy of pentoxifylline with aspirin in the treatment of frostbite in rats. Indian J Med Res 1998;107:239–45.
156. Rabb JM, Renaud ML, Brandt PA, Witt CW. Effect of freezing and thawing on the microcirculation and capillary endothelium of the hamster cheek pouch. Cryobiology 1974;11(6):508–18.
157. Raine TJ. Antiprostaglandins and antithromboxanes for treatment of frostbite. Surg Forum 1980;31:557.
158. Rakower SR, Shahgoli S, Wong SL. Doppler ultrasound and digital plethysmography to determine the need for sympathetic blockade after frostbite. J Trauma 1978;18(10):713–18.
159. Raman SR, Jamil Z, Cosgrove J. Magnetic resonance angiography unmasks frostbite injury. EMJ 2011;28(5):450.
160. Reus WF, Robson MC, Zachary L, Heggers JP. Acute effects of tobacco smoking on blood flow in the cutaneous micro-circulation. Br J Plast Surg 1984;37(2):213–15.
161. Rinfret AP. Cryobiology in cryogenic technology. New York: Wiley; 1962.
162. Rintamaki H. Predisposing factors and prevention of frostbite. Int J Circumpolar Health 2000;59(2):114–21.
163. Robson MC, Heggers JP. Evaluation of hand frostbite blister fluid as a clue to pathogenesis. J Hand Surg [Am] 1981;6(1):43–7.
164. Robson MC, Krizek TJ, Wray RC. Care of the thermally injured patient. In: Management of trauma. Philadelphia: WB Saunders; 1979.
165. Rosenthall L, Kloiber R, Gagnon R, et al. Frostbite with rhabdomyolsis and renal failure: Radionuclide study. AJR Am J Roentgenol 1981;137(2):387–90.
166. Rossis CG, Yiacoumettis AM, Elemenoglou J. Squamous cell carcinoma of the heel developing at site of previous frostbite. J R Soc Med 1982;75(9):715–18.
167. Rothenberger J, Held M, Jaminet P, et al. Development of an animal frostbite injury model using the Goettingen-Minipig. Burns 2014;40(2):268–73.
168. Rubin G. The patellar tendon-bearing orthosis. Bull Hosp Joint Dis 1972;33:155.
169. Russell KW, Imray CH, McIntosh SE, et al. Kite skier's toe: an unusual case of frostbite. Wilderness Environ Med 2013;24(2):136–40.
170. Saemi AM, Johnson JM, Morris CS. Treatment of bilateral hand frostbite using transcatheter arterial thrombolysis after papaverine infusion. Cardiovasc Intervent Radiol 2009;32(6):1280–3.
171. Salimi Z, Wolverson MK, Herbold DR, Vas W. Frostbite: Experimental assessment of tissue damage using Tc-99m pyrophosphate. Radiology 1986;161(1):227–31.
172. Sands WA, Kimmel WL, Wurtz BR, et al. Comparison of commercially available disposable chemical hand and foot warmers. Wilderness Environ Med 2009;20(1):33–8.
173. Satybaldyev VM. Early diagnosis and prognosis of severity in frostbite of the extremities. Vestn Khir Im I I Grek 2003;162(1):46–8.
174. Schechter DC, Sarot IA. Historical accounts of injuries due to cold. Surgery 1968;63(3):527–35.
175. Schoning P. Experimental frost-bite in Hanford Miniature Swine. III. Sweat gland changes. Int J Exp Pathol 1990;71(5):713–16.
176. Schoning P, Hamlet MP. Experimental frost-bite in Hanford Miniature Swine. I. Epithelial changes. Br J Exp Pathol 1989;70(1):41–9.
177. Schoning P, Hamlet MP. Experimental frost-bite in Hanford Miniature Swine. II. Vascular changes. Br J Exp Pathol 1989;70(1):51–7.
178. Sheridan RL, Goldstein MA, Stoddard FJ Jr, Walker TG. Case records of the Massachusetts General Hospital. Case 41-2009. A 16-year-old boy with hypothermia and frostbite. N Engl J Med 2009;361(27):2654–62.
179. Shikama KY, Yamazaki T. Denaturation of catalase by freezing and thawing. Nature 1961;190:83–4.
180. Shumacker HB, White BH. Studies in experimental frostbite: The effect of heparin in preventing gangrene. Surgery 1947;22(6):900–9.
181. Simeone FA. The surgical volumes of the history of the United States Army Medical Department in World War II. Cold injury. Arch Surg 1960;80:396–405.
182. Snider RL, Porter JM. Treatment of experimental frostbite with intra-arterial sympathetic blocking drugs. Surgery 1975;77(4):557–61.
183. Snider RL, Rummell D, Merhoff GC, Porter JM. Intra-arterial sympathetic blockade in treatment of frostbite. Surg Forum 1974;25(0):237–9.
184. Souza DG, Cassali GD, Poole S, Teixeira MM. Effects of inhibition of PDE4 and TNF-alpha on local and remote injuries following ischaemia and reperfusion injury. Br J Pharmacol 2001;134(5):985–94.
185. Soyuncu S, Yigit O, Eken C. Frostbite injury related to chlorethane application. Wilderness Environ Med 2009;20(1):103–4.
186. Su CW, Lohman R, Gottlieb LJ. Frostbite of the upper extremity. Hand Clin 2000;16(2):235–47.
187. Syme D, Commission IM. Position paper: On-site treatment of frostbite for mountaineers. High Alt Med Biol 2002;3(3):297–8.
188. Taylor MS. Lumbar epidural sympathectomy for frostbite injuries of the feet. Mil Med 1999;164(8):566–7.
189. Trepman E, Donnelly P. Patellar tendon-bearing, patten-bottom caliper suspension orthosis in active Charcot arthropathy: Crutch-free ambulation with no weight bearing in the foot. Foot Ankle Int 2002;23(4):335–9.
190. Treves N, Pack GT. Development of cancer in burn scars: Analysis and report of 34 cases. Surg Gynecol Obstet 1930;51:749.
191. Twomey JA, Peltier GL, Zera RT. An open-label study to evaluate the safety and efficacy of tissue plasminogen activator in treatment of severe frostbite. J Trauma 2005;59(6):1350–4, discussion 4–5.

192. Urschel JD, Urschel JW, Mackenzie WC. The role of alcohol in frostbite injury. Scand J Soc Med 1990;18(4):273.
193. Uygur F, Sever C, Noyan N. Frostbite burns caused by liquid oxygen. J Burn Care Res 2009;30(2):358–61.
194. Uysal A, Koçer U, Sungur N, et al. Marjolin's ulcer on frostbite. Burns 2005;31(6):792–4.
195. Valnicek SM, Chasmar LR, Clapson JB. Frostbite in the prairies: A 12-year review. Plast Reconstr Surg 1993;92(4):633–41.
196. Van Dellen D, Tiivas CA, Jarvi K, et al. Transcranial Doppler ultrasonography-directed intravenous glycoprotein IIb/IIIa receptor antagonist therapy to control transient cerebral microemboli before and after carotid endarterectomy. Br J Surg 2008;95(6):709–13.
197. VanGelder CM, Sheridan RL. Freezing soft tissue injury from propane gas. J Trauma 1999;46(2):355–6.
198. Vaughn PB. Local cold injury—Menace to military operations: A review. Mil Med 1980;145(5):305–11.
199. Von Heimburg D, Noah EM, Sieckmann UP, Pallua N. Hyperbaric oxygen treatment in deep frostbite of both hands in a boy. Burns 2001;27(4):404–8.
200. Wanderer AA, Ellis EF. Treatment of cold urticaria with cyproheptadine. J Allergy Clin Immunol 1971;48(6):366–71.
201. Ward MP, Garnham JR, Simpson BR, et al. Frostbite: General observations and report of cases treated by hyperbaric oxygen. Proc R Soc Med 1968;61(8):787–9.
202. Warriner RAI, Hopf HW. Enhancement of healing in selected problem wounds. In: Feldmeier JJ, editor. Hyperbaric oxygen 2003: Indications and results. The Hyperbaric Oxygen Committee Report. Kensington, Md: Undersea and Hyperbaric Medical Society; 2003.
203. Washburn B. Frostbite: what it is–how to prevent it–emergency treatment. N Engl J Med 1962;266:974–89.
204. Weatherley-White RC, Sjostrom B, Paton BC. Experimental studies in cold injury. II. The pathogenesis of frostbite. J Surg Res 1964;4:17–22.
205. Wenzl JE, Burke EC, Bianco AJ. Epiphyseal destruction from frostbite of the hands. Am J Dis Child 1967;114(6):668–70.
206. West JB, Schoene RB, Milledge JS, Ward MP. High altitude medicine and physiology. 4th ed. London: Hodder Arnold; 2007.
207. Whayne TF, DeBakey ME. Cold injury, ground type. Washington, DC: Office of the Surgeon General, Dept of the Army; 1958.
208. Wilson O, Goldman RF. Role of air temperature and wind in the time necessary for a finger to freeze. J Appl Physiol 1970;29(5):658–64.
209. Yeager RA, Campion TW, Kerr JC, et al. Treatment of frostbite with intra-arterial prostaglandin $E_1$. Am Surg 1983;49(12):665–7.
210. Zacarian SA. Cryogenics: The cryolesion and the pathogenesis of cryonecrosis. In: Cryosurgery for skin cancer and cutaneous disorders. St Louis: Mosby; 1985. p. 1–30.
211. Zacarian SA. Cryosurgery for skin cancer and cutaneous disorders. St Louis: Mosby; 1985.
212. Zacarian SA, Stone D, Clater M. Effects of cryogenic temperatures on microcirculation in the golden hamster cheek pouch. Cryobiology 1970;7(1):27–39.

that neither cold nor wet is a prerequisite required to develop the injury. It appears more likely that NFCI is a reperfusion injury that develops after a sustained period of peripheral vasoconstriction.[123]

Epidemiologic studies relating to NFCI can be challenging because the *International Classification of Diseases* (ICD-10) does not offer a "code" for NFCI. However "Immersion hand and foot" (T69.0), "Chilblains" (T69.1), "Other specified effects of reduced temperature" (T69.8), and "Effect of reduced temperature unspecified" (T69.9) are available.[142] Frostbite has a separate and detailed ICD classification.

## MILITARY

In combat settings, there is rarely the time, equipment, or opportunity to apply appropriate remedies to NFCI. In the 1854 Crimean War, cold injury was documented more often among "the men in the trenches [who] were so restricted in their movements. . . . Frequently this position happened to be the bottom of a trench knee-deep in mud and water or half-filled with snow."[114] In November 1944, during World War II, American forces sustained 11,000 cases of trench foot.[136]

Nonfreezing cold injury has continued to affect armed forces. A study of 3 Commando Brigade (UK) during the Falkland Islands conflict in 1982 reported that 64% of the brigade appeared to have NFCI, with the proportion being higher (76%) within infantry units.[51] An evaluation of possible risk factors for NFCI during the conflict found that 1 year after exposure, there were no cases of cryoglobulinemia and no hematologic evidence to suggest that any of those who had developed cold injury had abnormal circulating proteins, plasma hyperviscosity, or indicators of alcohol abuse.[26] NFCI has been reported during operations in Afghanistan.[89]

Cold injury is not unique to operational deployments. In the 1990s, both the U.S. Army and the Israeli Defense Forces recorded that most NFCIs occurred during routine training exercises rather than during combat operations.[33,86,93]

## ETHNICITY

Historically, the first reports of increased susceptibility in certain ethnic groups (i.e., African Americans) to cold-weather injury (CWI) came from the American Civil War.[109] Also, an increased incidence of CWI was noted among African Americans in the extremely cold winter conflict in the Ardennes in 1944 during World War II.[136]

A major retrospective study of 2143 U.S. Army hospital admissions for CWI between 1980 and 1999 found the injury rate for men and women was similar, 13.9 and 13.3 per 100,000 soldiers, respectively.[33] Increased rank and experience were associated with a decrease in CWI. There were 3.3 times more African Americans than Caucasians hospitalized (95% confidence interval [CI], 3.1-3.7), and infantry and gun crews appeared to be at greater risk. Also, the number of soldiers admitted to the hospital between 1980 and 1999 was greatly reduced, from greater than 30 cases per 100,000 soldier-years to almost zero.

Young male African Caribbean natives in the British Army have a 30 times greater chance of developing peripheral cold injury and are more severely affected than their Caucasian counterparts following similar climatic exposure, using similar clothing and equipment. Pacific Islanders are at a 2.6 times increased risk, while being a Gurkha appeared protective.[18] Peripheral vascular responses to a local cold stress were studied in four groups of Indians: South Indians, North Indians, Gurkhas, and high-altitude natives (HANs) of 3500 m (11,483 feet). The heat output and cold-induced vasodilation were highest in HANs, with the lowest observed in South Indians.[83]

## PREVALENCE

In most North Atlantic Treaty Organization (NATO) countries, the prevalence of NFCI appears to be static or decreasing among military personnel. In the British military, however, there appears to be a marked increase in the incidence of reported CWI. Over a 4-year period, the reporting rate increased from 9 to 30 per 1000 recruits, with the majority of cases (90%) reported during field-based training. Independent factor analysis demonstrated that African Caribbean recruits were 13.2 times (95% CI, 9.5-18.4; $p < 0.01$) more likely to report cold injury and 27.3 times (95% CI, 16.3-45.9; $p < 0.01$) more likely to be medically discharged than were Caucasians.[139]

This increase in NFCI in the United Kingdom (UK) military might be caused by greater exposure, lower threshold to diagnose the condition, increased awareness, or recruiting a different and more sensitive population. Alternatively, the observed increase may be incorrect and caused by a type I error (poor specificity of the tests used to diagnose NFCI or excessive credulity) or type II error (poor sensitivity of the tests used to diagnose NFCI). Also, other countries may be failing to diagnose and report the condition.[64]

## CIVILIAN

The environmental conditions that can produce NFCI in military settings are also found in the context of wilderness medicine. Outdoor recreation may lead to cold, dehydrated, exhausted, and wet hikers exposed to the elements for an extended period. These individuals may be unwilling or unable to take the time and effort to care for their wet boots and socks, and they may be unaware of the risks inherent to the situation. Other civilian populations at risk for NFCI include homeless people,[143] older adults,[103] and alcoholic persons.[123]

### Personal Factors

Proper protective equipment and appropriate use are important factors reducing the incidence of NFCI. Factors affecting the incidence of frostbite are closely related to those affecting NFCI. A surprisingly high incidence of frostbite has been reported in mountaineers. In one study the mean incidence was 366 per 1000 population per year. Mild (grade 1) injury (83.0%) and involvement of the hands (26.4%) and feet (24.1%) were most common. There was a significant correlation between lack of proper equipment (odds ratio, 14.3) or guide ($p < 0.001$) and the injury. Inappropriate clothing, lack or incorrect use of equipment, and lack of knowledge of how to deal with cold and severe weather were cited as the main reasons for the injury.[58]

Cold injury is uncommon in Antarctica. Despite this, NFCI warrants a continued high profile because under most circumstances, it may be regarded as an entirely preventable occurrence.[19] Prolonged heavy-load carriage during a 109-day Arctic expedition may have impaired blood flow or nerve conduction in the hands and inhibited cold acclimatization. The contrary was observed in the feet, where there was improvement in cold acclimatization despite developing moderate trench foot.[97]

### Civilian Case Reports

Laden and colleagues[78] reported that cold injury occurred to a diver's hand after a 90-minute dive in 6°C (42.8°F) water. With the advent of "technical diving," characterized by going deeper (often in cold water) for longer periods, and "adventure tourism," it was suggested that this extremely painful condition would likely increase in prevalence.

Elderly patients typically present to the hospital after collapse and a period of immobilization on the floor. A case of bilateral trench foot in an immobile elderly patient has been reported.[138]

# PHYSIOLOGY

## SKIN: A THERMOREGULATORY ORGAN

Thermoregulation as a major function of human skin is achieved by large fluxes in cutaneous blood flow.[80] The metabolic requirements of skin are fixed and relatively modest. Large fluctuations in cutaneous blood flow are primarily determined by the individual's thermoregulatory needs. Arteriovenous anastomoses (AVAs) abound in the extremities. AVAs are coiled, muscular-walled vessels approximately 35 μm in diameter and have minimal basal tone. They are under dual control: central

hypothalamic via the sympathetic nervous system and direct local control, dilating under warm conditions and constricting in reaction to a cold stimulus. The two effects are additive. Cutaneous vessels are controlled by sympathetic adrenergic vasoconstrictor fibers, and vascular smooth muscles have both α- and β-adrenergic receptors. When core temperature exceeds 37.5°C (99.5°F), the hypothalamus reduces vasoconstrictor drive to AVAs and vasodilation occurs. As a result, a low-resistance shunt in the dermal venous plexus opens, which in turn increases local heat loss. Under cold conditions, sympathetic tone increases, resulting in local arteriovenous vasoconstriction and reduced cutaneous blood flow.

Under basal conditions, a 70-kg (154-lb) person has total cutaneous blood flow of 200 to 500 mL/min. With external heating to maintain skin temperature at 41°C (105.8°F), this may increase to 7000 to 8000 mL/min, while cooling the skin to 14°C (57.2°F) may diminish it to 20 to 50 mL/min.

Cutaneous vascular tone is inversely related to ambient temperature. Cold-induced vasoconstriction is attenuated by $\alpha_2$-adrenergic blockers and by sympathetic inhibition. Reduction in ambient temperature results in insertion of more $\alpha_2$-adrenergic receptors from the myocyte Golgi apparatus into the plasma membrane, raising the affinity for the sympathetic neurotransmitter norepinephrine. At the same time, endothelial nitric oxide synthase (eNOS) activity declines, resulting in vasoconstriction of the AVAs. Core temperature has a strong influence over cutaneous sympathetic vasomotor activity.

The vascular endothelium regulates local vascular tone by secreting vasoactive agents, including the vasoconstrictor endothelin and the vasodilators nitric acid and prostacyclin. Endothelin causes long-lasting vasoconstriction and is elevated in hypoxia, preeclampsia, and hemorrhagic stroke.

## ORTHOSTASIS

Orthostasis (standing upright) or lowering a limb below heart level causes immediate reduction in local blood flow; cutaneous perfusion is reduced by approximately two-thirds as a result of the poorly understood venoarteriolar response. It is thought that this response helps maintain central arterial pressure during standing and also reduces dependent edema formation. Long periods of sitting or standing tend to exacerbate this response.

## COLD-INDUCED VASODILATION

When the hand or foot is cooled to 15°C (59°F), maximal vasoconstriction and minimal blood flow occur. If cooling continues to 10°C (50°F), vasoconstriction is interrupted by periods of vasodilation and an associated increase in blood and heat flow. This cold-induced vasodilation (CIVD), or "hunting response," occurs in 5- to 10-minute cycles to provide some protection from the cold. Prolonged repeated exposure to cold increases CIVD and offers some degree of acclimatization. Eskimos, Lapps, and Nordic fishermen have a strong CIVD response and short intervals between dilations, which may contribute to maintenance of hand function in the cold environment.[55] CIVD responses are more pronounced when the body core and skin temperatures are warm (hyperthermic state) and suppressed when they are cold (hypothermic state), when compared to normothermia.[28,29,98] Cheung and colleagues[21] investigated if CIVD responses of one finger can predict the responses of other fingers, as well as whether the CIVD of fingers could predict CIVD responses of the feet and toes. They found that CIVD is highly variable across the fingers and is not a generalizable response across either digits or limbs. Paradoxical CIVD will normally prevent tissue damage, but in conditions such as Raynaud's phenomenon, the vessels of the toes and fingers exhibit an exaggerated and sustained vasoconstriction response, resulting in blanching numbness and paresthesias, and in severe cases can result in tissue loss.

Individuals with a weak CIVD response to experimental cold-water immersion of the fingers in a laboratory setting have a higher risk for local cold injuries when exposed to cold in real life.[30] A strong correlation exists between the mean temperature of the fingers during cold-water immersion and toes during cold-air exposure ($r = 0.83$; $p < 0.01$), showing that a weak CIVD response in the hand is related to a weak response in the foot.[131] Felicijan and associates[40] found evidence for significant enhancement of the CIVD response after brief high-altitude acclimatization; these changes were especially prominent in the feet of Alpinists compared with controls.

Temperatures of the extremities can drop surprisingly quickly in the field. Toe temperature of 10 individuals was monitored in the field in Arctic Norway (minimum air temperature, −27°C [−16.6°F]. The lowest skin temperature recorded was 1.9°C (35.4°F). The mean estimated time for toe temperature to cool from 25°C (77°F) to 5°C (41°F) was 109 minutes (standard deviation [SD], 10.2) at an ambient temperature of −21°C (−5.8°F). One person experienced a toe temperature below 5°C (41°F) for 2.9 hours during a 27-hour period. Surprisingly, none of the participants demonstrated clinical signs of cold injury, but this does not mean that this exposure was without risk.[127]

The cutaneous microcirculation of skin was assessed in patients with sequelae from local cold injuries. All patients reported cold intolerance 3 to 4 years after the primary CWI, sustained during military service.[7] Transcutaneous oxygen tension was decreased, but oxygen reappearance time, oxygen recovery index, postocclusive reactive hyperemia, and venoarterial reflex were normal. No capillary nailfold abnormalities were found. Local cold injuries appear to cause disturbances in the CIVD and impair cold tolerance and may increase the risk for future cold injuries. Evidence suggests disturbances of reflex mechanisms mediated by the central nervous system. Neurophysiologic factors seemed more important than ischemic mechanisms in the pathophysiology of late sequelae with peripheral CWI.

# PATHOPHYSIOLOGY

Continuous exposure to a cold, wet environment causes breakdown of skin, directly cools nerves in the area of exposure, and causes prolonged vasoconstriction. NFCI is primarily caused by prolonged vasoconstriction, which in turn causes direct injury to the vessels (and endothelium) that supply nerve, fat, and muscle cells.[62,92,123] Pain, fear, constrictive footwear, and immobility interact in maintaining vasoconstriction through a heightened sympathetic nervous system response or by mechanically limiting blood flow (Figure 10-1). The length or degree of exposure needed to evoke these changes and thus NFCI is unclear. Nevertheless, the level of risk appears to be inversely proportional to tissue temperature and directly proportional to duration of insult.[13,124] Lengthy exposure to a temperature of about 10°C (50°F) will result in similar injury as a short exposure to a temperature of 1°C (33.8°F). Repeated exposure is likely to cause a more significant injury than a single exposure of longer duration.[72]

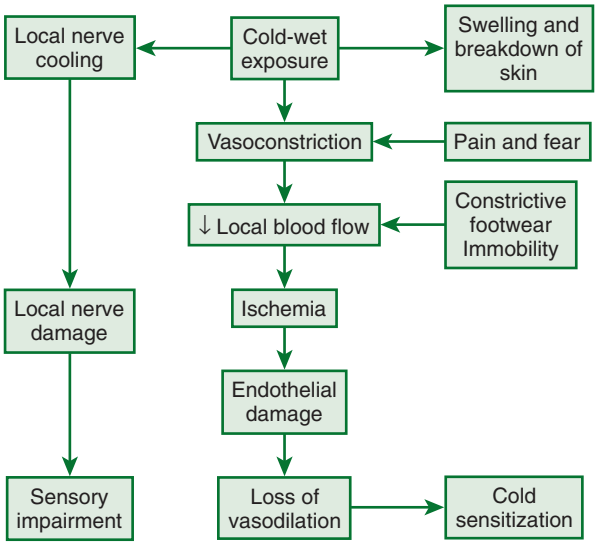



**FIGURE 10-1** Schematic of factors and mechanisms that contribute to nonfreezing cold injuries.

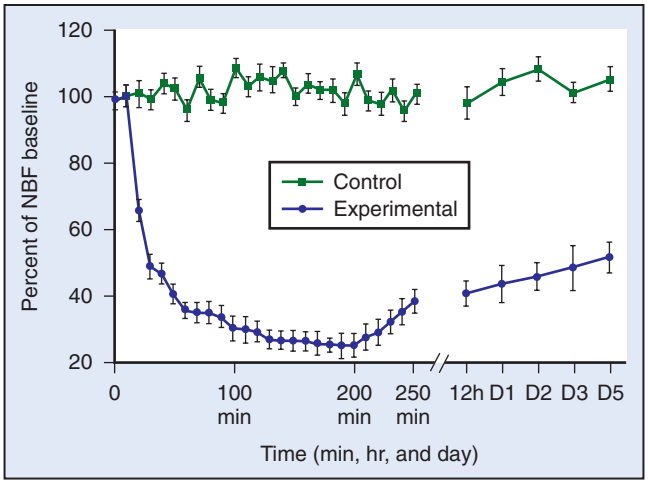



**FIGURE 10-2** Laser Doppler mean nerve blood flow *(NBF)* in control and experimental animals at 10-minute intervals during nerve cooling and rewarming (up to 250 minutes) and at follow-up examination immediately before sacrifice (at various times up to 5 days). Note that the NBF falls steeply over 20 minutes and reaches its nadir (25% of baseline) 180 minutes after the onset of cooling. NBF remains significantly reduced up to 5 days after cold injury. *(Modified from Jia J, Pollock M: The pathogenesis of non-freezing cold nerve injury: Observations in the rat,* Brain *120:631, 1997.)*

## NERVE INJURY

Nerve cooling has been suggested as contributing to the etiology of NFCI. Large myelinated fibers (C fibers) are most susceptible to prolonged cold exposure.[67,75,76,110] In severe NFCI, characteristic peripheral nerve damage and tissue necrosis occur.[68] Clinical sensory tests indicate damage to both large- and small-diameter nerves. The prolonged cold injury affects blood vessels serving these large myelinated fibers, with subsequent ischemia causing a decrease of oxygen to the nerve, resulting in the appearance of a primary nervous system injury[71,72] (Figures 10-2 to 10-5). In NFCI, nerve injury is ultimately likely to be multifactorial, consisting of both direct nerve fiber damage and a vascular component.[73]

## VASCULAR INJURY

Vasoconstriction is mediated by presynaptic vesicle release of norepinephrine and neuropeptide Y from sympathetic nerve fibers that interact postsynaptically on smooth muscle at $\alpha_{2c}$–adrenergic receptors[9,23] and Y1 receptors.[118] Recent work demonstrated that cold-induced vasoconstriction is mediated by rho kinase.[126] The prolonged decrease in blood flow caused by vasoconstriction causes direct injury to capillary endothelium. Studies indicate that the endothelial lining separates from underlying cells, leaving "gaps."[38] Leukocytes and platelets fill in these gaps and accumulate, further decreasing capillary blood flow and leading to ischemia and eventually tissue hypoxia (Figure 10-6).

Microvascular thrombosis after reperfusion injury is believed to play a pivotal role following cold injury, with cold-damaged endothelial cells central to the process.[91] Reperfusion results in formation of free radical species, leading to further endothelial damage and edema.[71]

Apparently, CIVD is a physiologic protective response attempting to prevent vascular injury and tissue ischemia. Unfortunately, this response is lost or impaired in certain situations, including (but not limited to) hypoxia,[102] dehydration,[28] sleep deprivation,[50] and hypothermia.[28] There also appears to be a genetic component, with African Caribbean persons possessing a blunted CIVD response.[63] In sickle cell patients, there is net vasoconstriction, instead of the normal vasoconstriction response being overcome by activation of the alerting response–induced vasodilation.[90]

## ANIMAL MODELS

Animal models have been developed to understand the underlying pathophysiology of NFCI. Thomas and colleagues[124] developed a rat model of NFCI by immersing the tail in 1°C (33.8°F) water for 6 to 9 hours and characterized the loss of CIVD as a prolonged decrease in tail blood flow followed by increased blood flow above baseline. This pattern is similar to that clinically observed in humans during the prehyperemic phase followed by the hyperemic phase.

Stephens and associates[118] recently used the rat tail model in an attempt to elucidate possible mechanisms that cause vascular endothelial damage. Their preliminary data suggest that acute cold-water exposure causes loss of nitric oxide–dependent endothelial function and possibly a change in smooth muscle contractility. Irwin,[67] using a rabbit hind limb model, demonstrated that

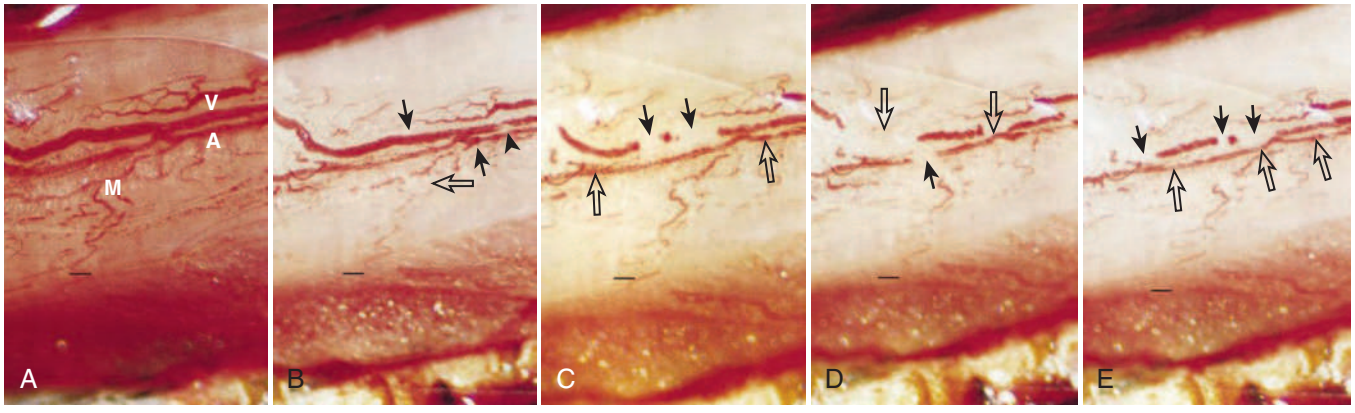



**FIGURE 10-3** Sciatic nerve epineurial microvessels before, during, and following nerve cooling (1° to 5°C [33.8° to 41°F]). **A,** Normothermia. Arteriole *(A),* venule *(V),* and metarterioles *(M)* have a normal appearance. **B,** One hour after the commencement of nerve cooling, the diameters of both the arteriole and venule are reduced by approximately 40%. Under a dissecting microscope, erythrocytes present a granular appearance in both vessels *(arrows).* Note occlusive aggregations *(open arrow)* in metarteriole and the suggestion of leukocyte clumping in the venule *(arrowhead).* **C,** Two hours after nerve cooling, segmental occlusive aggregates are seen in the venule *(arrows).* The arterioles contain prominent rouleaux *(open arrows).* **D,** Three hours after nerve cooling, there is stasis of flow in both vessels. An occlusive aggregate *(arrow)* is now seen in the arteriole, and those in the venule have extended *(open arrows).* **E,** After 1 hour of nerve rewarming (37.5°C [99.5°F]), the venule still exhibits multiple segmental occlusions *(arrows).* Erythrocyte granulations *(open arrows)* in the arteriole indicate poor reperfusion. *Bars* represent 100 mm. *(From Jia J, Pollock M: The pathogenesis of non-freezing cold nerve injury: Observations in the rat,* Brain *120:631, 1997.)*

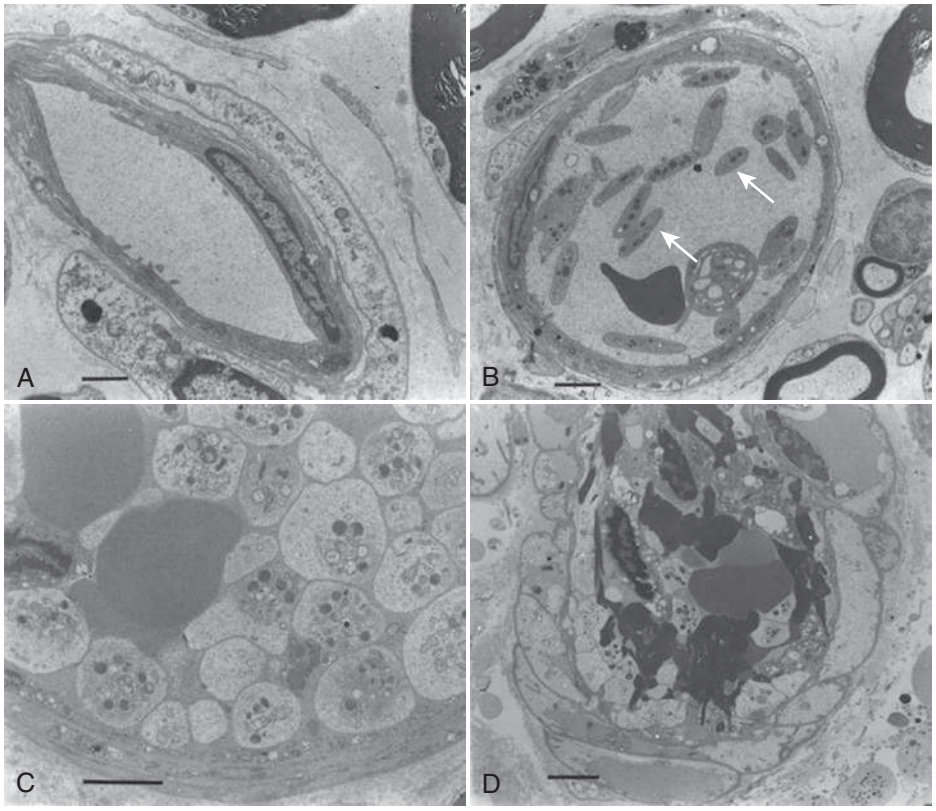



**FIGURE 10-4** Electron micrographs of endoneurial vessels in cooled sciatic nerve. **A,** An empty capillary with a degenerating pericyte 1 hour after nerve rewarming. *Bar* represents 2 µm. **B,** Aggregating platelets *(arrows)* 24 hours after cooling. *Bar* represents 2 µm. **C,** Platelets, adherent to the endothelium of a venule, show varying degrees of degranulation without pseudopod formation, 48 hours after nerve cooling. Two red blood cells are trapped within this platelet thrombus. *Bar* represents 1 µm. **D,** A thrombus formed of platelets, red blood cells, and fibrin 5 days after nerve cooling. The blood vessel wall is necrotic. *Bar* represents 2 µm. *(From Jia J, Pollock M: The pathogenesis of non-freezing cold nerve injury: Observations in the rat,* Brain *120:631, 1997.)*

cold-water immersion damaged large myelinated fibers while sparing small myelinated and unmyelinated fibers.

Nonfreezing cold injuries affect many different types of tissue. Pathologic examination of specimens displays a variety of lesions to the skin, muscle, nerve, and bone.[11,12,46] Muscles exhibit separation of the cells and damage of the muscle fibers, described as *acidophilic* and *hyalinized* (Zenker's hyaline degeneration). The myoplasm within muscle loses its cross-striation, and the healing muscle then appears to undergo fibrous tissue replacement.

One of the major pathologic processes in NFCI is progressive microvascular thrombosis following reperfusion of the ischemic limb, with cold-damaged endothelial cells playing a central role

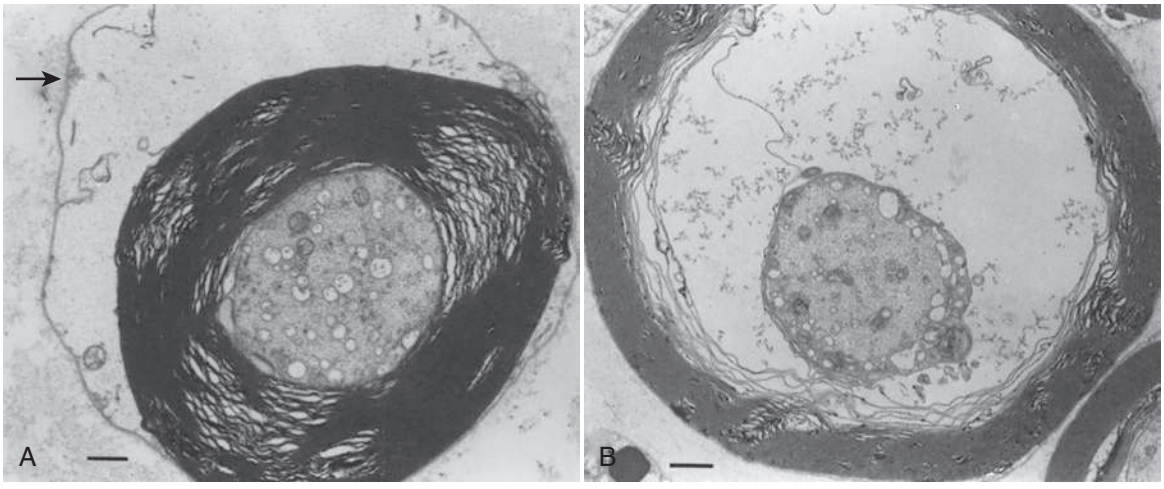



**FIGURE 10-5** Electron micrographs of cooled sciatic nerve fibers. **A,** A rat sciatic nerve fiber, 12 hours after nerve cooling, illustrating myelin unraveling and intramyelinic edema *(arrow)* . **B,** A rat sciatic nerve fiber 2 days after cooling, exhibiting a shrunken axon and marked periaxonal edema. Bars represent 1 µm. *(From Jia J, Pollock M: The pathogenesis of non-freezing cold nerve injury: Observations in the rat,* Brain *120:631, 1997.)*

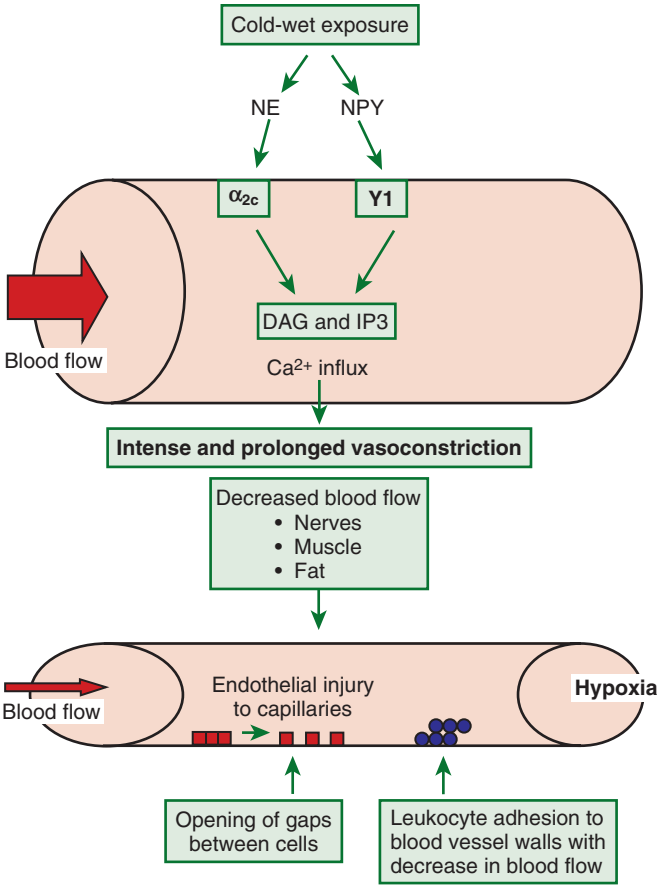



**FIGURE 10-6** Proposed hypothesis for the etiology of nonfreezing cold-induced injury (NFCI). $\alpha_{2c}$, Norepinephrine (NE) α-adrenergic receptor; *Y1,* neuropeptide Y (NPY) receptor; *DAG,* diacylglycerol; *IP3,* inositol triphosphate; *$Ca^{2+}$,* calcium.

in the outcome.[91] Reperfusion of previously ischemic tissues causes free radical formation, leading to further endothelial damage and subsequent edema. With restoration of blood flow, there is reintroduction of oxygen species within cells that further damages cellular proteins, DNA, and the plasma membrane. Free radical species may act indirectly in oxidation-reduction (redox) signaling to turn on apoptosis. Leukocytes may build up in small capillaries, obstructing them and leading to more ischemia.[72]

In an in vivo rabbit hind limb model subjected to 16 hours of cold-water immersion (1° to 2°C [33.8° to 35.6°F]), there was reduction in the number of myelinated nerve fibers of all sizes, most marked in large-diameter fibers, a feature consistent with ischemic neuropathy and reperfusion injury.[68] Unmyelinated fibers showed only minor damage. The resulting evidence suggests that both these mechanisms may contribute to the nerve injury. There is further extensive supporting evidence to establish that NFCI is associated with histologic and clinical evidence of nerve damage.[34,37,72,96]

Das and co-workers[31] demonstrated that quinacrine, an antioxidant, decreased damage to cell membrane phospholipids on their rewarming and reperfusion, although more recent studies have shown no benefit from antioxidant use.[121] Most importantly, both these studies used models that assumed that cold-induced nerve injury, rather than capillary or endothelial damage, is the primary etiologic cause of NFCI.

## RISK FACTORS

The risk factors associated with NFCI include the following (this is not meant to be an exhaustive list)[18,51,85,104,107,122,144]:

- Inadequate clothing
- Immobility
- Smoking
- Dehydration
- Altitude (hypoxia)
- Poor calorie intake
- Sleep deprivation and fatigue
- Hypothermia
- Damp environments/wet clothing
- Increasing age
- African Caribbean ethnicity
- Previous NFCI

## CLINICAL PRESENTATION

Nonfreezing cold-induced injury should be considered a syndrome, and presentation is variable. NFCI is insidious in onset, often with few objective clinical signs at presentation, and one must take into account the history and environment. After initial exposure, there are three stages of progression: prehyperemic, hyperemic, and posthyperemic. These phases often overlap, and the time course of each varies.

### PREHYPEREMIC PHASE

During the prehyperemic phase, the affected limb both during and immediately after cold exposure appears blanched, yellowish white, or mottled but seldom blistered[130] (Figure 10-7). Whayne and DeBakey[136] state that the degree of edema during this prehyperemic stage is less severe if the feet are intermittently rewarmed during the course of exposure. Whereas muscle cramps are common, pain is rare.[54,115] The most important diagnostic criterion is loss of a sensory modality, most often complete local anesthesia, which is distinct from premonitory feelings of extreme cold in the affected periphery. This almost invariably occurs in the foot, although hands can also be affected. With further exposure, the cold sensation leads to complete anesthesia with loss of proprioception, resulting in numbness and gait disturbances. This sensation has been described as "walking on air" or "walking on cotton-wool."[130] Capillary refill is sluggish, and pedal arterial pulses are usually absent, except using Doppler examination.[88] Intense vasoconstriction is the predominant feature of this stage.[57]

### HYPEREMIC PHASE

Within several hours after rewarming, the extremities become hot, erythematous, painful, and swollen (Figures 10-8 to 10-11), with full bounding pulses.[135] Impairment of the microcirculation is evidenced by delayed capillary refill[123] (Figure 10-12) and petechial hemorrhages.[56] Sensation returns first to proximal regions and then extends distally, rapidly progressing to severe, burning, or throbbing pain, and reaching maximal intensity in 24 to 36 hours.[128,130] Affected areas have marked hyperalgesia to light touch. This pain is aggravated by heat and dependent positioning and often worsens at night, when even the pressure of sheets

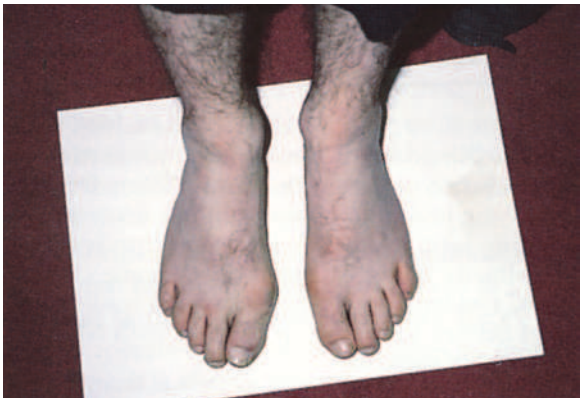


**FIGURE 10-7** Prehyperemic phase of immersion foot. These feet are still mostly numb and very cold to the touch. *(British Crown Copyright/MOD.)*

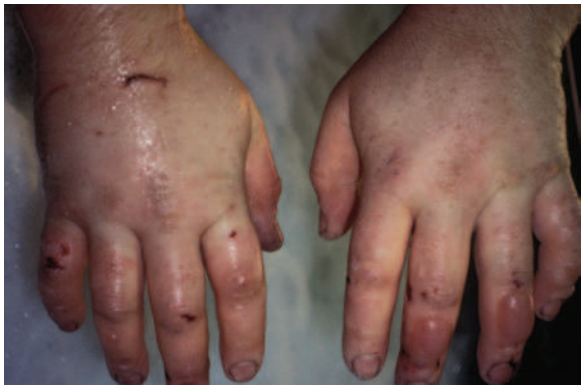


**FIGURE 10-8** Hyperemic phase of nonfreezing cold injury. This person spent 18 hours in winter bailing out a boat that threatened to capsize in Prince William Sound, Alaska. *(Courtesy James O'Malley, MD.)*

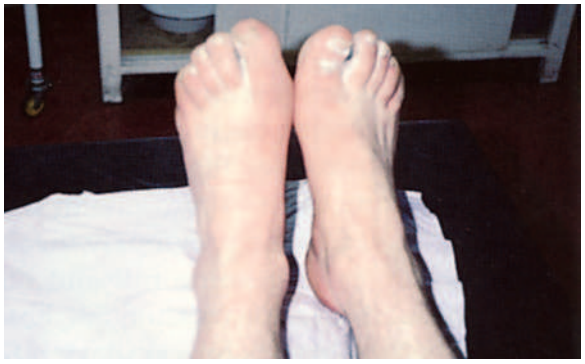


**FIGURE 10-9** Hyperemic phase of immersion foot in mild nonfreezing cold injury. Recruit of the British Royal Marines just returned from a field exercise feeling well. While showering, his feet rapidly became swollen, red, and painful. *(British Crown Copyright/MOD.)*

may be unbearable.[57] After 7 to 10 days, the nature of the pain changes to "shooting or stabbing."[128] The sensory deficits usually diminish, but paresthesias continue, and anesthesia may be extensive on the toes and plantar surfaces.[137] Vibratory sensation is reduced or lost, whereas proprioception is usually retained. Anhidrosis coincides with the extent of sensory loss.[123]

Vascular injury is evident in vessel reactivity. Skin temperature gradients are absent, with digits often as warm as or warmer than the groin or axillae. When the affected limbs are lowered, blood pools, turning the extremity a deep purple-red

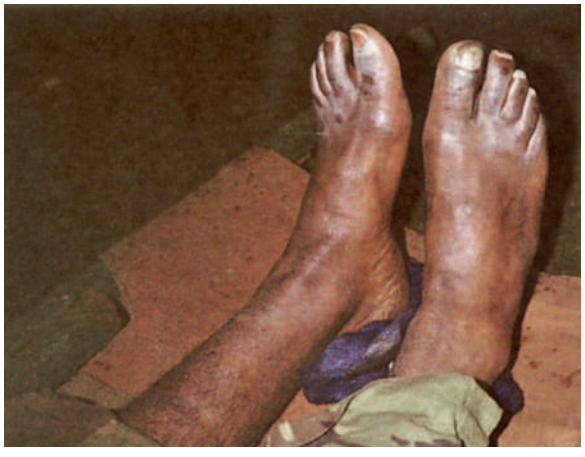


**FIGURE 10-10** Hyperemic phase of immersion foot. The characteristic redness of the stage is absent due to the pigmented skin, but the feet are swollen and painful. *(British Crown Copyright/MOD.)*

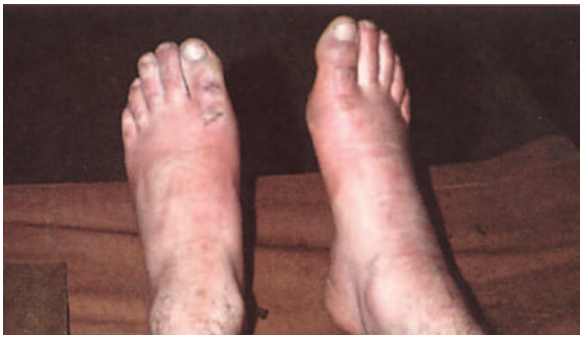


**FIGURE 10-11** Hyperemic phase in moderately severe nonfreezing cold injury. Swelling, redness, and persistent pain in the feet of an infantry soldier from the Falklands War. *(British Crown Copyright/MOD.)*

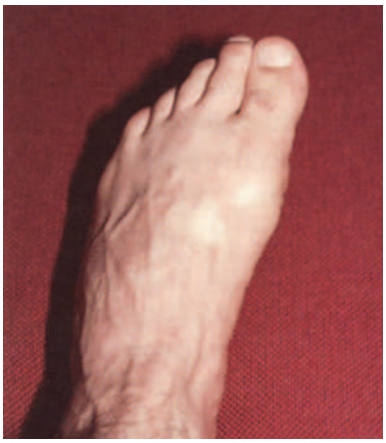


**FIGURE 10-12** Hyperemic phase in mild nonfreezing cold injury. There is delayed capillary refill in the dorsum of the foot. The examiner's two fingers resting on the skin for 10 seconds was sufficient to blanch the capillaries. When the pressure was removed, the blanched patches disappeared very slowly, reflecting impaired microcirculation. *(British Crown Copyright/MOD.)*

color, whereas blanching occurs when the limb is raised. Tense edema becomes marked during this stage. Blisters containing serous or hemorrhagic fluid may form, indicating more severe injury.[123] The superficial epidermis becomes thick, indurated, and desquamated. Eschars form (Figures 10-13 and 10-14) and eventually slough, leaving a pink dermis (Figure 10-15). In more severe cases, the skin may become gangrenous (Figure 10-16); this is rare, and with appropriate care the gangrene is usually minimal.[3,135,136]

Muscles may show weakness with impaired electrical responses, slowing of plantar deep tendon reflexes, and intrinsic muscle atrophy.[128,130] In milder cases, this stage peaks at 24 hours; in more severe cases, the hyperemic phase may take 6 to 10 weeks to resolve.[123]

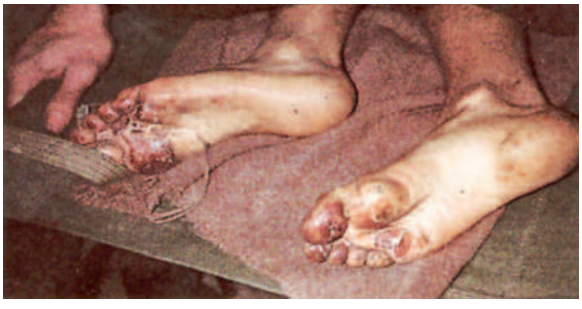


**FIGURE 10-13** Severe nonfreezing cold injury. This Argentinian soldier had been unable to care for his feet for many weeks. *(British Crown Copyright/MOD.)*

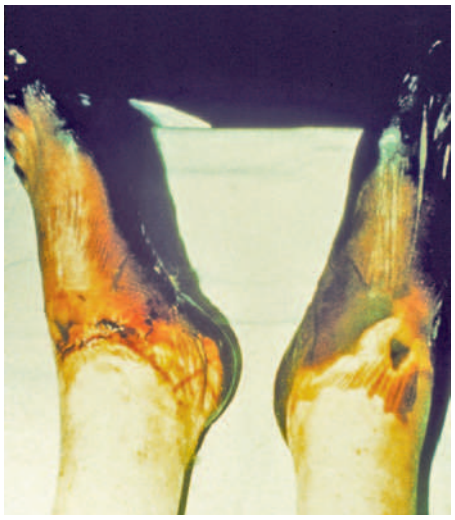


**FIGURE 10-14** Severe nonfreezing cold injury in an Argentinian mine worker who wore his boots for 47 straight days during the Falklands War. *(Courtesy M. P. Hamlet.)*

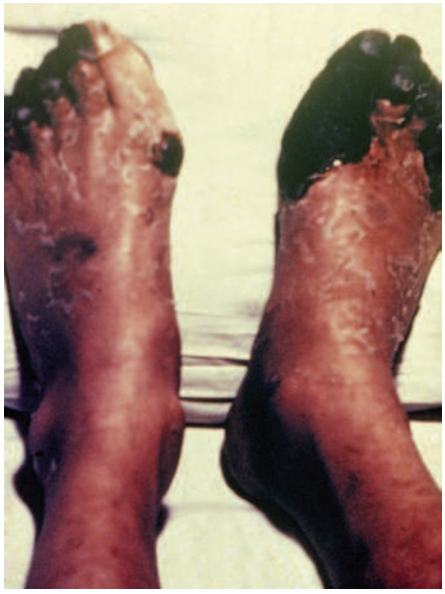


**FIGURE 10-15** Severe nonfreezing cold injury in a British sailor during World War II. *(Courtesy M. P. Hamlet.)*

## POSTHYPEREMIC PHASE

The posthyperemic phase lacks obvious physical signs. In mild cases, this phase may be absent;[130] in other patients, it may last weeks, months, or years after the hyperemic phase has subsided.[88,128] The extremities transition from consistent warmth to coolness, with affected areas having an abnormal cooling response. Extremities become cold sensitive, remaining so for hours after exposure despite normal warming processes.

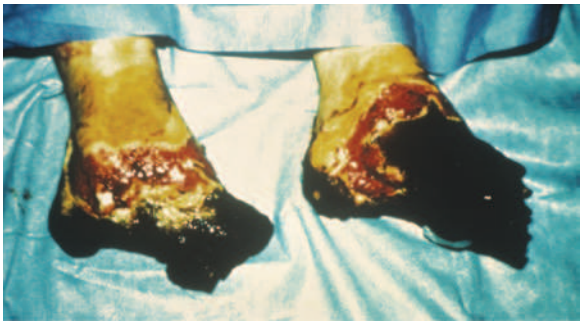


**FIGURE 10-16** The Argentinian mine worker seen in Figure 10-14, several weeks later. *(Courtesy M. P. Hamlet.)*

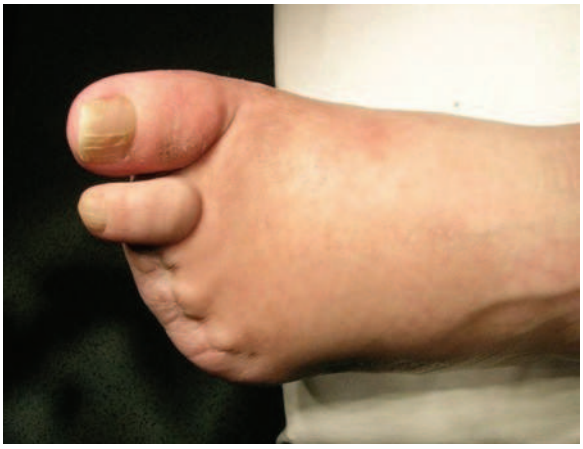


**FIGURE 10-17** Patient 24 months after nonfreezing cold injury. Amputation of third, fourth, and fifth toes on the left foot. *(Courtesy Christopher H.E. Imray, MD.)*

After 6 to 10 weeks, patients often complain of spontaneous hyperhidrosis, and sweat rashes are common in areas with heavy perspiration.[128] On a warm day, socks are quickly soaked; extremities may sweat excessively, even when cold. Hyperhidrosis predisposes to chronic paronychial infections. Sweating may be more pronounced at the margins of anhidrotic and analgesic areas.[130]

During this posthyperemic phase, the paresthesias and extreme pains consistent with the hyperemic phase have usually resolved, replaced by dull aches and anesthesias that may persist for months to years.[136] Recurrent edema of the feet, return of paresthesias, and further blistering are common, especially after long walks. Intrinsic muscle and ligament atrophy tends to resolve,[130] but in severe cases, fibrous scarring may lead to rigidity and permanent contracture of the toes.[137] Decalcification of bones as seen in osteoporosis is frequently observed, but this tends to reverse.[129] Immobility and pain in severe cases may lead to prolonged convalescence of 6 months or more.[137]

In the most severe cases, gangrene can develop, and ablative surgery in the form of amputation of digits or occasionally major lower-limb amputation becomes necessary. The neuropathic tissue is susceptible to local trauma, ulceration, and eventually local osteomyelitis and sinus development[64] (Figures 10-17 to 10-19). Partial foot amputations result in significant alterations in the functional biomechanics of the foot. Since this is often associated with alterations in the sensory nerve supply to the feet, disabling problems can persist[64] (Figure 10-20).

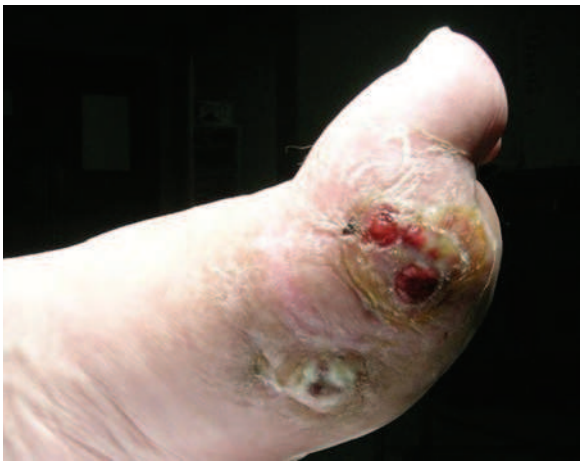


**FIGURE 10-18** Same patient as in Figure 10-17, 24 months after NFCI, with chronic discharging sinuses from osteomyelitis of first metatarsal. *(Courtesy Christopher H.E. Imray, MD.)*

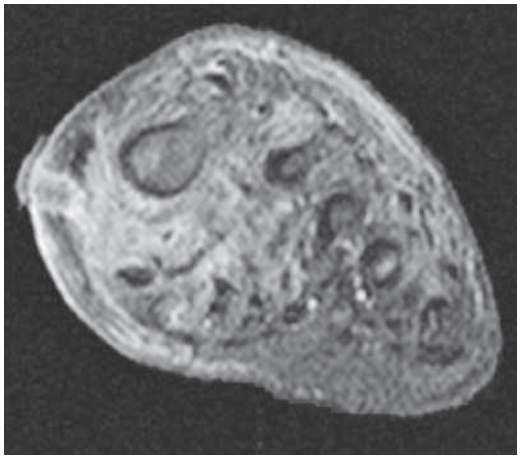


FIGURE 10-19 Magnetic resonance imaging scan of the patient in Figures 10-17 and 10-18, 24 months after nonfreezing cold injury, with chronic discharging sinuses from osteomyelitis of the first metatarsal head. *(Courtesy Christopher H.E. Imray, MD.)*

# TREATMENT

## HYPOTHERMIA

The treatment required for the general effects of cold is different from that needed for localized NFCI. Core temperature must be raised while the extremities are kept cool.[135-137] Injured feet should be elevated and exposed to steady, cool air from a fan. Extremity cooling lowers the metabolic requirements to a point where vascular oxygen supply can sustain tissue demand. Continuous cooling brings rapid improvement in pain, edema, and vesiculation.[135,137] Local cooling should be continued until pain is relieved, circulation has recovered, and hyperemia subsides.[137] The affected extremities should never be rubbed, which may compound the injury.[2]

## REWARMING

Treatment is limited to symptomatic relief and reversing ischemia while minimizing disease progression. Rewarming injured tissues increases metabolic demand of damaged cutaneous cells to a greater extent than the supply capability of the injured subcutaneous blood vessels.[140] Tissue anoxia and endothelial cell injury, coupled with reflex vasodilation, lead to fluid transudation, increasing edema, skin necrosis, and worsening pain.[135,137] Rapid rewarming should be avoided.

## SYMPATHECTOMY

Recovery during the posthyperemic phase may be hastened with physiotherapy and exercise to rehabilitate atrophied intrinsic muscles.[136,137] Lumbar sympathectomy has been theorized to reduce disabling contracture by decreasing vascular tone, increasing circulation, and hastening collagen and fibrous tissue absorption. In severe cases of NFCI exhibiting atrophic rigid feet, small case studies have shown symptomatic improvement after sympathectomy,[137] but other authors believe there is little therapeutic advantage to the procedure.[135]

## TISSUE-FREEZING COMPLICATIONS

Frostbite and NFCI injuries do not necessarily occur in isolation, so when assessing an individual, both diagnoses need to be considered as possibilities. After exposure to severe cold, careful appraisal of the injury is required if optimal treatment is to be given.

## DRUGS

The diagnosis of an NFCI is often difficult or delayed. In view of involvement of the α-adrenergic receptors in control of the peripheral circulation and the apparent noradrenergic sensitization,[45] it was thought that vasodilators or α-adrenergic blocking drugs might be beneficial. To date, however, no evidence supports this approach.

Painful rewarming and persistent pain are features of NFCI, so it is important to attempt to alleviate pain at an early stage. Simple analgesics may be of benefit. In a pilot study, Thomas and Oakley[123] used quinine salts (200 to 300 mg, given at night), which appeared more successful than regular analgesics, although others since then have not supported their use. Since 1982, the standard treatment in the UK armed forces, first proposed by Riddell,[106] has been amitriptyline hydrochloride, in doses of 50 or 100 mg at night. Incremental increases in dosage may be required with both drugs if "breakthrough" pain occurs after initial relief.[43] In centers receiving major trauma or burn patients, it is becoming increasingly standard practice to start a drug for neuropathy treatment early in the patient's care, to help minimize chronic neuropathic pain.[5,84] Although no specific trials have studied this in NFCI, it is advisable to consider starting a neuropathy agent as early as possible.

## OCCUPATIONAL MEDICINE

Depending on the patient's profession, occupational medicine review may be required. This will be the case if patients work in environments that put them at risk of repeated NFCI.

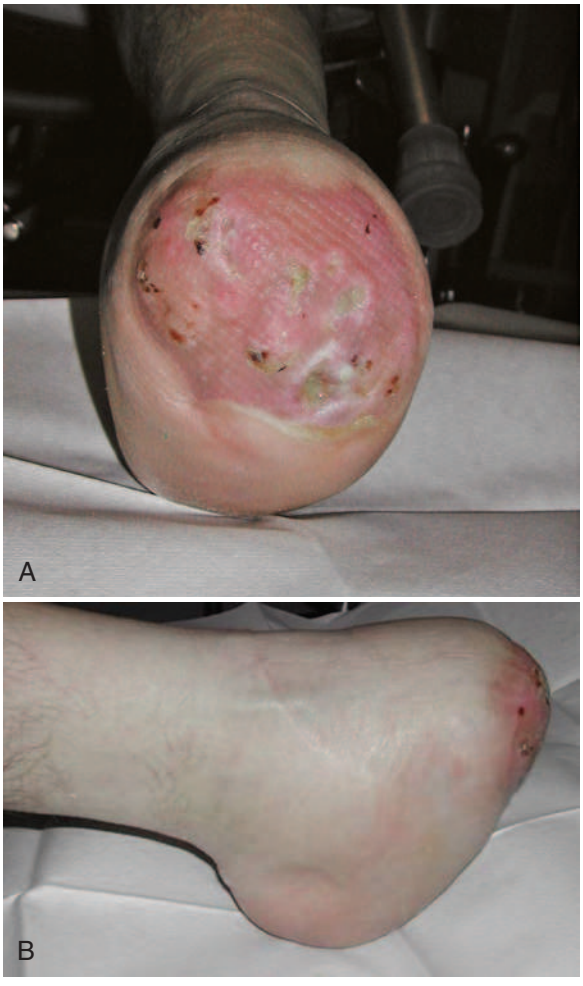



FIGURE 10-20 A guillotine transmetatarsal amputation of left foot was undertaken 6 months after severe nonfreezing cold injury. The patient was treated with delayed primary split-skin grafting. This photo was taken 12 months after the original injury. The graft has taken but is now ulcerated as a result of the shear forces generated by walking on the insensate tissue. *(Courtesy Christopher H.E. Imray, MD.)*

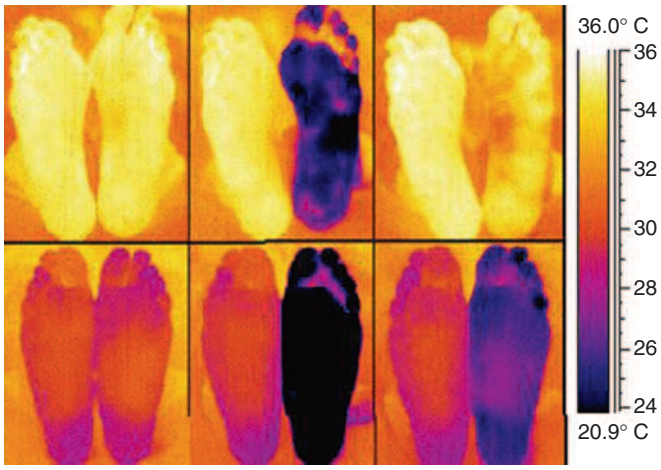



**FIGURE 10-21** Infrared thermography in the assessment of the consequences of nonfreezing cold injury (NFCI). The upper sequence of three images was taken from an uninjured, asymptomatic control; the lower sequence from a patient who had sustained NFCI and was subsequently complaining of sensitivity to the cold. In both control and patient, the first *(left)* image was taken after resting in an ambient air temperature of 30°C (86°F). The second *(center)* image was taken immediately after the foot had been immersed in water at 15°C (59°F) for 2 minutes. The final *(right)* image was taken 5 minutes after removal from the water, again in 30°C (86°F) air. The upper series shows feet that were warm at rest, which rewarmed briskly after mild cold stress, recovering almost completely within 5 minutes after removal from the water. The lower series shows a severe degree of cold sensitization; the feet were much colder than the surrounding air at rest, and once cooled, took a long time to rewarm, remaining much cooler than the control foot at 5 minutes after immersion. The scale at far right indicates the color-temperature relationship. *(British Crown Copyright/MOD. Reproduced with the permission of Her Britannic Majesty's Stationery Office. From Thomas J, Oakley H. Nonfreezing cold injury. In Pandolf KB, Burr RE, editors: Textbook of military medicine: Medical aspects of harsh environments. Vol 1. Washington, DC, 2002, Office of the Surgeon General, Borden Institute, pp 467-490.)*

## ASSESSING INJURY SEVERITY

Following the initial injury, increased sensitivity to cold develops. There are often surprisingly few objective clinical signs. A careful history of appropriate cold-weather exposure, clear history of the typical rewarming symptoms and signs, detailed examination, and special investigations all build a picture consistent with NFCI. Corroborative evidence from medical records is vital.

### SPECIAL INVESTIGATIONS

Infrared (IR) thermography can be used to assess the individual's response to a standardized cold stress and may be helpful in confirming the diagnosis, assessing injury severity, and monitoring recovery (or otherwise) from NFCI (Figure 10-21). However, although used extensively by the UK military, IR thermography is not widely used elsewhere or conclusively validated.[65,130] There appears to be significant variability in the response of some individuals to the current IR thermography test. As a result, interest is focusing on the use of gentle exercise before the cold sensitivity test, as well as laser Doppler flowmetry to improve the assessment used to classify NFCI.[36] Careful experimental design to validate any potential new tests against suitable controls both before and after exposure will be required.

## PREVENTION

The simplest way to prevent NFCI is to avoid prolonged exposure to cold, wet environments. This can be difficult to implement because of varying conditions and individual susceptibility. In military conflicts, completing the assigned mission is most important and may require performing in a cold, wet environment for sustained periods in a cramped, immobile position. During mountain rescues, individuals may be so focused on helping to save others that they do not take adequate care of themselves.

Prevention can be achieved by encouraging people to remain active and increase blood flow to the feet, rotating personnel out of cold-wet environments on a regular basis, keeping feet dry by early changing of wet socks, maintaining body core temperature by limiting sweat accumulation into clothing and dressing in layers, and educating personnel about the early signs and symptoms of NFCI. Changing socks two or three times throughout the day is mandatory in cold, wet environments. Military sources suggest that optimal care entails air drying feet for at least 8 hours of every 24 hours.[17,143] Vapor-barrier boots do not allow sweat from the foot to evaporate, and in some situations, this increases maceration.[4] Boots should be taken off each day, wiped out, and dried. Footwear should not constrict blood flow; sizing is important, as is educating the user not to tie shoelaces too tightly. To achieve an adequate level of self-care, education must impart a sense of individual responsibility, while expedition leaders still monitor and ensure that standards are maintained.

Prophylactic treatment with silicone preparations has proved effective in clinical studies.[48] The protective effect is thought to result from prevention of hyperhydration of the stratum corneum.[17,35] However, stickiness, adherence of sand and grit to the foot, and product bulkiness made it marginally acceptable to infantrymen in combat situations.[48] In small clinical trials, silicone ointment applied only to the sole of the foot instead of to the entire foot (thus reducing surface area exposed to dirt retention, amount of material transported by the soldier, and dollar cost) was sufficient to prevent NFCI.[35]

Because of the apparent increasing incidence of NFCI in the British military, a number of additional preventive steps have been taken, including improved education of personnel about prevention measures, equipment, and early recognition (Figure 10-22).

The severity of the injuries affecting the military appears to be relatively mild compared with civilian NFCI injuries (see Figures 10-17 to 10-19) and military historical controls (see Figures 10-13 to 10-16). This raises the question as to whether there is (1) a continuous spectrum of disease, (2) a bimodal


**FIGURE 10-22** British Army information "credit card."

distribution of the disease with milder and more severe forms of NFCI, or whether (3) the commonly presenting form now seen is the same disease process investigated in the past. Part of the problem may lie in the UK military's decision to use IR thermography as one of the bases on which the diagnosis, severity, and progression of NFCI are determined.

One approach to the high levels of NFCI noted would be to consider screening potential recruits. This requires a test with high sensitivity and specificity. However, individual variation in the control of peripheral blood flow is so great that none of the assessments currently available meets these requirements.[15,28,30,123]

Reducing the incidence of cold injury in military training requires striking a delicate balance between training realism and safety. While training in demanding environments runs real risks of injuring personnel, the benefits to them in the development of field-craft skills are vital if they are to avoid NFCI.[123]

## MORE SEVERE INJURIES

Nonfreezing cold injury can vary in severity from mild to severe. In severe cases, cold sensitization is so serious that individuals are unable to work outside. Edema and hyperhidrosis often occur, making the individual susceptible to fungal infections. Chronic pain resembling causalgia or reflex sympathetic dystrophy may occur. The profound sensory loss may lead to minor or major lower-limb amputation. Ongoing care within a specialist foot clinic using custom-made shoes and insoles appears to improve functional outcome. Multidisciplinary team approaches, such as healing of the ulcerated neuropathic foot using patella tendon–bearing orthoses, have been described.[77] NFCI pain is often so severe as to require tricyclic antidepressants, which should be instituted at an early stage.[66,123] Failure to do so increases the risk of developing severe chronic pain resistant to all subsequent treatment modalities. Early involvement of pain specialists is important.

## TRENCH FOOT (IMMERSION FOOT)

Trench foot and immersion foot are clinically and pathologically indistinguishable but have different etiologies. The term *trench foot* originated during the trench warfare of World War I,[136] when soldiers wore wet boots and socks for prolonged periods.[8] *Immersion foot* was first medically documented during World War II among shipwreck survivors whose feet had been continuously immersed in cold water.[27] Both injuries occur when tissue is exposed to cold and wet conditions at temperatures ranging from 0° to 15°C (32° to 59°F). Colder temperatures decrease the time required to induce NFCI.[13,115] Severe nerve damage from immersion foot has been seen after exposure periods of 14 to 22 hours.[128,130] Immersion foot injury may extend proximally and involve the knees, thighs, and buttocks, depending on the depth of immersion.[137]

## PERNIO (CHILBLAINS)

Pernio (perniones) or chilblains are localized, inflammatory, bluish red lesions caused by an abnormal reaction to a cold, damp environment. This mild form of cold injury is prevalent in the temperate climates of northwestern Europe[81] and is found worldwide throughout temperate and northern zones.[49,87,88,99] Pernio is less common in very cold climates, where well-heated houses and adequate warm clothing are common.[100]

In a recent study of 111 patients, 67 (60.4%) were males and 44 (39.6%) females; 89 (80.2%), 90 (81.1%), and 90 (81.1%) patients had onset in relation with lower temperature (<10°C [50°F]), relatively low atmospheric pressure (<1500 kPa), and higher relative humidity (>60%), respectively. Susceptibility to chilblains appeared to increase when ambient temperature was less than 10°C (50°F) and relative humidity was more than 60%.[105]

Acute pernio has a seasonal incidence, with reversible symptoms more common in cold weather. The acute form is seen primarily in schoolchildren and young adults younger than 20, with the highest incidence in adolescent females.[81] It can occur in mildly cold settings such as logging, kayaking, snowmaking,[57] winter horseback riding, and hiking.[101] Pernio can be caused by brief cold exposure (30 minutes), often appearing several hours after exposure, with the skin lesions fully developed within 12 to 24 hours.[99] Characteristic locations for these lesions are the feet, hands, legs, and thighs. Single or multiple, erythematous, purplish, edematous lesions form, with vesicles in severe cases. Symptoms include intense pruritus, burning, or pain, often worsened by subsequent warmth. The lesions of acute pernio are self-limited and usually resolve within a few days to 3 weeks,[100] occasionally leaving residual hyperpigmentation.[25] Although the healing process appears to occur as the plaques resolve, pain often persists. Subsequent mild cold exposure may trigger paresthesias, edema, and skin scaling.[57]

Chronic perniosis usually progresses over several winters after repeated episodes of acute pernio, rarely progressing from the initial injury to chronic irreversible skin changes within a single season.[81] Repeated episodic seasonal lesions may become edematous, with permanent discoloration and subcutaneous nodule formation. The nodules are firm and painful, ultimately rupturing, which provides pain relief and leaves a shallow ulcer with pigmented atrophic skin. These ulcers may grow larger and coalesce, remaining open, which leads to permanently swollen extremities, scaly pigmented skin, and unremitting pain aggravated by light pressure.

Pernio is thought to be caused by prolonged cold-induced vasoconstriction with subsequent hypoxemia and vessel wall inflammation.[49,69] Subcutaneous arterial vasoconstriction is documented by both pathologic[81] and arteriographic studies.[116] Histologic examinations show lymphocytic vasculitis and papillary dermal edema with pervasive inflammatory changes.[49,69,81] The differential diagnosis includes lupus erythematosus, Raynaud's phenomenon, polycythemia vera, atheromatous embolization, erythema nodosum, and livedo vasculitis with ulcerations.

Treatment of pernio is accomplished by drying and gently massaging the affected skin. Active warming above 30°C (86°F) significantly worsens the pain and should be avoided.[57] Although therapeutic regimens in the literature include nicotinic acid,[53] ultraviolet irradiation,[61] thymoxamine,[70] intravenous calcium combined with intramuscular vitamin K,[42] corticosteroids,[47] and sympathectomy in severe cases,[81] few have proved to be either effective or universally accepted. Nifedipine (20 mg three times daily) has been effective for treatment of severe perniosis. Patients treated had a significantly reduced time for clearance of lesions, decreased pain and irritation of existing lesions, and less development of new pernio.[49,108]

Preventing pernio is relatively simple. Recommended prophylactic measures include minimizing cold exposure with suitable clothing when outdoors and maintaining adequate warm temperatures indoors.

## RAYNAUD'S PHENOMENON

This eponymous phenomenon was first identified by Maurice Raynaud in 1862, who described "local asphyxia of the extremities." Raynaud's phenomenon is a paroxysmal vasospastic and subsequently vasodilatory arteriolar response to temperate or occasionally emotional stressors. This can include changes in temperatures, not only cold exposure,[52] and is essentially arterial hyperresponsiveness and vasoconstriction in susceptible individuals.[59] The classic observed color change, common in digits, is white (following the initial vasospastic response) to blue (indicating hypoxia) and finally to red, with subsequent vasodilation on rewarming. The final stage is often associated with burning pain.

Broadly, Raynaud's can be divided into primary and secondary. Raynaud's phenomenon is the *primary* form, typically affecting women in their 20s to 30s, with no obvious underlying cause. Raynaud's syndrome, or *secondary* Raynaud's, is when the phenomenon has an underlying cause, sometimes presenting as the first sign of a systemic condition, such as systemic sclerosis.[52] The vascular defect in primary Raynaud's is thought to be primarily functional with a hyperresponsiveness causing symptoms, whereas secondary Raynaud's often has underlying vascular and microvascular abnormalities.[59]

Primary Raynaud's is unlikely to cause digital ischemia and usually has normal nailfold capillaries and erythrocyte sedimentation rate (ESR). By definition, it does not progress to irreversible tissue damage,[60] although the symptoms can be painful and distressing. In contrast, general secondary Raynaud's is more likely to present in older age groups (>30), and individuals are more likely to develop tissue damage.[52]

### PREVALENCE

Prevalence varies with geography and gender. Surveys showed 15% of patients reporting Raynaud's phenomenon,[113] although prevalence varies depending on the definition of the disease. Higher altitude is thought to increase prevalence.[82] It is two to nine times more common in women.[32] Although not fully understood, a relationship to hormonal factors is believed to exist, particularly in view of the gender predominance. Digital vascular reactivity in the preovulation period similar to that seen with Raynaud's suggests a role for estrogen.[79] Use of a vibratory tool and a genetic component have also been implicated.[60]

### PATHOGENESIS

The pathogenesis differs between primary and secondary Raynaud's and has not been fully elucidated. Intravascular factors related to underlying conditions, such as increased viscosity in Waldenström's macroglobulinemia or platelet activation, are seen in secondary Raynaud's syndrome.[52] Structural abnormalties in the vasculature do not occur in primary Raynaud's phenomenon, although some seemingly primary Raynaud's cases have later been revealed to be secondary, with subsequent tissue damage. Interestingly, Raynaud's phenomenon preferentially affects the digits, with the thumb less affected,[22] possibly because of its shorter length.[60]

As mentioned earlier, $\alpha_2$-adrenergic receptors attenuate cold-induced vasoconstriction, as illustrated by the use of intraarterial administration of $\alpha_1$- and $\alpha_2$-agonists and antagonists and effects on finger blood flow.[24] Thus, it is thought that abnormalities in this control is responsible for Raynaud's phenomenon.[60] This condition primarily affecting extremities can therefore by partly explained by the increase in $\alpha_2$-receptor responsiveness in distal arteries.[24]

Control of vasoconstriction and vasodilation is complex. It is not known in Raynaud's phenomenon whether the production of vasodilators is reduced or their effects on receptors are impaired.[60] However, further work is directed at the use of exogenous nitric oxide (NO), which can be given topically to increase digital microvascular blood flow.[6] A more detailed discussion can be found in a recent review.[60]

### DIAGNOSIS

Primary Raynaud's phenomenon does not usually require further investigation, although if one suspects secondary Raynaud's syndrome, perhaps because of the appearance of digital ulcers, advice should be sought regarding further investigation.[52]

### MANAGEMENT

Symptoms can be distressing and painful. Various strategies involve initially reducing exposure to sudden temperature changes by using gloves and hand warmers, and keeping hands warm. Smoking cessation is important because smoking decreases finger systolic pressures.[59] Although a large study did not find an association between Raynaud's phenomenon and cigarette consumption, smoking may impair delay physiologic improvement and increase severity of symptoms.[20]

Mild cold injury can result in a sensitization process that may resemble secondary Raynaud's disease, in particular cumulative cold injuries. Avoidance of further cold injuries until not sensitized is recommended.

Recent recommendations include exercising regularly and reducing stress.[119] Pharmacologic management has traditionally involved calcium channel blockers, particularly noncardioselective dihydropyridine for treatment and prophylaxis, and meta-anaylsis has shown significant improvement (weighted mean difference, −5; 95% CI, −9 to −0.99) for all calcium channel blockers and higher for nifedipine alone.[125] Nifedipine is currently the only medication licensed for use in the UK.[52] Side effects such as flushing and pedal edema can lead to poor compliance. No drugs are licensed by the Food and Drug Administration (FDA) for use in the United States. Others drugs being studied are fluoxetine and topical nitrates. *Ginkgo biloba* has shown improvement over placebo, with few side effects.[52]

## CRYOGLOBULINEMIA

Cryoglobulins are cold-precipitable serum immunoglobulins.[120] Cryoimmunoglobulins were first reported in a patient with multiple myeloma[144] and subsequently recognized to occur in a diverse group of hematologic malignancies, acute and chronic infections, and collagen vascular diseases.[117,132] Cryoglobulins are classified as three types. Type I cryoglobulins (10% to 15% of total) are composed of a monoclonal immunoglobulin, primarily IgG. Type II cryoglobulins (50% to 60%) are polyclonal, most frequently IgG and IgM. The IgM fraction usually has rheumatoid factor activity. Type III cryoglobulins (25% to 30%) are also composed of polyclonal IgG and IgM fractions.

In general, the higher the protein concentration, the higher is the temperature at which precipitation begins. Of clinical relevance is the composition of the cryoprecipitate. For example, IgM is intrinsically more viscous than IgG, and patients with monoclonal cryo-IgM have amplified hyperviscosity. Because extremity temperatures can reach 30° C (86°F), in vivo cryoprecipitation may directly contribute to impaired capillary blood flow.[57]

Many clinical conditions are associated with cryoglobulinemia.[120] Infections (viral, bacterial, fungal, parasitic), hematologic diseases (chronic lymphocytic leukemia, multiple myeloma), and autoimmune diseases (rheumatoid arthritis, pulmonary fibrosis, inflammatory bowel disease) are all associated with cryoglobulinemia. Hepatitis C virus (HCV) is considered a principal trigger of cryoglobulinemia. Serum cryoglobulin values do not usually correlate with clinical severity or disease prognosis,[120] but may serve as a marker of the disease.

Cryoglobulinemia is characterized by a clinical triad of purpura, weakness, and arthralgias. A large clinical trial showed that two-thirds of patients diagnosed with cryoglobulinemia initially presented with symptoms of skin lesions or Raynaud's disease–like vasomotor attacks. Mucosal bleeding, visual disturbances, and abdominal pain were less common. Cold sensitivity was apparent in less than half of these patients.[16] Symptoms associated with cryoglobulins include typical Raynaud's phenomenon, dependent purpura, cutaneous vasculitis with ulceration, retinal hemorrhages, coagulopathies, glomerulonephritis, renal failure, and cerebral thrombosis.

Treatment of cryoglobulinemia should be directed at the severity of symptoms and the disease causing the cryoglobulinemia. Because HCV is implicated in many cases of type II and III cryoglobulinemia, targeting HCV is the treatment of choice to eliminate cryoglobulinemia. Interferon, prednisone, and ribavirin have all been used to treat HCV and associated cryoglobulinemia. For non–HCV-associated cryoglobulinemia patients with mild to moderate symptoms (purpura, arthralgia, sensory neuropathy), immunosuppression with steroids and analgesics is the treatment of choice.[120] A low-antigen content diet (rice, fresh vegetables, fruit, tea) has been shown to improve purpura.[41] With severe manifestations of disease, such as renal failure, neurologic impairment, disabling paresthesias, or myalgias, plasmapheresis may be helpful in reducing the cryoimmunoglobulin concentration below a critical point to alleviate symptoms.[16] Plasmapheresis is used in conjunction with steroids or other drugs, since discontinuing plasmapheresis treatment usually causes reappearance of cryoglobulinemia.[120]

## COLD URTICARIA

Cold urticaria is characterized by development of localized or generalized wheals and itching after skin exposure (air, liquid,

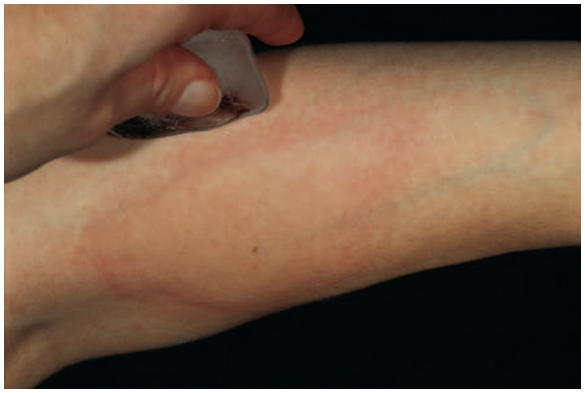


**FIGURE 10-23** Cold urticaria. The hive occurred within minutes of holding an ice cube against the skin. *(From Habif TP:* Clinical dermatology, *ed 4, Philadelphia, 2004, Mosby.)*

object) to cold[111] (Figure 10-23). It most frequently affects young adults, although primary cold urticaria can occur at any age. Women are twice as likely to be affected.[112] The incidence rate is about 0.05% of the population.

Symptoms are usually limited to cold-exposed skin areas.[111] Local symptoms include redness, itching, wheals, or edema of exposed skin. The wheals last approximately 30 minutes. Systemic reactions include fatigue, headache, dyspnea, and hypotension. Swimming in cold water is the most common trigger of severe reactions. This may lead to hypotension, fainting, shock, and possibly death.[10,56] Suffocation may also occur after consuming cold drinks because of pharyngeal angioedema.[111]

Secondary urticaria occurs in 5% of patients with cold urticaria.[56] The wheals are more persistent and may be associated with purpura and vasculitis on skin biopsy. This disorder is associated with an underlying disorder such as cryoglobulinemia, cold agglutinins, paroxysmal hemoglobinuria, or connective tissue disease.[133] In addition, a rare autosomal dominant familial form has its onset in infancy and is associated with arthralgias and leukocytosis.[134]

The cause of cold urticaria is unknown. Cold urticaria has been associated with viral or bacterial infections,[111,112] as well as infections of the upper respiratory tract, teeth, and urogenital tract. It has been reported to involve release of histamine,[74] leukotrienes, and other mast cell mediators,[112] possibly mediated by IgE and IgM. Support for an IgE-mediated mechanism comes from successful treatment[14] using an anti-IgE agent (omalizumab). The diagnosis of cold urticaria is made through the ice cube test in the majority of patients,[94] where a hive is induced by holding an ice cube to skin for 3 to 5 minutes. If the results are equivocal, a cold-water immersion test of submerging a forearm for 5 to 15 minutes in water at 0° to 8° C (32° to 46.4° F) establishes the diagnosis.

Treating cold urticaria with antihistamines is the most effective option. To reduce symptoms sufficiently requires dosing up to four times the recommended dose.[95,111,112] In addition, other therapies include leukotriene antagonists, cyclosporine, corticosteroids, and anti-IgE.[112] Individuals with severe reactions should have an emergency kit containing corticosteroids, antihistamines, and epinephrine. Based on the finding that infectious disease may be a trigger for cold urticaria, treatment with antibiotics may also be warranted.[112]

## REFERENCES

***Complete references used in this text are available online at expertconsult.inkling.com.***

# CHAPTER 11
# Polar Medicine

MARTIN RHODES AND HANS CHRISTIAN SØRENSON

As with much of wilderness medicine, polar medicine is largely derived from its setting. *Polar,* however, can be defined in several different ways. Geographically, the Arctic and Antarctic circles, at latitudes 66 degrees, 33 minutes north and south, delimit areas in which the sun does not rise or set on at least 1 day of the year, and determine the North Polar region ("The Arctic") and South Polar region ("The Antarctic"). A definition based on temperature is the 10° isotherm, which joins those areas in which the average temperature in the warmest month of the year is 10° C (50° F); this correlates roughly with the tree line.

For medical purposes, the definition of *polar* is more complex. Although climate and geography are clearly important, the salient features of polar medicine are logistic and experiential. Unlike high-altitude medicine or hyperbaric medicine, for example, polar medicine is not unified by an underlying pathophysiology. High-altitude medicine is a medical field because of the environment's effect on the human organism, but polar medicine is largely medical practice within a particular environmental setting.

Medical practice in isolated settings is paradigmatic of wilderness medicine; the patient population is essentially, if not literally, a small demographic island. A broad definition of *polar medicine,* therefore, could be "the practice of medicine in isolated settings within an extreme cold environment, distinguished by a scarce population, limited resources, and challenging logistics." It is the cold, remoteness, hostility, and unforgiving nature of the environment in which humans struggle to survive, let alone work, that make medicine in polar areas, and in particular Antarctica, so challenging.[69]

The environment itself defines polar medicine in another sense. So harsh are the poles that the simplest of mistakes can lead to harm. The average temperature at the South Pole in winter is –60° C (–76° F). At this temperature, exposed skin freezes within minutes. Prevention is everything, and thus polar medicine can be seen as example of preventive medicine in practice.

## THE DISTINCTION BETWEEN ARCTIC AND ANTARCTIC MEDICINE

Although the polar regions share the predominant attributes of cold, dark, isolation, and severe weather, they display many important contrasts. The Arctic has been described as a frozen sea nearly surrounded by land, whereas Antarctica is a land and ice mass circumscribed by ocean. The moderating effect of the

## REFERENCES


1. Adnot J, Lewis C. Immersion foot syndromes. Washington, DC: Office of the Surgeon General, Borden Institute; 1994.
2. Adnot J, Lewis C. Immersion foot syndromes. In: James W, Zajtchcuck RE, editors. Textbook of military medicine. Military dermatology. Washington, DC: Office of the Surgeon General, Borden Institute; 1994. p. 55–68.
3. Adnot J, Lewis C. Immersion foot syndromes. J Assoc Mil Dematol 1985;1(11):87–92.
4. Akers W. Paddy foot: A warm water immersion foot syndrome variant. II. Field experiments, correlation. Mil Med 1974;139: 613–18.
5. Aldington DJ, McQuay HJ, Moore RA. End-to-end military pain management. Philos Trans R Soc Lond B Biol Sci 2011;366(1562): 268–75.
6. Anderson ME, Moore TL, Hollis S, et al. Digital vascular response to topical glyceryl trinitrate, as measured by laser Doppler imaging, in primary Raynaud's phenomenon and systemic sclerosis. Rheumatology 2002;41(3):324–8.
7. Arvesen A, Rosen L, Eltvik LP, et al. Skin microcirculation in patients with sequelae from local cold injuries. Int J Microcirc Clin Exp 1994;14(6):335–42.
8. Atenstaedt RL. Trench foot: The medical response in the First World War 1914-18. Wilderness Environ Med 2006;17(4):282–9.
9. Bailey SR, Eid AH, Mitra S, et al. Rho kinase mediates cold-induced constriction of cutaneous arteries: role of alpha2c-adrenoceptor translocation. Circ Res 2004;94(10):1367–74.
10. Berman BA, Ross RN, Sly RM. Acquired cold urticaria. Cutis 1983; 31(1):20.
11. Blackwood W. Injury from exposure to low temperature: Pathology. BMJ 1944;4.
12. Blackwood W. Studies in the pathology of human immersion foot. Br J Surg 1944;31:320–50.
13. Blackwood W, Russel H. Experiments in the study of immersion foot. Edinb Med J 1943;50:385–98.
14. Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE. J Allergy Clin Immunol 2006;117(6):1415–18.
15. Brandstrom H, Grip H, Hallberg P, et al. Hand cold recovery responses before and after 15 months of military training in a cold climate. Aviat Space Environ Med 2008;79(9):904–8.
16. Brouet JC, Clauvel JP, Danon F, et al. Biologic and clinical significance of cryoglobulins: A report of 86 cases. Am J Med 1974; 57(5):775–88.
17. Buckels LJ, Gill KA Jr, Anderson GT. Warm water immersion foot. [Research reports.]. Nav Med Field Res Lab 1967;17(5):1–8.
18. Burgess JE, Macfarlane F. Retrospective analysis of the ethnic origins of male British army soldiers with peripheral cold weather injury. J R Army Med Corps 2009;155(1):11–15.
19. Cattermole TJ. The epidemiology of cold injury in Antarctica. Aviat Space Environ Med 1999;70(2):135–40.
20. Cherniack M, Clive J, Seidner A. Vibration exposure, smoking, and vascular dysfunction. Occup Environ Med 2000;57(5):341–7.
21. Cheung SS, Mekjavic IB. Cold-induced vasodilatation is not homogenous or generalizable across the hand and feet. Eur J Appl Physiol 2007;99(6):701–5.
22. Chikura B, Moore TL, Manning JB, et al. Sparing of the thumb in Raynaud's phenomenon. Rheumatology 2008;47(2):219–21.
23. Chotani MA, Flavahan S, Mitra S, et al. Silent alpha(2c)-adrenergic receptors enable cold-induced vasoconstriction in cutaneous arteries. Am J Physiol Heart Circ Physiol 2000;278(4):H1075–83.
24. Coffman JD, Cohen RA. Role of alpha-adrenoceptor subtypes mediating sympathetic vasoconstriction in human digits. Eur J Clin Invest 1988;18(3):309–13.
25. Corbett D, Benson P. Military dermatology. In: Pandolf KB, Burr RE, editors. Textbook of military medicine. Washington, DC: Office of the Surgeon General; 2002. p. 22–37.
26. Craig RP. Military cold injury during the war in the Falkland Islands 1982: an evaluation of possible risk factors. J R Army Med Corps 2007;153(Suppl. 1):63–8, discussion 9.
27. Critchley M. Shipwreck survivors: A medical study. London: J & A Churchill; 1943.
28. Daanen HA, Ducharme MB. Finger cold-induced vasodilation during mild hypothermia, hyperthermia and at thermoneutrality. Aviat Space Environ Med 1999;70(12):1206–10.
29. Daanen HA, van de Linde FJ, Romet TT, Ducharme MB. The effect of body temperature on the hunting response of the middle finger skin temperature. Eur J Appl Physiol Occup Physiol 1997;76(6): 538–43.
30. Daanen HA, van der Struijs NR. Resistance Index of Frostbite as a predictor of cold injury in arctic operations. Aviat Space Environ Med 2005;76(12):1119–22.
31. Das DK, Iyengar J, Jones RM, et al. Protection from nonfreezing cold injury by quinacrine, a phospholipase inhibitor. Cryobiology 1991; 28(2):177–84.
32. De Trafford JC, Lafferty K, Potter CE, et al. An epidemiological survey of Raynaud's phenomenon. Eur J Vasc Surg 1988;2(3): 167–70.
33. DeGroot DW, Castellani JW, Williams JO, Amoroso PJ. Epidemiology of U.S. Army cold weather injuries, 1980-1999. Aviat Space Environ Med 2003;74(5):564–70.
34. Denny-Brown D, Adams RD, et al. The pathology of injury to nerve induced by cold. J Neuropathol Exp Neurol 1945;4:305–23.
35. Douglas JS Jr, Eby CS. Silicone for immersion foot prophylaxis: Where and how much to use. Mil Med 1972;137(10):386–7.
36. Eglin C, Golden F, Tipton M. The effect of gentle exercise prior to a cold sensitivity test used to classify non-freezing cold injury. In Prevention of cold injuries; 2005; Neuilly-sur-Seine, France; 2005.
37. Emmelin N, Trendelenburg U. Degeneration activity after parasympathetic or sympathetic denervation. Ergeb Physiol 1972;66:147–211.
38. Endrich B, Hammersen F, Messmer K. Microvascular ultrastructure in non-freezing cold injuries. Res Exp Med Zeitschrift fur die gesamte experimentelle Medizin einschliesslich experimenteller Chirurgie 1990;190(5):365–79.
39. Ervasti O, Juopperi K, Kettunen P, et al. The occurrence of frostbite and its risk factors in young men. Int J Circumpolar Health 2004; 63(1):71–80.
40. Felicijan A, Golja P, Milcinski M, et al. Enhancement of cold-induced vasodilatation following acclimatization to altitude. Eur J Appl Physiol 2008;104(2):201–6.
41. Ferri C, Pietrogrande M, Cecchetti R, et al. Low-antigen-content diet in the treatment of patients with mixed cryoglobulinemia. Am J Med 1989;87(5):519–24.
42. Fitzgerald KJ. Cure for chilblains. Med J Aust 1980;1(13):676.
43. Francis T, Oakley E. Cold injury. In: Tooke J, Lowe GE, editors. A textbook of vascular medicine. London: Arnold; 1996. p. 353–70.
44. Francis TJ. Non freezing cold injury: A historical review. J R Nav Med Serv 1984;70(3):134–9.
45. Francis TJ, Golden FS. Non-freezing cold injury: the pathogenesis. J R Nav Med Serv 1985;71(1):3–8.
46. Friedman NB. The pathology of trench foot. Am J Pathol 1945; 21(3):387–433.
47. Ganor S. Corticosteroid therapy for pernio. J Am Acad Dermatol 1983;8(1):136.
48. Gill KA Jr. Report of a field study on silicone ointments MDX-4-4056 and MDX-4-4078. Vol XVII, No 16 [Research reports]. Nav Med Field Res Lab 1967;17(16):1–7.
49. Goette DK. Chilblains (perniosis). J Am Acad Dermatol 1990;23(2 Pt 1):257–62.
50. Golden FS. Physiological changes in immersion hypothermia, with special reference to factors which may be responsible for death in the early rewarming phase.: Leeds.; 1979.
51. Golden FS, Francis TJ, Gallimore D, Pethybridge R. Lessons from history: Morbidity of cold injury in the Royal Marines during the Falklands Conflict of 1982. Extrem Physiol Med 2013;2(1):23.
52. Goundry B, Bell L, Langtree M, Moorthy A. Diagnosis and management of Raynaud's phenomenon. BMJ 2012;344:e289.
53. Gourlay RJ. The problem of chilblains. BMJ 1948;1(4551):618.
54. Green R. Frostbite and kindred ills. Lancet 1941;2:689–93.
55. Greenfield AD, Shepherd JT, Whelan RF. Cold vasoconstriction and vasodilatation. Ir J Med Sci 1951;(309):415–19.
56. Habif T. Physical urticarias. In: Clinical dermatology. St Louis: Mosby; 2004. p. 146–7.
57. Hamlet M. Non freezing cold injuries. In: Auerbach PS, editor. Wilderness medicine. 4th ed. St Louis: Mosby; 1994. p. 129–34.
58. Harirchi I, Arvin A, Vash JH, Zafarmand V. Frostbite: Incidence and predisposing factors in mountaineers. Br J Sports Med 2005;39(12):898–901, discussion.
59. Herrick AL. Pathogenesis of Raynaud's phenomenon. Rheumatology 2005;44(5):587–96.
60. Herrick AL. The pathogenesis, diagnosis and treatment of Raynaud phenomenon. Nat Rev Rheumatol 2012;8(8):469–79.
61. Holti G, Ingram J. Physiotherapy in dermatology. Lancet 1963;1: 141–2.
62. Horwitz O, Montgomery H, Sayen A, Mescon H. Experimental immersion foot. II. Functional and histological changes in the rabbit leg exposed to water at 3 degrees C, and therapeutic trial of cortisone and of inhaled oxygen. J Clin Invest 1954;33(3):370–6.
63. Iampietro PF, Goldman RF, Buskirk ER, Bass DE. Response of Negro and white males to cold. J Appl Physiol 1959;14:798–800.
64. Imray C. Personal communication, 2010.
65. Imray C, Grieve A, Dhillon S, Caudwell Xtreme Everest Research Group. Cold damage to the extremities: Frostbite and non-freezing cold injuries. Postgrad Med J 2009;85(1007):481–8.

66. Imray CH, Oakley EH. Cold still kills: cold-related illnesses in military practice freezing and non-freezing cold injury. J R Army Med Corps 2005;151(4):218–22.
67. Irwin MS. Nature and mechanism of peripheral nerve damage in an experimental model of non-freezing cold injury. Ann R Coll Surg Engl 1996;78(4):372–9.
68. Irwin MS, Sanders R, Green CJ, Terenghi G. Neuropathy in non-freezing cold injury (trench foot). J R Soc Med 1997;90(8):433–8.
69. Jacob JR, Weisman MH, Rosenblatt SI, Bookstein JJ. Chronic pernio. A historical perspective of cold-induced vascular disease. Arch Intern Med 1986;146(8):1589–92.
70. Jaffe GV, Grimshaw JJ. Thymoxamine for Raynaud's disease and chilblains. Br J Clin Pract 1980;34(11–12):343–6.
71. Jia J, Jia J, Pollock M. The synergistic enhancement of pathology in intermittently cooled nerve. Chin Med J 2000;113(3):241–5.
72. Jia J, Pollock M. The pathogenesis of non-freezing cold nerve injury: Observations in the rat. Brain 1997;120(Pt 4):631–46.
73. Jia J, Pollock M, Jia J. Cold injury to nerves is not due to ischaemia alone. Brain 1998;121(Pt 5):989–1001.
74. Kaplan AP, Garofalo J, Sigler R, Hauber T. Idiopathic cold urticaria: in vitro demonstration of histamine release upon challenge of skin biopsies. N Engl J Med 1981;305(18):1074–7.
75. Kennett RP, Gilliatt RW. Nerve conduction studies in experimental non-freezing cold injury. I. Local nerve cooling. Muscle Nerve 1991;14(6):553–62.
76. Kennett RP, Gilliatt RW. Nerve conduction studies in experimental non-freezing cold injury. II. Generalized nerve cooling by limb immersion. Muscle Nerve 1991;14(10):960–7.
77. Khaira HS, Coddington T, Drew A, et al. Patellar tendon bearing orthosis: Application as adjunctive treatment in healing of lower-limb tissue loss. Eur J Vasc Endovasc Surg 1998;16(6):485–8.
78. Laden GD, Purdy G, O'Reilly G. Cold injury to a diver's hand after a 90-min dive in 6 degrees C water. Aviat Space Environ Med 2007;78(5):523–5.
79. Lafferty K, De Trafford JC, Potter C, et al. Reflex vascular responses in the finger to contralateral thermal stimuli during the normal menstrual cycle: A hormonal basis to Raynaud's phenomenon? Clin Sci (Lond) 1985;68(6):639–45.
80. Levick JR. Cardiovascular physiology. 5th ed. Boca Raton, Fla: CRC Press; 2010.
81. Lynn RB. Chilblains. Surg Gynecol Obstet 1954;99(6):720–6.
82. Maricq HR, Carpentier PH, Weinrich MC, et al. Geographic variation in the prevalence of Raynaud's phenomenon: A 5 region comparison. J Rheumatol 1997;24(5):879–89.
83. Matthew L, Purkayastha S, Nayar H. Variation in susceptibility to cold injury in Indians. Int J Biometeorol 1979;23(3):263–70.
84. McGreevy K, Bottros MM, Raja SN. Preventing chronic pain following acute pain: Risk factors, preventive strategies, and their efficacy. Eur J Pain Suppl 2011;5(2):365–72.
85. McLatchie G, Lennox C. The soft tissues: Trauma and sports injuries. Oxford: Butterworth-Heinemann; 1993.
86. Melamed E, Glassberg E. [Non-freezing cold injury in soldiers]. Harefuah 2002;141(12):1050–4, 90.
87. Mills W, Pozos R. Low temperature effects on humans. In: Encyclopedia of human biology. New York: Academic Press; 1991. p. 117–28.
88. Mills WJ Jr, Mills WJ III. Peripheral non-freezing cold injury: immersion injury. Alaska Med 1993;35(1):117–28.
89. Mitchell J, Simpson R, Whitaker J. Cold injuries in contemporary conflict. J R Army Med Corps 2012;158(3):248–51.
90. Mohan JS, Marshall JM, Reid HL, et al. Comparison of responses evoked by mild indirect cooling and by sound in the forearm vasculature in patients with homozygous sickle cell disease and in normal subjects. Clin Auton Res 1998;8(1):25–30.
91. Mohr WJ, Jenabzadeh K, Ahrenholz DH. Cold injury. Hand Clin 2009;25(4):481–96.
92. Montgomery H. Experimental immersion foot: Review of the physiopathology. Physiol Rev 1954;34(1):127–37.
93. Moran DS, Heled Y, Shani Y, Epstein Y. Hypothermia and local cold injuries in combat and non-combat situations: The Israeli experience. Aviat Space Environ Med 2003;74(3):281–4.
94. Neittaanmaki H. Cold urticaria: Clinical findings in 220 patients. J Am Acad Dermatol 1985;13(4):636–44.
95. Neittaanmaki H, Myohanen T, Fraki JE. Comparison of cinnarizine, cyproheptadine, doxepin, and hydroxyzine in treatment of idiopathic cold urticaria: Usefulness of doxepin. J Am Acad Dermatol 1984; 11(3):483–9.
96. Nukada H, Pollock M, Allpress S. Experimental cold injury to peripheral nerve. Brain 1981;104(Pt 4):779–811.
97. O'Brien C, Frykman PN. Peripheral responses to cold: Case studies from an Arctic expedition. Wilderness Environ Med 2003;14(2): 112–19.
98. O'Brien C, Young AJ, Lee DT, et al. Role of core temperature as a stimulus for cold acclimation during repeated immersion in 20 degrees C water. J Appl Physiol 2000;89(1):242–50.
99. Olin J. Other peripheral arterial diseases. In: Cecil textbook of medicine. 21st ed. Saunders; 2000. p. 365–7.
100. Page EH, Shear NH. Temperature-dependent skin disorders. J Am Acad Dermatol 1988;18(5 Pt 1):1003–19.
101. Price RD, Murdoch DR. Perniosis (chilblains) of the thigh: Report of five cases, including four following river crossings. High Alt Med Biol 2001;2(4):535–8.
102. Purkayastha SS, Sharma RP, Ilavazhagan G, et al. Effect of vitamin C and E in modulating peripheral vascular response to local cold stimulus in man at high altitude. Jpn J Physiol 1999;49(2): 159–67.
103. Ramstead KD, Hughes RG, Webb AJ. Recent cases of trench foot. Postgrad Med J 1980;56(662):879–83.
104. Rav-Acha M, Heled Y, Moran DS. Cold injuries among Israeli soldiers operating and training in a semiarid zone: A 10-year review. Mil Med 2004;169(9):702–6.
105. Raza N, Sajid M, Suhail M, Haroon ur R. Onset of chilblains in relation with weather conditions. J Ayub Med Coll Abbottabad 2008; 20(2):17–20.
106. Riddell IC, Royal Navy (Ret); formerly Principal Medical Officer, Commando Training Centre Royal Marines, Lympstone, Devon, England. Personal communication, 1982.
107. Roberts DE, Berberich JJ. The role of hydration on peripheral response to cold. Mil Med 1988;153(12):605–8.
108. Rustin MH, Newton JA, Smith NP, Dowd PM. The treatment of chilblains with nifedipine: The results of a pilot study, a double-blind placebo-controlled randomized study and a long-term open trial. Br J Dermatol 1989;120(2):267–75.
109. Savitt TL. Medicine and slavery: The disease and health care of blacks in antebellum Virginia. Champaign, IL: University of Illinois Press; 1981.
110. Shurtleff D, Gilliat R, Thomas J. An assessment of peripheral nerve damage in the rat following non-freezing cold exposure: An electrophysiological and histopathological examination: Naval Medical Research Institute; Jan 1993.
111. Siebenhaar F, Degener F, Zuberbier T, et al. High-dose desloratadine decreases wheal volume and improves cold provocation thresholds compared with standard-dose treatment in patients with acquired cold urticaria: A randomized, placebo-controlled, crossover study. J Allergy Clin Immunol 2009;123(3):672–9.
112. Siebenhaar F, Weller K, Mlynek A, et al. Acquired cold urticaria: Clinical picture and update on diagnosis and treatment. Clin Exp Dermatol 2007;32(3):241–5.
113. Silman A, Holligan S, Brennan P, Maddison P. Prevalence of symptoms of Raynaud's phenomenon in general practice. BMJ 1990; 301(6752):590–2.
114. Smith J, Ritchie J, Dawson J. Clinical and experimental observations on the pathology of trench frostbite. J Pathol 1915;20:159–90.
115. Smith J, Ritchie J, Dawson J. On the pathology of trench frost-bite. Lancet 1915;11:595–8.
116. Spittel J, Spittell P. Chronic pernio: Another cause of blue toes. Int Angiol 1992;11(1):46–50.
117. Steinhard MJ, Fisher GS. Essential cryoglobulinemia. Ann Intern Med 1955;43:848–58.
118. Stephens D, Saad AR, Bennett LA, et al. Damage to vascular endothelium and smooth muscle contribute to the development of nonfreezing cold injury n the rat tail vascular bed in vitro. 13th International Conference on Environmental Ergonomics; 2009; Boston; 2009. pp 177-81.
119. Summaries NIfHaCECK. Raynaud's phenomenon: NICE; 2014.
120. Tedeschi A, Barate C, Minola E, Morra E. Cryoglobulinemia. Blood Rev 2007;21(4):183–200.
121. Teixeira F, Pollock M, Karim A, Jiang Y. Use of antioxidants for the prophylaxis of cold-induced peripheral nerve injury. Mil Med 2002; 167(9):753–5.
122. Tek D, Mackey S. Non-freezing cold injury in a Marine infantry battalion. J Wilderness Med 1993;4:353–7.
123. Thomas J, Oakley H. Nonfreezing cold injury. In: Pandolf KB, Burr RE, editors. Textbook of military medicine, vol. 1. Medical aspects of harsh environments. Washington, DC: Office of the Surgeon General, Borden Institute; 2002. p. 467–90.
124. Thomas JR, Shurtleff D, Schrot J, Ahlers ST. Cold-induced perturbation of cutaneous blood flow in the rat tail: A model of nonfreezing cold injury. Microvasc Res 1994;47(2):166–76.
125. Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. Rheumatology 2005;44(2): 145–50.
126. Thompson-Torgerson CS, Holowatz LA, Flavahan NA, Kenney WL. Cold-induced cutaneous vasoconstriction is mediated by rho kinase

in vivo in human skin. Am J Physiol Heart Circ Physiol 2007; 292(4):H1700–5.
127. Travis S, Mugridge T, Golden FS. Toe temperatures during Arctic training. Mil Med 1990;155(4):162–6.
128. Ungley C, Blackwood W. Peripheral vasoneuroapathy after chilling. Lancet 1942;2:447–51.
129. Ungley CC. Immersion foot and immersion hand (peripheral vasoneuropathy after chilling). Bull War Med 1943;4(2):61–5.
130. Ungley CC, Channell GD, Richards RL. The immersion foot syndrome. 1946. Wilderness Environ Med 2003;14(2):135–41, discussion 4.
131. Van der Struijs NR, Van Es EM, Raymann RJ, Daanen HA. Finger and toe temperatures on exposure to cold water and cold air. Aviat Space Environ Med 2008;79(10):941–6.
132. Volpe R, Bruce-Robertson A, Fletcher AA, Charles WB. Essential cryoglobulinaemia: Review of the literature and report of a case treated with ACTH and cortisone. Am J Med 1956;20(4):533–53.
133. Wanderer AA, Grandel KE, Wasserman SI, Farr RS. Clinical characteristics of cold-induced systemic reactions in acquired cold urticaria syndromes: Recommendations for prevention of this complication and a proposal for a diagnostic classification of cold urticaria. J Allergy Clin Immunol 1986;78(3 Pt 1):417–23.
134. Wanderer AA, Hoffman HM. The spectrum of acquired and familial cold-induced urticaria/urticaria-like syndromes. Immunol Allergy Clin North Am 2004;24(2):259–86, vii.
135. Webster D, Woolhouse F, Johnson J. Immersion foot. J Bone Joint Surg Am 1942;24(4):785–94.
136. Whayne T, DeBakey M. Cold injury, ground type. Office of the Surgeon General, US Department of the Army, Washington, DC. 1958:1-51.
137. White J, Scoville W. Trench foot and immersion foot. N Engl J Med 1945;24(4):785–94.
138. Williams GL, Morgan AE, Harvey JS. Trench foot following a collapse: assessment of the feet is essential in the elderly. Age Ageing 2005;34(6):651–2.
139. Williamson K, Izard R. Epidemic of non-freezing cold injury in the British Army. J R Army Med Corps 2007;153(2):143.
140. Wilson O, Goldman RF. Role of air temperature and wind in the time necessary for a finger to freeze. J Appl Physiol 1970;29(5):658–64.
141. Reference deleted in proofs.
142. World Health Organization. International statistical classification of diseases and related health problems. Geneva: WHO; 2015.
143. Wrenn K. Immersion foot. A problem of the homeless in the 1990s. Arch Intern Med 1991;151(4):785–8.
144. Young AJ, Castellani JW. Exertion-induced fatigue and thermoregulation in the cold. Comparative biochemistry and physiology. Part A. Mol Integr Physiol 2001;128(4):769–76.

surrounding North Polar waters contrasts with the cooling effect of altitude on the Antarctic plateau, which lies at approximately 2835 m (9301 feet) and accounts for the approximately 40°C (72°F) difference in wintertime low temperatures between the two polar regions. On a plot of temperature versus humidity, the polar plateau is more similar to Mars than to the rest of the earth. The flora and fauna are unique to each area. The Arctic has an abundance of land- and sea-based animals as well as migratory birds and plant life. On the other hand, the Antarctic has no permanent land-based animals, although there are migratory birds, as well as a rich marine life and limited plant life.

The differences in population patterns mark an important north-south disjunction in polar studies in general and in polar medicine in particular. The northern polar regions above 66 degrees latitude comprise a frozen sea that is surrounded by eight countries, each with its unique set of populations and medical care services. The countries of the Arctic are Canada, Finland, Greenland (Denmark), Iceland, Norway, Russia, Sweden, and the United States. Together, they make up approximately 8% of the earth's surface. Human population is scattered throughout the Arctic, with several relatively large urban areas, but for the most part, the Arctic is sparsely populated, totaling less than 1% of the world's population.[128] The overall estimated population of the Arctic as defined by the Antarctic Monitoring and Assessment Programme (AMAP) is approximately 4 million; indigenous peoples make up 10% of that population, and they constitute the majority of the total population in Greenland and in sparsely settled areas of northern Alaska and Canada.[51,65] Within the Arctic there are eight major indigenous peoples and more than 30 minority groups. Some of these peoples have separate governments, languages, and socioeconomic possibilities.

There are no indigenous peoples in Antarctica, which is regulated by the Antarctic Treaty, with 12 original and currently a total of 49 signatory countries, although only 28 contribute to the decision-making process.[5] This complex treaty helps delineate the relationships of the countries that are active in Antarctica and how the continent is to be best preserved and used for peaceful purposes. Seven countries claim territorial rights, which are held in abeyance while the treaty remains in force.[5] Of the 79 stations in Antarctica, 39 are operated year-round.[25] The total population living in Antarctica, all seasonal, now exceeds 4400 persons in the summer and well over 1100 in the winter.[20]

In the Arctic, there are two distinct but interacting populations, the indigenous Arctic inhabitants and visitors and immigrants. These populations have distinct but overlapping spectra of medical problems. Many of the medical problems among the Inuit, Sami, Chukchi, Nenet, and other northern groups are those of populations making the often Faustian demographic and cultural transition to a Western industrialized society. Thus, medical practice among these groups is similar to that among many other displaced indigenous populations. In some senses, the current illnesses and health risks of the indigenous Arctic populations are the results of contamination from distant sources and contact with other cultures.[15] In contrast, all medical problems in Antarctica occur in visitors, whether these visitors are staying for days or a year or more. Until the 1980s, the vast majority of these visitors, whether tourists, expeditioners, or scientists, were young and fit, and the medical problems they encountered reflected this. They were usually related to the environment or to trauma. The Antarctic visitor demographic has changed remarkably since then. Not only is there a steadily increasing number of older visitors with age-related medical problems, but now younger expeditioners and adventure sports participants visit on guided, commercial trips. They generally have little, if any, polar experience and are increasingly from countries with no tradition of polar life. This lack of experience renders them much more susceptible to environmental risks.

# IMPORTANCE OF POLAR MEDICINE

## INCREASES IN TOURISM AND EXPEDITIONS

The combined geographic polar regions cover about one-sixth of the earth's surface. Their territory in the imagination has been enlarged by several remarkable expeditions, and recent stunning photographic and video images have added to the popularity of the polar regions. This was fueled by worldwide interest in the celebrations of 2012 and 2013 marking the centenary of Amundsen and Scott's arrival at the South Pole. Despite or because of the forbidding environment, tourism of various sorts is increasing.[81] The Arctic is a trendy destination. An estimated 1.5 million tourists visit the Arctic each year, up from 1 million in the prior decade.[127] In 1980, it was estimated that a total of 31,000 paying tourists, adventurers, or guests of national scientific expeditions had ever visited Antarctica, but its increasing lure has led to explosive growth. According to International Association of Antarctica Tour Operators (IAATO) statistics, 37,405 tourist, staff, and crew visited Antarctica by air or ship in 2013-2014. Since 1989, tourists have visited approximately 200 sites, including 20 research stations in the Antarctic Peninsula region, the most common site for tourists. About 50 of these sites have received more than 100 visitors in any one season, and about the same number have been visited only once. Most visits are to one of 35 sites. Fewer than 10 sites receive around 10,000 visitors each season. The British Antarctic Survey (BAS) monitors Port Lockroy and maintains an ongoing program on the effects the 10,000 visitors per year have on wildlife and ecology of the area.[53,81]

Concerns about the dramatic increase in tourism and its effect on the ecosystem have led to a movement to limit the total number of tourist visits per year. The World Wildlife Fund and the United Nations have proposed guidelines to developing ecofriendly tourism in the Arctic. The guidelines cover its impact on the environment as well as on local populations. In April 2009 the consultative countries of the Antarctic Treaty endorsed a proposal to limit the size of cruise ships and the number of tourists who can go ashore at any one time and eventually make it binding to all parties.[127]

This increasing number of visitors and expeditioners has created interest in polar medicine, in particular as it relates to land-based and extreme expeditions. Wilderness medicine courses specific to polar medicine are now offered. Tourist vessels generally carry a physician and sometimes a nurse. The occasional expeditioner who needs rescue or assistance from a scientific station uses scarce resources.[26,81] One peculiar phenomenon is that when patients and medical/rescue/evacuation resources are from different countries, a complex flurry of high-level diplomatic interchange must often occur before help can be rendered.

Perhaps the most notable tourist fatalities were associated with the ill-fated skydiving venture at the South Pole, which resulted in the deaths of three of the four participants,[48] and the Air New Zealand Flight 901, a scheduled sightseeing DC10 that in 1979 crashed into Mt Erebus with death of all 257 people aboard.[87]

Hazards are inherent in any expedition and may well be the attraction for some participants. To be allowed to participate in risky activities, some tourists may fail to declare serious medical problems that later precipitate emergency medical evacuation. Thus, one real concern is increased risk taking and the consequences, or the dilemma between what is reasonable and what is foolhardy. From a medical perspective, making a risk assessment is multifactorial and differs for people, places, and goals. Hazards of an evacuation need to be assessed for both the patient and rescuers. Setting guidelines and anticipating needs in pre-event preparation are the keys to successful evacuation.[49] Because of the occasional tourist in need of expeditious medical evacuation, IAATO and other governmental groups have suggested requiring insurance to defray the costs associated with these evacuations. An increasing number of travel companies now insist on such insurance. A dedicated medical evacuation from continental Antarctica will cost upward of $250,000. There is also discussion of the ethical versus medicolegal implications of whether to render aid. The overriding issue should be care of the patient. In practice, there is a great deal of mutual assistance between companies and governments when life is at risk.

## GEOPOLITICAL CONCERNS

The interests of governments in polar regions have not lagged behind those of tourists. Political and territorial concerns have

been important in both polar regions. With increasing exploration of mineral and oil reserves and fishing potential, migrating humans will continue to bring medical problems with them. Although the Antarctic Treaty of 1959 prohibits territorial or commercial claims, seven nations have made sectoral claims on the continent. Some of these claims overlap and in the future may lead to a less-than-peaceful resolution. In early 2010, however, Australia failed to pursue Japan legally for ramming and sinking an antiwhaling boat in Antarctic waters supposedly governed by Australia. The most common reason given was that Australia feared that the International Court of Justice would nullify all territorial claims to and national governance over parts of the continent.

In 2007, the Russian minisubmarines Mir-1 and Mir-2 descended to 4300 m (14,108 feet) in the Arctic Ocean and placed a Russian flag on the seabed under the North Pole. The Russians were hoping that soil samples would prove that its Siberian ridge was directly connected to the Lomonsov Ridge, an underwater crest 1996 km (1240 miles) long running across the Arctic, and would lend credence to their territorial claim.

Concern about the environmental impact of increasing human activity in polar regions seems to be tempering the pace of development. As national resources diminish, however, the Antarctic may come under increasing pressure to open up to extraction industries, similar to the situation in the Arctic.

### INCREASES IN RESEARCH ACTIVITIES

Scientific research has been a part of polar exploration throughout this century. There are scientific and medical journals devoted to the polar regions, and thousands of articles are indexed each year in the *Antarctic Bibliography* (http://www.coldregions.org/antinfo.htm). The *International Journal of Circumpolar Health* (http://ijch.fi/Issues.htm) is a richer source for health issues in polar regions. Antarctic research continues to expand. All the continent's permanent stations are primarily there to support research. The largest study is the IceCube project at the South Pole station, which uses a series of downward-looking detectors spread over a square kilometer to look for traces of the notoriously elusive neutrinos. Neutrinos are produced when neutrons transform into protons during nuclear reactions. The detectors do not detect the neutrinos themselves, but rather the blue light emitted by the breakdown particle (a "muon") produced when a neutrino collides with an ice molecule. The source of these neutrinos coming up through the ice to the detectors may be black holes, gamma ray bursts, or supernova remnants and other extragalactic events. The muon preserves the direction of the original neutrino and thus points back toward its cosmic source. The IceCube project is at the forefront of astronomy and particle physics research. In 2014, a report on 3 years of analysis demonstrated a total of 37 high-energy neutrino strikes. The largest of these, detected on December 4, 2012, is nicknamed "Big Bird" and is the highest-energy neutrino interaction ever observed.[1] The South Pole also hosts two large telescopes.

Another huge project involving many countries at multiple sites across the Antarctic continent is ice-core drilling, designed to catalog climate change over tens of thousands of years. Other scientific endeavors include marine biology and ocean dynamics research; atmospheric and climatologic research, including air cleanliness monitoring and ice sheet movements; medical research (primarily at Japanese and Chinese stations)[84]; biologic research (ecosystems, penguins, seals, bacteria, lichen); seismic monitoring; aerial and sea floor mapping with unmanned vehicles in the harsh environment; paleontology; meteorite searches; and demonstrations of alternative power in extreme circumstances (e.g., wind generators at New Zealand's Scott Base).

Some observers have discerned a north-south split, perceiving research in Antarctica as having more of a political motivation and that in the Arctic as being more practical. For both scientific and political reasons, an important part of scientific research in polar regions concerns environmental issues. The remoteness of these regions enhances their value as benchmarks for studies of pollution. Indeed, several worrisome facts have been revealed about the contamination of formerly pristine wilderness, such as widespread radioactive contamination, the prolonged effective half-life of radioactive fallout deposits,[120,129] and increased chemical contamination, particularly in animals high on the food chain, with persistent organic compounds, heavy metals, and other contaminants affecting the environment and food supply.[71,129] Widening of the Antarctic ozone hole (discovered by BAS scientists in 1985) carries implications of increased ultraviolet (UV) radiation. As occupational and environmental health issues draw more attention, this aspect of polar medicine assumes greater importance.[30,31]

## BRIEF HISTORY OF HUMAN HABITATION IN POLAR REGIONS

A perspective on the contrasts between Arctic and Antarctic medicine may be sharpened by a brief summary of human habitation in polar areas. Humans are known to have inhabited Arctic regions for at least 4500 years. Anthropologists have uncovered evidence for several waves of population migration from Siberia through northern Canada to Greenland. Each of these migrations was probably linked to climatic conditions, and each resulted in a distinct set of cultures. The general pattern was of a nomadic life with population densities of approximately one person per 400 $km^2$ (154.4 square miles).[55,123] In more recent times, this long-established and remarkable adaptation to a hostile environment has been disturbed. The pace of cultural change increased dramatically during the second half of the 19th century, when the whaling industry moved into Hudson Bay, leading to sustained contact between Europeans and the Inuit. In the early part of the 20th century, religious missions, trading company posts, government stations, church missions, and eventually medical clinics and schools began to encourage permanent settlements, roughly quadrupling the population density.[55] In some areas, such as Eurasia, large industrial and mining cities arose. This change in population distribution has at times led to conflict between indigenous and European cultures, and it has had significant environmental and medical consequences.[130]

The known history of human exploration of Antarctica, unlike that of the Arctic, is quite recent. Recorded sightings of the continent date only to around 1800, and "winter-over" sojourns did not occur for another century. Waves of settlement also occurred in Antarctica: sealing in the early 19th century, whaling in the early 20th century, and scientific exploration since the mid-20th century.[123] The heroic era of Antarctic exploration occupied the early years of the 20th century, with exploits such as the highly publicized race for the South Pole between Roald Amundsen and Robert Scott in 1911; the extraordinary survival of the crew of the 1914 *Endurance* expedition, led by Ernest Shackleton;[64] and the heroic survival of Douglas Mawson, an Australian geologist who wintered alone after other expedition members perished.[75] Perhaps because of these and other dramatic events, and the absence of an indigenous population and a scarcity of easily exploited resources, human activities in the Antarctic have retained a somewhat more expeditionary flavor than in the Arctic. This has helped shape the contrasts in medical practice between the northern and southern polar regions.

## ARCTIC MEDICAL PROBLEMS

### EFFECTS OF CULTURAL AND DEMOGRAPHIC TRANSITION

The Arctic is not a homogeneous region. Although the population is only approximately 4 million, it is very diverse, with few features in common except the latitude of residence and hours of daylight. Medical problems among indigenous populations in the Arctic, approximately 10% of the total population, are characteristic of displaced aboriginal people elsewhere in the world. The wide-ranging interrelated factors include demographics, socioeconomic and physical environments, personal health practices, and availability of good-quality and culturally appropriate health care services.[13,56] Although increased contact with industrialized cultures has brought benefits, it has also brought many problems. Some of the benefits include greatly improved life expectancy,

largely because of a decrease in morbidity and mortality from infectious diseases and diseases of childhood (prevented by vaccines). Nevertheless, in indigenous Arctic peoples of the United States, Canada, and Greenland, infant mortality is higher and life expectancy is lower compared with Arctic dwellers in Nordic countries.[101] For many years, health care has lagged behind national norms in the Canadian Arctic, with infant mortality 2 to 3.5 times the national average.[118] Age-adjusted death rates are also telling, with 8.4 per 1000 Northern Canadian people, compared with 5.8 per 1000 for the Canadian national average; 14.3 per 1000 in Greenland; and up to 29.2 per 1000 in parts of Russia. Other striking statistics reveal a suicide rate in Nunavik six times that of the southern provinces of Canada,[63,124] and an unintentional accidental death rate three to four times higher than the national average. Tuberculosis has decreased but is still unacceptably prevalent at 47 per 100,000 persons. Diabetes mellitus has increased to 5% of the population of 30- to 39-year-olds, compared with 1% in the general Canadian population. In a population in whom dental caries were previously almost unknown, the need for restorative dental work is up to 60%. Widely prevalent alcoholism and tobacco use greatly contribute to these problems.[11,45,118]

As the Arctic environment and indigenous Arctic populations make the cultural and demographic transitions to a Western industrialized way of life, the spectrum of medical problems has shifted. Changing social patterns have resulted in disturbing trends: increasing numbers of young adolescent mothers, rising prevalence of gonorrhea and syphilis among Greenlanders, and concerns about other transmissible diseases, such as viral hepatitis and acquired immunodeficiency syndrome (AIDS).[80,134] The unwanted pregnancy/birth rate ratio in Greenland is approximately 1:1. Changes from the traditional diet and lifestyle have led to increased obesity, diabetes, cardiovascular disease, and mental health problems, including depression, binge drinking, alcoholism, and higher suicide rate.[13,118,124]

## ENVIRONMENTAL AND OCCUPATIONAL HEALTH PROBLEMS

Transboundary pollutants, primarily from Eurasia and the North American continent, have made deep and lasting changes.[11] The Arctic, once viewed as pristine, is now considered a pollutant sink. Even so, promising new data reflect that strict environmental control (e.g., bans/restrictions on uses and emissions of persistent organic pollutants [POPs]) is working.[51] The nuclear accident at Chernobyl in April 1986 led to cesium-134 and cesium-137 levels in reindeer meat 50 to 100 times those considered safe, forcing destruction of the Sami reindeer herds. During that same time, lake fishing and berry picking were curtailed because of contamination.[40,130] Fortunately, research 20 years after this accident demonstrates thriving flora and fauna even in the most contaminated areas, demonstrating a rebounding environment. Nevertheless, the young people exposed to the nuclear accident have shown an impressive increase in thyroid cancers, and those exposed to the highest doses of radiation show an increase in leukemias, solid cancers, and circulatory system diseases.[119] Industrial emissions from neighboring regions, including an estimated 100 million tons of sulfur dioxide, have led to the "Arctic haze" phenomenon, a gradual whitening of the historically deep-blue Arctic sky.[40]

Environmental impacts have had direct health consequences.[11,45] During the last 500 years, industrial pollution has led to a sevenfold increase in lead levels in human tissues in the Arctic.[40] Another survey found blood mercury levels above the normative limit in more than 10% of Sami reindeer herders in northern Finland. In North Greenland, a study revealed that in 84% of human mothers, blood mercury levels were above the World Health Organization provisional limit.[42] Oceans, rivers, and lakes reveal contamination and concentration of heavy metals in fish.[130] Further contamination of the food chain with long-lasting POPs, including polychlorinated biphenyls (PCBs) and many organic pesticides, is increasingly identified.[31] Long-term consequences of environmental pollutants on the health of the Arctic dwellers continue to be studied.[30] Recent work suggests that the endocrine-disrupting effects of PCBs may have changed the normal ratio of male-to-female births from 1.05 to 1.02 in the past 30 years.[13] It has been documented that the concentrations of PCBs in breast milk are seven times higher in the Arctic than in Quebec.[118] As previously noted, fallout from radioactive testing has caused river pollution, and other environmental degradations have affected the food chain, with an increase in certain cancers noted in both animals and humans.[137] Fear of the effect of pollutants has caused many to abandon or significantly limit their consumption of traditional foods (e.g., marine mammals, fish, terrestrial mammals, birds). Unfortunately, this can have negative nutritional effects, such as obesity, diabetes, and increased cardiovascular disease, and in some cases relative malnutrition.[41] Tragically, POPs, even in low concentrations, have been shown to cause increased risk for diabetes, so both consumption of traditional foods and changes in diet to processed foods have contributed to the increased rate of diabetes in these regions.[51] In some areas, consumption of traditional marine foods has led to blood levels of mercury exceeding current recommendations. Local health departments have to weigh overall nutritional benefits of traditional land and marine food sources against the potential long-term risks of neuropsychological and other potential health problems, particularly in newborns and infants.[71]

Fortunately, new trends show human exposure to pollutants in the Arctic is decreasing. For example, the number of Arctic childbearing-age women with excessive levels of PCBs, mercury, and lead is decreasing. This is believed to be a result of dietary changes and increased awareness of the problem. However, new research is demonstrating many additional chemicals, some newly developed, that have the potential to collect in the Arctic food chain, so ongoing research, identification of these chemicals, and their regulation are essential to continue improving the health of indigenous peoples.[51]

Nontoxicologic factors also make important contributions to Arctic morbidity and mortality. Accidents are more prevalent in the Arctic. In younger (up to age 35) Inuit groups, injuries account for approximately one-third of all deaths.[17] Although it has continued to decline since the early 1990s, it is striking that Alaska's occupational mortality is just over twice that of the U.S. national average mortality per 100,000 workers. However, this is greatly improved from five times the national average in the 1990s.[89] With establishment of the Alaska surveillance system in 1991, work-related deaths have decreased by approximately 65%, including a significant reduction in commercial fishing deaths and a sharp decline in helicopter logging–related deaths.[24] These data reflect in part the inherently hazardous working conditions and occupations and possible demographic biases of a young population. Other factors, however, may play a role. Because aircraft are a predominant mode of transportation in polar regions, it is not surprising that Alaska accounted for greater than one-third of all air crashes in the United States and 20% of the fatalities from 1990 to 2008.[88] Nonscheduled or commuter plane (<30 seats) flights, commonly used in isolated areas, pose a risk for fatal crash six times that of scheduled airline flights, a figure not surprising given the often extremely challenging flying conditions (terrain, weather, and isolated landing sites with limited navigational aids and operator error). In recent years, the pilot occupational fatality rate has fallen from 298 to 148 per 100,000 (less than twice the rate for all U.S. pilots), thought to result largely from increased awareness and proactive intervention in the industry, such as the implementation of automated remote weather stations, Global Positioning System (GPS), and terrain avoidance hardware and software.[88] Overall, the mortality rate for Alaska natives is 939 per 100,000 per year, compared with the overall U.S. rate of 698.9 per 100,000 per year.[51]

## PSYCHOSOCIAL HEALTH PROBLEMS

With social disruption and increased environmental and occupational health risks, psychological problems in the Arctic have achieved greater visibility in recent years. For a variety of reasons, stress seems to be higher in winter. One survey of over 7000 adults living north of the Arctic Circle found a prevalence of midwinter mental distress of 14% in men and 19% in women.[43]

Most other studies suggest that this figure may be low. One study among Inuit found that 22%, or one in five, experience depression during the winter months, and 7% appeared to have seasonal affective disorder.[39] Cultural stress, erosion of traditional lifestyles, and substance abuse are all contributory factors.[13] Studies investigating scientific staff at Arctic research stations are relatively uncommon but show patterns of sleep disturbances, depression, and alcohol use reminiscent of those in Antarctic stations.

The double apparent risk factors of high latitude and displaced indigenous populations have made alcohol abuse and concomitant violence a serious problem in the Arctic. In Greenland, one in three Inuit dies a violent death, and about 25,000 adults consume 28 million cans of beer a year, one of the highest per capita consumptions of alcohol in the world. Prevalence of "binge drinking" among Arctic peoples ranges from 12% to 39%, with male greater than female rates. Fetal alcohol syndrome is 13% higher in Alaska than in the continental United States.[13] One study compared alcohol consumption by the Greenland Inuit with nonindigenous local inhabitants and found that alcohol consumption was less among the Inuit. However, other studies found the reverse.[63]

Accidents are the leading cause of death in the Arctic, and one-third of these are estimated to be alcohol related. In the Canadian Arctic, alcohol consumption is 1.5 times the national average, and Inuit and Indians 15 to 24 years old have a suicide rate up to 11 times the national average. In some communities, for boys and men ages 15 to 29, suicides are the most common form of injury leading to death. It should be no surprise that life expectancy is lower, and infection rates for many diseases (e.g., tuberculosis, meningitis, syphilis) higher than in neighboring countries. Inuit communities have significantly lower incomes, and their housing is crowded and of poor quality. Traditional hunting and fishing no longer provide sufficient food or income to support many families. The association between poor health and social deprivation is well established.[63,86]

## CURRENT AND FUTURE TRENDS

In summary, indigenous populations of the Arctic show lower life expectancy, higher rates of infectious diseases, higher infant mortality, and higher rates of injuries and suicides compared with norms in their respective countries.[51] Fortunately, there are encouraging signs related to Arctic health care. The incidence of low birth weight, 5.5% in the central Canadian Arctic, has decreased, although it is still higher than that among non-Arctic dwellers.[13] Tuberculosis, which incapacitated up to 20% of the Canadian Inuit by 1950, has largely been brought under control, although the rate of occurrence is still as much as 10 times the national average.[17] In Greenland, there has been significant reduction in perinatal deaths. Having been 40 per 1000 births in 1975, it decreased to 25 per 1000 in 1995 and 15 per 1000 in 2009.[16] This is as a result of national guidelines, improved training, and introduction of ultrasound screening. High-risk pregnancies are identified as early as possible, with childbirth planned to occur in the main hospital in Nuuk, West Greenland. Despite these improvements, perinatal mortality is still significantly higher than for the rest of the developed world. This is the inevitable consequence of life in the polar regions. With long transfer-to-hospital distances, weather-dependent logistics, and limited medical resources, a sudden unexpected premature birth or obstetric complication is at high risk for a poor outcome. Trends in environmental and occupational health problems show increased monitoring, intervention, and improvement. Unfortunately, the age-adjusted incidence of diabetes mellitus is dramatically rising among First Nations populations.[28]

An important development in recent years has been the institution of trauma registries to track and target significant causes of morbidity and mortality. Recent research emphasizes that injury prevention is not solely a function of safer design of equipment but also a complex interplay of environment, activity, and people, notably including personal risk-taking behavior. If current trends continue toward greater economic independence and education of Arctic peoples, such potentially modifiable adverse health behaviors may recede in importance in coming years.[61,62]

There is increasing acknowledgment that isolated Inuit communities offer rich grounds for research. For example, a 2014 study from Greenland demonstrated that bacille Calmette-Guérin (BCG) vaccination significantly lowered the incidence of *Mycobacterium tuberculosis* infection and tuberculosis in Greenlandic children and young adults. This study was possible because the BCG vaccination, introduced there in 1955, was temporarily halted from 1991 to 1996 because of nationwide policy changes.[78]

# ANTARCTIC MEDICAL PRACTICE

Medical practice, problems, and their study in the Antarctic are somewhat different from those in the Arctic. Extreme isolation makes Antarctic medicine unique. Because of the remoteness, it may not be possible to medically evacuate (medevac) a patient for weeks or even months. It might be easier to medevac from the International Space Station than from some of the more remote Antarctic stations.[36] In general, the population residing at national Antarctic programs is adult, relatively young, and physically and mentally healthy. As previously, noted, however, the number of tourists of all ages visiting the Antarctic has increased dramatically, bringing with them a broad range of acute and chronic medical conditions.

## NATIONAL ANTARCTIC PROGRAMS

There are approximately 30 summer-only and 42 year-round national Antarctic program bases spread around the Peninsula and continent. The newest of these is the Chilean summer-only base, Glacier Union.

Winter-over personnel, including those spending a year or more at a time in Antarctica, are required to pass medical screening that varies in intensity with the various national programs. Most stations only house adults. There are two exceptions: Chile and Argentina have families living at their principal bases, Villa las Estrellas and Esperanza on King George Island. To date, 11 children have been born there. Some believe that the decision to house families here was politically driven to reinforce their respective sovereignty claims. All stations have some form of medical care, usually a station physician. The more temporary camps have varied medical support, ranging from first-aid wilderness responders to paramedics or midlevel providers with limited medical supplies. In general, the permanent year-round bases have more sophisticated facilities, with radiographic, laboratory, surgical, and dental provisions and a reasonably well-stocked pharmacy for expected emergencies. There is at least one physician and sometimes nurses and ancillary medical personnel.

## MEDICAL STATIONS IN ANTARCTICA

Medical facilities in the Antarctic polar regions can be conveniently divided into permanent and expeditionary facilities. As a result of community expectations and long-term commitment to research in Antarctica, a notable shift from an expeditionary to an operational attitude has occurred in many of the Antarctic programs. Figures 11-1 to 11-3 show the expeditionary facilities at Union Glacier field camp. This unit can be flown in and out of Antarctica by cargo plane.

What type of physician is needed? To paraphrase Grant,[36] the physician cannot be too specialized in approach; broad knowledge and a wide range of practical skills are necessary to provide good Antarctic medical care. Specialization in emergency medicine or the equivalent seems to be a suitable choice, especially to deal with emergencies. Bases usually have no room for anesthetists, surgeons, dermatologists, or psychiatrists; one person covers these roles. However, huge advances in satellite and video teleconferencing (VTC) enable polar physicians to access advice, counsel, and guidance. For a significant proportion of the Antarctic population, it is still extremely difficult and costly to evacuate patients.[36]

The following is a description of the personnel and facilities in the U.S. Antarctic Program; other nations maintain similar facilities. McMurdo Station (MCM) (Figures 11-4 to 11-8) has the largest population: about 200 in the winter and 1200 in the

**FIGURE 11-1** Medical facility, Antarctic Logistics and Expeditions Field Camp, Union Glacier. *(Courtesy Martin Rhodes.)*

**FIGURE 11-2** Medical facility, Antarctic Logistics and Expeditions Field Camp, Union Glacier. *(Courtesy Martin Rhodes.)*

**FIGURE 11-3** Medical facility, Antarctic Logistics and Expeditions Field Camp, Union Glacier. *(Courtesy Martin Rhodes.)*

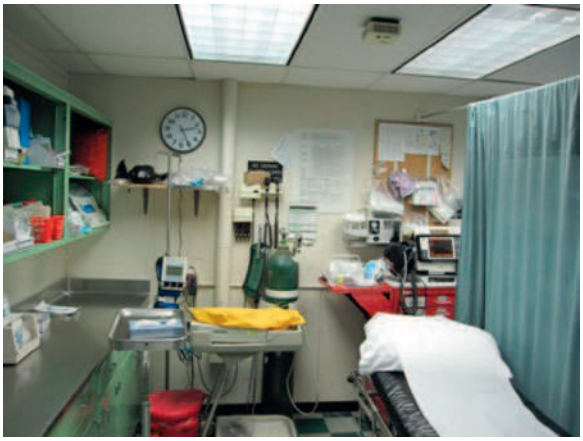


**FIGURE 11-4** McMurdo Station medical facility—main area. *(Courtesy Kenneth V. Iserson.)*

**FIGURE 11-5** McMurdo Station medical facility—pharmacy. *(Courtesy Kenneth V. Iserson.)*

**FIGURE 11-6** McMurdo Station medical facility—reception area. *(Courtesy Kenneth V. Iserson.)*

**FIGURE 11-7** McMurdo Station medical facility—side view. *(Courtesy Kenneth V. Iserson.)*


**FIGURE 11-8** McMurdo Station medical facility sign. *(Courtesy Kenneth V. Iserson.)*

summer. Whereas the winter MCM and South Pole populations are isolated, their summer populations constantly have an influx of rotating personnel that bring new diseases. In the summer season, the medical component is staffed with two physicians, a physician's assistant or nurse practitioner, an Air Force flight surgeon, a dentist, a radiologic technologist, a laboratory technician, and a physical therapist. In the winter, the staff is composed of one physician, a physician's assistant, and a physical therapist. All are cross-trained on site. (Other large national stations provide necessary additional training in advance.) In addition, MCM has a full fire department with paramedics who respond to emergencies on station. The South Pole population peaks at 250-plus in summers and reaches a nadir of about 50 in the winter. There is one physician, a physician's assistant or nurse practitioner, and a volunteer trauma team trained on station. Palmer Station is the smallest, with a population of 45 in the summer and a low of 10 to 20 persons in the winter. There is one physician, and volunteers are trained on site to provide assistance. How well these volunteers can function was demonstrated in 2009 when the station's physician developed a peritonsillar abscess. She had one of the station emergency medical technicians needle-drain and then incise it under topical and local anesthesia. She then used VTC and an intraoral camera to consult with an otolaryngologist based in the United States. She improved within a few days.[29]

The Australian stations have one physician. Before deployment, there is a 2-week training course for two of the crew in operating-theater nursing skills and for two persons in anesthesia assisting. The predeployment training has proved valuable, as was clearly demonstrated in the case of a scientist who fell into a crevasse and suffered serious injuries, including internal bleeding, that required on-site surgery (Figure 11-9).[106]

All permanent U.S. medical facilities have digital radiograph and ultrasound capabilities, laboratory equipment for blood chemistries and cardiac enzymes, and the capability to perform immunologic testing for β-hemolytic *Streptococcus,* infectious mononucleosis, and influenza A, as well as common resuscitative equipment, including Life Pak 12 and Zoll monitor/defibrillators, portable ventilators, and crash carts similar to those in most emergency departments.

The pharmacies are well stocked and cover a broad range of potential medical problems. There is no blood storage, but in the event of significant bleeding, a "walking blood bank" (walk-in donor system) is activated. To facilitate this process, all winter-over and most summer personnel are blood-typed and screened for hepatitis B and C and human immunodeficiency virus (HIV). After a series of acute cholelithiasis cases, South Pole winter-over personnel are now screened with ultrasound for gallbladder disease. The Australian physician undergoes prophylactic appendectomy. Otherwise, the experience has been that early antibiotic therapy can abort an acute appendicitis attack, allowing the appendix to be removed electively at a later time.

The South Pole does not have 24-hour satellite coverage, but year-round stations have facilities for telemedicine, including live camera, still photos, fax, and digital radiography for transmission and consultation via satellite and the Internet. VTC, used for many years in Antarctica by multiple programs,[36] came of age at the South Pole in 2002 with a midwinter repair of a patellar tendon rupture. The tendon was surgically reattached by the base physician under the direction of consultants at major medical centers via live video and voice connection. Various physicians at Antarctic stations are also able to consult with colleagues via VTC, such as with the South Pole medical staff's successful management of a severely hypotensive tourist in 2009 with VTC input from MCM clinicians. In addition, telemedicine has been used for diagnosis and consultation in the treatment of a wide variety of ailments, including acute cholecystitis, ophthalmologic lesions, pancreatitis, pericarditis, fracture treatment, psychological consultations, radiologic reports, and many other situations. Telemedicine has improved the quality and availability of sophisticated care in these and other remote, hostile environments.

Medevacs are frequently dangerous and costly. Summer is the only season during which some stations can be reached for an evacuation. Winter evacuations are infrequent, very dangerous, and costly. Logistically, it may be 2 or more weeks before a rescue can take place, and for some stations, it may not even be

**FIGURE 11-9** Trauma and rescue teams are frequently composed of volunteers and at least one experienced, trained individual. This rescuer is practicing for possible extrication of a victim from a crevasse. *(Courtesy Betty Carlisle.)*

**FIGURE 11-10** Historic midwinter rescue at the South Pole. Twin Otter aircraft flown by pilots from Canadian Kenn Borek Air Service.

possible. A historic medical evacuation from the South Pole was undertaken in winter 2001 with the first successful landing of a twin Otter aircraft in full darkness at a temperature of −68.9°C (−92°F) (Figure 11-10). This event, while fraught with danger, has opened new possibilities and has been repeated.[18,21]

To increase further the ability to provide medical assistance, even during the winter months, the U.S. Air Force recently proved their capability of landing C-17 aircraft at MCM using night-vision goggles and made successful air drops of critical equipment at the South Pole. Certainly, however, prevention through careful screening of candidates and increased use of telemedicine as a way to avoid medevacs still remains the ultimate goal.

To reduce the number of medical crises and need for urgent medical evacuations, all participants must pass a "physical qualification test." Medical clearance criteria are used as a screening tool. To establish appropriate guidelines, evidence-based criteria from the medical literature, historical data of the U.S. Antarctic Program, and guidelines from other programs, such as the National Aeronautics and Space Administration (NASA), the Peace Corps, and the U.S. Navy, that have activities in remote areas were used. What appears to be lacking is screening for body mass index and alcoholism. However, up to 30% of *all* medical evacuations (both emergent and urgent) have been for trauma; that is, they were not related to the evaluation criteria. Of emergent and urgent evacuations, 10% were for gastrointestinal (GI) and 8% for cardiovascular reasons (Figure 11-11). Considering only truly emergent medical evacuations, 28% were for cardiovascular and 28% were for GI reasons. Figure 11-12 is a chart showing the number of medevacs from MCM and the South Pole station.

## SOMATIC HEALTH PROBLEMS

Many of the primarily somatic health problems in Antarctica relate to cold, altitude, and trauma and are thoroughly covered in the chapters on these topics. In a midwinter setting where a tossed mug of coffee freezes before the liquid hits the ground, the dangers of frostbite are clear. Anyone gasping for breath after climbing the six flights of stairs with 92 steps from the tunnel to the living area of the South Pole's elevated station, or who has lost 5 kg (11 lb) in the first 2 weeks merely from resting tachycardia and tachypnea, can appreciate the physiologic stresses of rapid ascent to an equivalent of 3200 m (10,499 feet). Likewise, the dangers of UV exposure at altitude with an ozone hole and snow surface reflectance of 80% to 90% can become painfully evident to the unwary visitor.[22,117]

### Cold-Related Problems

Cold is a dominant factor in polar medicine. It can be a source of humor, such as the infamous "300 Degree Club" at the South Pole. Membership requires sprinting, while somewhat less than

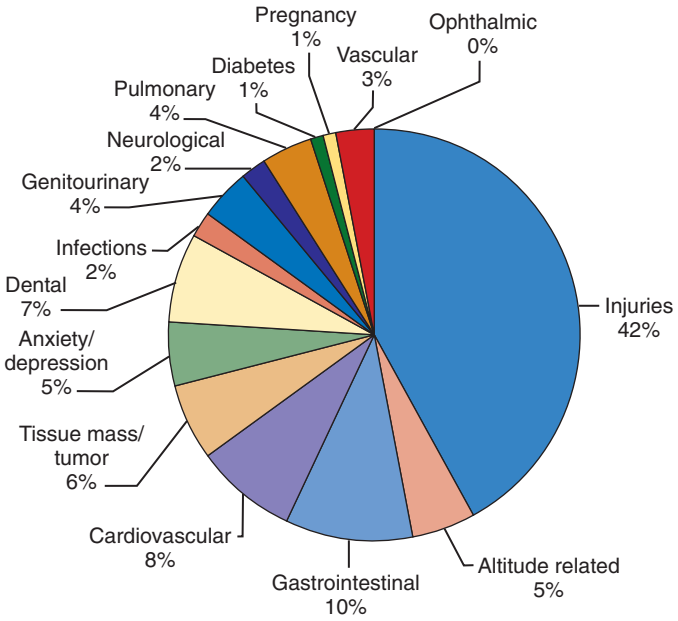



**FIGURE 11-11** Evacuations for medical reasons, with percentages of 5-year totals (1998-2003). *(From Mahar H [Safety and Health Officer, OPP/NSF]: Medical clearance criteria: Revalidation study. Personal communication, 2003.)*

completely clothed, from a 93.3°C (200°F) sauna to the Pole outside at an ambient temperature of −73.3°C (−100°F) or lower. Similarly, the quintessential polar first-aid story involves creative solutions to the problem of finding warm fluids,[3] but it would be reckless to forget the ever-present danger of such a hostile environment. Windchill typically drops the effective temperature on exposed skin far below −73°C. It has been estimated that under the most severe winter conditions, an inactive person in full polar clothing could undergo a life-threatening drop in core temperature in only 20 minutes. Airplane refueling crews and others working with liquids at polar ambient temperatures are constantly reminded that even a small splash can mean instant frostbite.[34]

Rescue and treatment are complicated by the additional need for both victim and rescuer to avoid hypothermia and frostbite.[55,57] Disorientation and confusion from hypothermia,

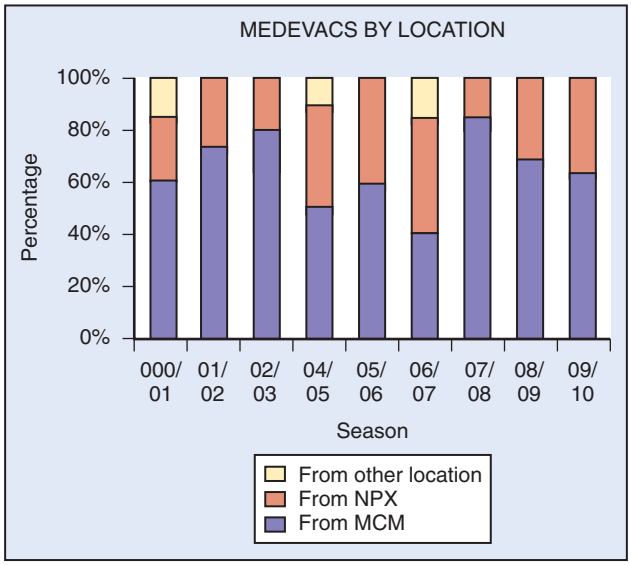



**FIGURE 11-12** Number of medical evacuations (medevacs) from McMurdo Station *(MCM)* and the South Pole station *(NPX)*.

**FIGURE 11-13** Clothing is an important topic in polar medicine. A researcher prepares to leave the station for an extended time at –56.7°C (–70°F). The total weight of his clothes is 11.5 kg (25.4 lb). Notice the multiple layers for each area of the body. *(Courtesy Stephen Warren.)*

clumsiness from bulky clothing, and degraded performance characteristics of equipment and intravenous (IV) fluids can complicate otherwise straightforward procedures. A recent case report describes almost immediate freezing of fluid in IV lines and shattering of the plastic IV tubing despite vigorous attempts to warm them.[57] Simple devices commonly used in warmer settings, such as air splints and pneumatic antishock garments, would be similarly unusable. In more sophisticated equipment, batteries rapidly fail, unwinterized mechanical moving parts seize up, and metal objects become dangerous sources of frostbite.

Clothing, not normally considered a medical topic, assumes special importance in the polar environment[76,104] (Figure 11-13). Although the clothing used for many polar research programs in the summer seems adequate, a strong argument can be made for specialized winter gear, possibly adapted from the space program, that would allow relatively delicate manipulation of scientific equipment while offering protection from the cold. In fact, at temperatures below those of most military specifications, material properties of equipment, including plastic electrical insulation, create unexpected hazards, such as splitting of insulation and other plastics, and extreme rigidity of cables and hoses such that they cannot be used. Fortunately, the importance of ergonomic issues in the design of machinery and clothing for polar conditions is receiving increased attention.[47,132] There is new research on use of personal heaters, which are particularly effective for extreme cold and for sedentary work in the cold.[110] Phase-change material can store latent heat and then release it during periods of low activity.[104] These newer materials will allow thinner gloves with high thermal protection to be worn for work in the cold that requires dexterity, and they will be particularly effective for persons whose efforts alternate between heavy work that can produce sweating and light work with associated cooling (Figure 11-14). In addition, as phase-change material clothing becomes readily available, clothing will be lighter and less bulky, particularly advantageous when doing intricate work in the cold as well as alternating active with sedentary work in the cold.

## Altitude Illnesses

Altitude illness can be a major issue at many Antarctic stations, camps, and research locations, including the South Pole, Vostok, and Mt Erebus. A literature-based approach to preventing altitude illness with the least possible adverse outcomes over the season was to administer acetazolamide (Diamox), 250 mg twice per day, starting 24 hours before altitude exposure. Participants voluntarily took this medication for an additional 3 days of exposure. If the individual still had symptoms, such as observed periodic breathing or headache, the dose would be increased to three times a day. Dexamethasone (Decadron), 4 mg twice a day beginning the day of ascent, was used as an alternative for persons who had experienced serious side effects or allergic reactions, who had an allergy to sulfa-containing medications, or who had no notice before having to ascend to high altitude. This was also continued for 3 days at altitude. After 3 days at altitude, the body's own compensatory mechanisms have had time to adjust to the new environment, and the medication is no longer needed.

Because medication use was voluntary, complications seen from not taking it included high-altitude pulmonary edema requiring use of a Gamow bag before urgent evacuation, relative hypoxemia, and decreased work tolerance. Complications from taking acetazolamide included dehydration and electrolyte abnormalities in patients who were already ill or had severe underlying diseases.[54] See Chapters 2 and 3 for current recommendations for prophylaxis and treatment of high-altitude–related illnesses.

## Nutritional Studies

Nutrition occupies a key niche throughout the history of polar expeditions. Early expeditions in both polar regions provided several examples of nutritional illnesses, including scurvy and possible hypervitaminosis A and lead poisoning. More sophisticated nutritional analyses have been possible during recent expeditions,[117,121] and advances continue to be made in development of lightweight but nutritionally dense rations. When participants in endurance events are well trained, it is possible to compete without loss of lean body mass.[73] Although many prolonged, unsupported expeditions include an element of malnutrition or even starvation, protein synthesis is still active.[121,122]

During a Canadian-Soviet transpolar ski trek, participants skiing approximately 20 km/day (12.4 miles/day) at a speed of about 3.5 km/hr (2.2 miles/hr) while carrying 37- to 45-kg (81.6- to 99.2-lb) packs showed increased strength, decreased body fat, and increased high-density lipoprotein cholesterol. A paradoxical drop in aerobic power was noticed, perhaps because of intensive pretraining and conditioning, as well as increased efficiency of skiing as the trip progressed. More recently, in a nonsupported, two-man, 86-day trans-Greenland trip, well-trained and experienced skiers eating an adequate caloric diet had little if any significant impairment. Their average energy intake in rugged terrain was 28 to 34 kilojoules (kJ) per day (6688 to 8121 calories/day) and in level terrain 14 to 16 kJ/day (3344 to 3822 cal/day).[34] Although applicability of these figures to more sedentary polar

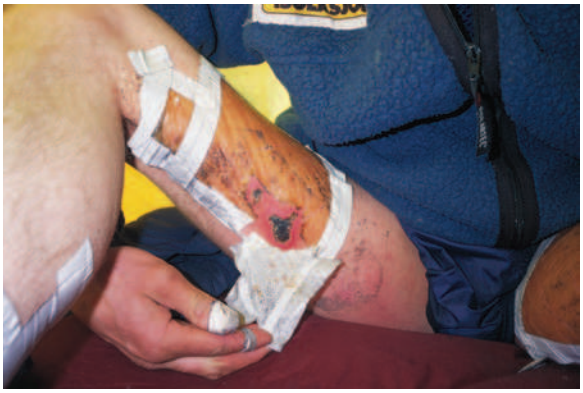


**FIGURE 11-14** Frostbite on thigh with eschar. Newer phase-change materials would have prevented this injury. This skier across Antarctica suffered frostbite when he removed one layer of insulating clothing to avoid sweating on a calm sunny day. When a wind came up, it caused frostbite through the wind pants and light insulation. *(Courtesy Borge Ousland.)*

sojourners is probably limited, work is being done to alter the diets of more sedentary expeditions to improve the lipid profile of participants.[74] Better availability of common foods and fresh fruits and vegetables during the summer and frozen foods in the winter at the permanent stations allow participants to choose a healthier diet. However, frequent fried and high-fat food intake leads to elevation of lipid profiles and the associated increase in cardiovascular risks. Some studies have demonstrated that it is possible to make simple and acceptable changes in food preparation that have a significant impact on lowering cardiovascular risk factors of winter-over personnel.[7,74]

An area that has received increased attention involves the possibility that the prolonged low dose of sunlight may have long-term effects on bone metabolism and immune and cardiovascular systems. One study showed a decrease in the 25-hydroxy metabolite of vitamin D (25OHD) as UV radiation ceased. However, the active metabolite 1,25-dihydroxyvitamin D (1,25[OH]2D) did not show such variation.[105] A few studies have demonstrated significant decreases in serum vitamin D as measured by 1,25(OH)2D and associated increases in serum osteocalcin during the dark period, possibly indicating bone remodeling.[138] Another study, in which low doses of vitamin D were given, showed increased bone mass in lumbar vertebrae and leg bones, but no bone mass increase in the pelvis or upper extremities. This was thought to be the result of vigorous activity over the winter. The study also showed a decrease in serum calcium and 25OHD levels during the winter.[90] A study was undertaken in the 2003-2004 Antarctic summer and followed 53 Australian expeditioners for 2 years. It showed that they became vitamin D deficient after just a few months; after 12 months, this began to result in loss of bone density. Further study is planned to identify the minimal dose of supplementation needed to prevent deficiency and whether these expeditioners have greater risk for developing osteoporosis later in life.[58] Because many participants return for successive winters, further studies are needed to delineate possible long-term effects of bone mass after redeployment.

## Infection and Epidemiology

With particular reference to the space station analogy, a number of studies have taken advantage of the physical isolation of Antarctic stations as a natural laboratory for infectious disease epidemiology. Because microorganisms are believed not to survive the extreme cold long enough to be carried in by winds, midwinter respiratory tract infection outbreaks in the absence of outside contacts have suggested that such organisms could persist in clothing or other fomites.[102]

Despite a widely reported leukopenia, decrease in cell-mediated immunity, and decreases in salivary IgA and IgM during the isolation of wintering over, it is not clear whether persons emerging from Antarctic stations are more susceptible to infection,[33] or whether the changes in immunity are related to the stress associated with a winter-over.

## Circadian Rhythms, Endocrine Studies, and Sleep Research

Pioneering studies of Natani and colleagues[83] on sleep electroencephalograms at the old South Pole station demonstrated clear patterns of sleep disturbances and "free cycling" of the sleep–activity cycle. Some of these findings have been extended in more recent studies. For example, among four subjects at a small winter-over camp, summer sleep cycles synchronized within the group and with clock time. During 126 days of sunless winter, rhythms free-cycled in all four people and then resynchronized with reappearance of the sun.[60] The degree of synchrony versus free cycling appears to depend on a number of factors, notably *zeitgeber* strength (an environmental agent or event that provides the cue for setting or resetting a biologic clock, i.e., activities, social contacts, and the most important zeitgeber in nature, light).[35] Studies in Indian stations also confirm continuing sleep pattern changes.[14]

A number of studies have examined the effect of prolonged polar residence on diurnal variations in the level of melatonin. Its important role in free radical scavenging and sleep regulation is beginning to be elucidated.[59] Melatonin has been studied as a chronobiotic and is used as a supplement to treat circadian rhythm disorders.[6,113] Of the various studies using melatonin to treat sleep disorders, including delayed sleep phase and for night-shift workers, most have only small numbers of participants. Although the initial studies are promising, more research needs to be done. It appears that exogenous melatonin can be used effectively for most persons. The short-term side effects (headache, nausea, drowsiness) are few. There are no long-term studies. Use of blue-enriched white light in the workplace improved alertness, performance, and sleep quality, as well as daily resetting of the melatonin cycle.[32,79,113]

Other endocrine fluctuations also appear to be correlated with the length of the day.[127] Some endocrine studies have examined the effects of prolonged residence in polar regions with a longer-than-diurnal time constant. Twenty-four-hour urinary excretion of catecholamines increases in the cold, but social stresses appear to overwhelm climatic determinants of catecholamine metabolism, correlating with increases in diastolic blood pressure and pulse during the year.[44] A more consistent pattern of elevated thyroid-stimulating hormone (TSH), decreased free thyroid hormones, and increased triiodothyronine ($T_3$) clearance after several months has been demonstrated. It has been suggested that rapid clearance of $T_3$ is caused by the cold. A pattern of increased pituitary release of TSH in response to IV thyrotropin-releasing hormone and increased serum clearance of orally administered $T_3$ has been identified and dubbed the "polar $T_3$ syndrome."[27] The full clinical significance of these findings remains unclear, but the $T_3$ may well be related to the winter-over syndrome (see later).[91,99] Several studies that used thyroxine ($T_4$) supplementation noted improvement in midwinter cognitive function, mood, and vigor.[106,109,131]

## Environmental Health Issues

Because of Antarctica's isolation, it seems a particularly disturbing site for litter and pollution. As in the Arctic, events such as the early problems with a nuclear reactor at MCM (since removed) and the 1989 oil spill from the *Bahia Paraiso* near Palmer Station, as well as studies by groups such as Greenpeace, have focused attention on environmental health risks in the Antarctic.[82,129] Environmental inspections at a broad range of Antarctic stations have raised concern about toxic effluents and heavy-metal residues, as well as radioisotopes used for research. To address these issues, a number of countries have begun to implement more responsible waste management and water-monitoring policies and are taking corrective actions. Most have active recycling programs in place, and many cleanups are in progress or have been completed. Currently, most stations, including all U.S. stations, discharge raw sewage. Proposals are in place to find a way to ameliorate the contamination from raw sewage that is discharged into the sea and into large bubble holes in the ice for the inland stations. The BAS Rothera Station installed a sewage treatment plant, with significant improvement in the near-shore marine environment.[50,52,77]

## Occupational Health and Injury Prevention

Rigorous studies of risk are important for injury prevention. Unfortunately, they are complex and often bedeviled by challenges, including controversial data, multiple variables, and biases. For example, for purposes of occupational epidemiology, it may ultimately prove useful to stratify the Antarctic sojourner population into groups such as sport expeditions, military, commercial, and scientific, but the health behaviors of these groups overlap, and few studies have gone beyond aggregate descriptive statistics. There is no current system for archiving these data, except by individual programs or organizations; therefore much of the data is not available for review. There were plans to address this issue at the Council of Managers of National Antarctic Programs (COMNAP) at the planning meeting for the International Polar Year of 2007-2008.[10] Unfortunately, because of funding issues, this has not been done.[37]

Even from these broad statistics, some figures emerge that may be useful cognitive anchors. There were 16 fatalities from 1947 to 1999 in the Australian Antarctic Program, but only one fatality in the past decade. Among 3500 scientists and support

personnel (2000 person-years), there were four medical deaths, two myocardial infarctions, one case of appendicitis, one perforated gastric ulcer, and one cerebral hemorrhage. The remainder of the events were accidents involving falls, head injuries, hypothermia, drowning, crush injury, and burns.[68,70]

There have been 60 deaths in the U.S. Antarctic Program since 1946.[2] These can be ranked by cause: aviation, 61%; vehicles, 11%; ships, 7%; recreational, 7%; station/industrial, 5%; field activities, 5%; and other, 4%.[72] Although it is difficult to adhere to standard occupational safety practices when in a remote location, new guidelines and serious efforts in some of the programs have led to improved worker and participant safety.

A review of data for the Australian National Antarctic Research Expedition (ANARE) 2002-2003 season listed the following reasons for medical consultation: medical (e.g., upper respiratory, GI), 39%; injuries (sprains, strains, dermatologic, lacerations, fractures), 27%; follow-up visits, 24%; and preventive (immunizations, midyear examinations, wellness programs), 10%.[19] For the 2004-2005 season, Antarctica New Zealand (ANZ) reported musculoskeletal, 42%; medical (e.g., upper respiratory infections, GI), 22%; other injuries, 20%; dermatologic, 15%; and preventive, dental, and other, 8%.[103] Usually, most visits are related to injuries, and the next most frequent medical clinic visits are attributable to upper respiratory infections. Environmental problems include dry skin and fissures, particularly on fingertips as a result of cold and very dry conditions. Cyanoacrylate glue hastens healing of disabling fingertip and heel fissures.[8] Cold-induced urticaria, frostnip, and frostbite are frequently underreported, except for moderate to severe cases. Small nasal bleeds occur frequently, but they rarely require treatment beyond instruction to use petrolatum or antibiotic/antiseptic ointment once or twice daily to protect the delicate nasal epithelium, which easily becomes dehydrated or can sustain frostnip. Although the bulk of care is limited to routine visits, the pathologic conditions encountered even among this carefully screened population have included myocardial infarctions, massive GI bleeds, unreported Crohn's disease, bowel obstructions, acute cholelithiasis with pancreatitis, pulmonary emboli, massive head injuries, fractures, crush injuries, newly diagnosed schizophrenia, and cancer.

## Fire Safety

In light of the extreme cold, it is somewhat counterintuitive that fire is a major concern and significant danger at all Antarctic stations. This surprising assessment rests on a number of factors. Cold temperatures severely limit the utility of water for fire suppression. Firefighting equipment may become inoperative in extreme cold, and frequent high winds can fan fires. The extremely low absolute humidity in many polar regions results in an even lower relative humidity when outside air is warmed in station dwellings. This in turn leads to increased static electricity and dryness of combustibles, already at risk from frequent use of space heaters. In addition, alternative food, shelter, and fuel are limited.

Elaborate predeployment training, frequent on-site drills, and keen awareness of potential fire hazards have correlated with a satisfactory fire safety record to date, but this good fortune cannot be taken for granted. One of the most life-threatening events was the explosion and fire at Vostok in 1982, leaving the station essentially without power or adequate heat. Only one person died, but there were several injuries, and the winter crew had to endure 8 months without a power plant to supply heat.[107] In 2001 the BAS Rothera Station lost its new Bonner Lab building when an electrical short started a fire. No one was injured, but with 50- to 70-knot winds, little could be done to save the station.[12] Although fire-suppression systems are built into the newer buildings, a historic A-frame building at New Zealand's Scott Base burned down in May 2009 and, much more seriously, a two-story building at Russia's Progress Station burned down in October 2008, killing one person and seriously injuring two others. Because the building contained their radio equipment, they could not contact the outside world for 4 days after the event. Fatal fires continue; in 2012, two staff members died in a fire at Brazil's Comandante Ferraz base on King George Island. In Antarctica, fire is an ever-present threat.

## National Programs' Responsibilities for Tourist Safety

As transportation increasingly opens up previously inaccessible areas, this image attracts growing tourist traffic and, with it, heated debate from both legal and environmental viewpoints.[116] The essential medicolegal issue is the extent of governmental organizations' responsibility for medical care of participants in nongovernmental activities, whether scientific, political, or commercial. Although this discussion started much earlier, it is ongoing.[81] When a tourist group requires aid beyond its own capabilities, whose responsibility is it? To what extent should a research station with limited medical supplies be required to divert some of those supplies to an individual who presumably bears responsibility for planning his or her own medical coverage? By default, stations provide what assistance they can, although they often try to bill tourist companies and their insurance agencies for costs involved in patient treatment or transport. The Antarctic Treaty Consultative Meeting XXXI provided attendees with a list of guidelines recommended before trips to Antarctica, including travel insurance, contingency plans, and other necessary equipment.[4]

## Air Safety

As in the Arctic, reliance on aircraft for transportation has highlighted the critical importance of air safety. The worst Antarctic air accident was the crash of an Air New Zealand tourist "flightseeing" DC-10 on Mt Erebus in November 1979.[87] This accident killed all 257 people aboard and temporarily ended such flights, although IAATO records indicate that overflights are now happening with new guidelines in place. There have been 35 air-related fatalities in the U.S. Antarctic Program since 1946 from crashes related to either fixed-wing or rotor aircraft.[72,116] A ski-equipped LC-130 Hercules crashed at the remote D-59 camp in 1971 (Figure 11-15). Fortunately, none of the 10 crew members aboard was injured. During a salvage operation in 1987, however, another LC-130 bringing supplies to D-59 crashed nearby, killing two and injuring nine. More recently, a helicopter crash occurred in the dry valleys; both the pilot and passenger were seriously injured. After a weather delay, they were extricated and evacuated to New Zealand for definitive care.[19,85] With better weather prediction and increased safety standards, the accident profile is improving. However, in 2010, there was a fatal helicopter crash near the Dumont d'Urville station that killed four persons. In January 2013, a Kenn Borek Air DHC-6 Twin Otter crashed near the summit of Mt Elizabeth in the Queen Alexandra range on a flight from the South Pole to the Italian base at Terra Nova Bay. All three crew members perished.


**FIGURE 11-15** LC-130 Hercules partially stuck in a hidden crevasse, demonstrating the inherent hazards of working in Antarctica. *(Courtesy National Science Foundation photo archive.)*

## PSYCHOSOCIAL HEALTH PROBLEMS

As the U.S. *Polar Manual* explained in 1965, "No psychiatric case ever got better in the cold."[46] For many, polar living arrangements and psychosocial issues may be more important than the strictly medical or environmental factors. Psychiatric problems are mentioned even in reports of early expeditions, and almost any participant in expeditions will recognize Thor Heyerdahl's observation: "The most insidious danger on any expedition where men have to rub shoulders for weeks is a mental sickness that might be called 'expedition fever'—a psychological condition that makes even the most peaceful person irritable, angry, furious, absolutely desperate because his perceptive capacity gradually shrinks until he sees only his companions' faults while their good qualities are no longer recorded by his grey matter."[126]

Most psychological problems, primarily sleep disturbances, are minor and temporary. Many disturbances are more related to the social environment than to the physical environment.[93,112] Appropriate lighting or changes in photo periodicity (the duration of daylight and darkness in a 24-hour period) help improve mood and sleep.[95,133] In addition to appropriate exercise facilities, opportunities for quality mental stimulation and frequent contact with friends and family via the Internet and telephone can help maintain stability. Except for insomnia, which may be endemic, the incidence of psychiatric problems is lower than expected in the overall population.

Not all psychiatric events are benign. One author witnessed an acute psychosis in a worker who was threatening to set fire to the base and kill a colleague with a shovel, apparently the result of the stress of a dysfunctional work relationship.

Many nations use formal and informal psychological screening, especially for participants planning to winter-over in Antarctica. How well the screens function is debatable. A British study showed that an extensive psychological screening examination weeded out many participants with problems with "defensive-hostility" and "emotion-focused coping." Simple interviews did not identify these problems.[38]

### Alcohol Abuse

Adjustment to psychosocial stresses in polar communities depends on a complex array of sociocultural factors. One coping mechanism is alcohol use. As in many isolated communities at high latitudes, alcohol use can disrupt or lubricate social interactions. In the U.S. Antarctic Program, summer support-staff members have been terminated for alcohol abuse, and both summer and winter-over staff are occasionally prohibited from purchasing alcohol. In some cases, interventions with group support are effective. At many Antarctic stations, alcohol is easily available and may be subsidized. In some stations, rations can be excessive or nonexistent. Observations are that at least 50% of recreational injuries are alcohol related. Recommendations have called for routine monitoring of alcohol levels of anyone involved in an accident,[116] or even prohibition of alcohol at Antarctic stations. However, as with prohibition in other countries, this might create more problems than it might solve. Judicious use of monitoring can help identify persons who may need intervention before an accident happens.

### Psychoneuroimmunology

Psychological stress at research stations may arise from several sources. One is the environment itself; environmental severity has been found to be an independent predictor of hostility and anxiety after wintering over.[94] Perhaps more important is the perception of the environment. Newcomers to the South Pole station are usually observed wearing a full 12-kg (26.5-lb) polar outfit at −20° C (−4° F) for several weeks after arrival. By midwinter, the same individuals think little of walking short distances in only workout shorts and a T-shirt at −60° (−76° F).

Stress can also result from disjunction between a person's original motivation for joining the program and the realities of life in the station, that is, the sociocultural environment. This may be the greatest determinant of difficulties.[94] Studies suggest that people who go to Antarctic stations to seek thrills or to challenge themselves often have more difficulty sustaining their motivation and performance than those who go to accomplish a scientific mission or even those primarily motivated to earn money. In general, older individuals who are somewhat introverted are able to set work goals and work toward them, and persons who have broadly defined hobby interests seem to cope better with the social isolation and dynamics of wintering over. One study found that members with low social coherence reported significantly more depression, anxiety, and anger than did individuals belonging to expeditions with high social cohesion.[92,134]

## SMALL-GROUP DYNAMICS

In addition to external climate and internal motivational factors, stress can arise from interpersonal interactions. Although there are many exceptions, participants in the Antarctic program often speak of a tendency for personnel to form cliques or microcultures. People may cluster according to ordinary personal chemistry, along lines of OAE (Old Antarctic Explorer) versus novice, winter-over versus summer status, or according to scientific, civilian, or military affiliation. With time, such social clusters can be a source of support or of friction. In an attempt to unify the core group, winter-overs participate in a mini–Outward Bound type of group bonding experience before deployment.

Social isolation is an important factor in polar communities, although this isolation has been lessened by modern communications and transportation. A number of studies have drawn parallels between group processes in polar stations and those in other isolated and confined environments, such as submarines or in space. As space travel becomes a reality, studies on group selection, leadership style, and interaction between the isolated group and headquarters take on urgency.[36,66,97,135] Collaborative efforts are being made between many stations and space agencies, in particular the European Space Agency (ESA) and the NASA program.[112]

Cross-cultural and cross-gender issues by research groups are currently being studied at the international station, Concordia, particularly as an analog for long-distance space missions. Whereas in some areas cross-gender differences increase difficulties, in others they are beneficial. Further studies on rigorous selection criteria and training before deployment will avoid the problems that have occurred with sexual harassment. It is thought that the positive effect of better communication, less rude behavior, and increased supportive environment outweigh the negative effect. Other stations have already gone through this process.[66,112]

### Winter-Over Syndrome

Stressors such as those mentioned previously can result in what has been termed the *winter-over syndrome*. The historically oft-mentioned "Big Eye" or "20-foot stare in a 10-foot room" seems to be less common now, perhaps because the stations are increasingly comfortable and have stimulating environments. However, the constellation of depression, hostility, sleep disturbances, and impaired cognition still seems to be both common and underreported.[98,99,109] The winter-over syndrome is not a static condition but a time- and individual-dependent process. At the South Pole research station, for example, winter-over staff characteristically report a recognizable pattern of fluctuating activity and mood. There is often a mixture of relief, pride, and fearful anticipation as the last LC-130 flight departs in mid-February, followed by a period of frenetic activity to beat inventory deadlines, file resupply orders, launch projects, and prepare the station for winter. As work and recreation routines develop, mood generally drops with the setting sun. A rise in mood occurs toward sunrise but is followed with anticipation, increase in anxiety, and stress as the arrival of the first return flight draws near. Studies at the Australian stations of Mawson and Macquarie Island suggest that the influx of new staff at station opening may actually be associated with increased depression.

### Seasonal Affective Disorder

A probable contributor to and confounder of the winter-over syndrome is the apparently fairly consistent exacerbation of stress and depression under conditions of winter or night, leading to seasonal affective disorder (SAD). Subsyndromal SAD (S-SAD) may be a better definition of what is experienced by many who

winter-over in the dark latitudes.[96] Further studies indicate that S-SAD may be part of the $T_3$ syndrome.[99] Correlations with melatonin levels have been shown to be associated with the frequent sleep disturbances at higher latitudes, both with advanced or delayed phases and with increased latency.[6,133] In some studies, melatonin's chronobiotic properties are used to resynchronize the individual's sleep.[6] Other studies have demonstrated the effectiveness of light therapy in helping resynchronize the body.[133] SAD may be no more prevalent in Antarctica than at lower latitudes; some of the depressive symptoms may well be the result of social isolation or related to seasonal changes.[100]

### Beneficial Effects of Isolation

An interesting point is that isolation may have positive as well as negative effects.[100] Isolation is not synonymous with loneliness and depression, as Amundsen reported from his sojourn at Framheim. In fact, a subset of "professional isolates" may actually prefer polar stations to "normal" society.[125] In some cases, reentry and adaptation to the rest of the world can take up to 6 months. The positive effect of isolation may be reflected in a 1992 study of somatic complaints that compared U.S. Navy volunteers who qualified for winter duty in Antarctica and wintered-over, with those who were physically qualified but were assigned elsewhere because of the limited number of winter assignments. Those who spent the winter in Antarctica had fewer illnesses and hospitalizations after the winter-over period. These volunteers were followed an average of 5.4 years after the winter period. It was also noted that the complex psychophysiologic symptoms experienced during the winter-over period were probably adaptive coping mechanisms. Coping led to a process of negotiation leading to compromise, which frequently led to finding new strategies or resources that could be used for subsequent stressful experiences. Newer studies confirm the salutogenic effect of completing a long-term contract in an isolated environment.[92,100]

### Screening and Selection

Based on the preceding findings, several attempts have been made to refine the selection and screening processes for successful polar and space sojourners. It is not surprising that previous successful polar experience seems to be among the best predictors of subsequent high performance. Biographic data, peer ratings, psychometric testing, and interviews all seem helpful in selection, although each has weaknesses and inconsistencies. Recent studies have suggested that team climate significantly related to the perception of good leadership.[115] More research needs to be done to explore the characteristics and behaviors that constitute effective leadership, in order to guide selection of crew and leader.[15,115] Early studies led to the tripartite "ability, stability, compatibility" criteria for successful participation in the Antarctic programs.[38] This simple but useful scheme recognizes that technical skill, emotional equilibrium, and interpersonal skills all play important roles in an individual's performance and internal satisfaction. It would be desirable to improve measurement and predictive usefulness of these factors; such studies remain at the active frontier of Antarctic research.[38]

## TOURISTS

The vast majority of tourists visit the Antarctic on ships around the Peninsula. The International Association of Antarctic Tour Operators has more than 100 members from 19 countries. A wealth of information, guidance, and statistics about Antarctic tourism is found on their website (www.iaato.org). Landing tourists come on vessels carrying 6 to 500 passengers. There are some larger ships (500 to 3000 passengers) that offer "cruise-by" sightseeing trips without landing. Visits usually take place at ice-free coastal areas in the austral summer from November to March. Landings of short duration (usually 1 to 3 hours) are made by inflatable boat (Zodiac) and occasionally by helicopter. There are currently three operators offering land-based trips. IAATO figures show that in 2013-2014 there were 37,405 tourists by sea and land.[53] This is actually a reduction from the peak figure of 47,225 in 2007-2008 and results from the restrictions now placed on larger vessels, although the figure is rising annually.

Tourist visitors can be broadly divided into two groups, "sightseeing" and "expedition/adventure sport." Ship-based sightseers make up approximately 98% of the visitor total. A very small number travel to the continent itself, to visit, for example, the South Pole or emperor penguin colonies. There is little if any medical screening of ship-based tourists, and persons of all ages may travel. The financial expense of these cruises means that there is bias toward the older traveler who has accumulated wealth and has the time to spend it. A recent paper showed that more than half the respondents on an Antarctic cruise ship were older than 50, and 25% were over 60.[136]

Medical facilities on board ship vary widely, as do the experience and competence of accompanying medical professionals. The American College of Emergency Physicians published comprehensive guidelines to enhance medical care on board cruise ships, including specific requirements for physicians, such as 3 years of postgraduate/postregistration experience in general and emergency medicine. These are only guidelines and not requirements.[3a]

The medical problems encountered mirror those found in an urban setting, with additional risks of trauma (usually minor) from, for example, falls in the unfamiliar environment.

The expedition/adventure sport group is primarily involved in ski or mountaineering expeditions, with most professionally guided. These visitors are generally a fitter and younger population. In line with adventure sports worldwide, age and (lack of) experience are bars to participation. Other visitors are involved in sailing, kayaking, and scuba-diving trips. Some expeditions deploy motorized vehicles. At Union Glacier in 2014, there were two marathon and two ultramarathon running events.

## MEDICAL PROBLEMS

Many medical problems of activity in the extreme cold, including frostbite and hypothermia, are discussed elsewhere (see Chapters 6 through 10). Clinical entities particularly associated with polar ski expeditions include polar thigh, skier's thumb, and kite skier's toe.

### Polar Thigh

The clinical picture of polar thigh in both genders is an erythematous and frequently urticarial rash, predominantly on the anterior thigh, although it can also be seen on the sides (particularly medial) and back (Figures 11-16 and 11-17). If inadequately treated, and if behavioral modifications and clothing adjustments are not made, the rash progresses to frank ulceration. Despite appearances, infection is rarely demonstrated when microbiologic samples are taken. The exact etiology is not known. We believe that although cold may play a part, the main etiologic factor is mechanical abrasion. The action of skiing drives the leg into extension at the hip, and clothing is stretched over the leg. The thighs also generate a great deal of heat when exercising. Abrasion to the medial aspect is exacerbated in persons with bulkier thighs. This causation theory is supported by the

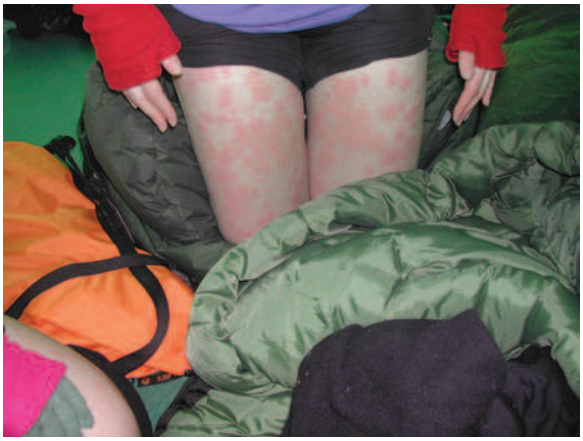


**FIGURE 11-16** Polar thigh. *(Courtesy Ian Davis.)*

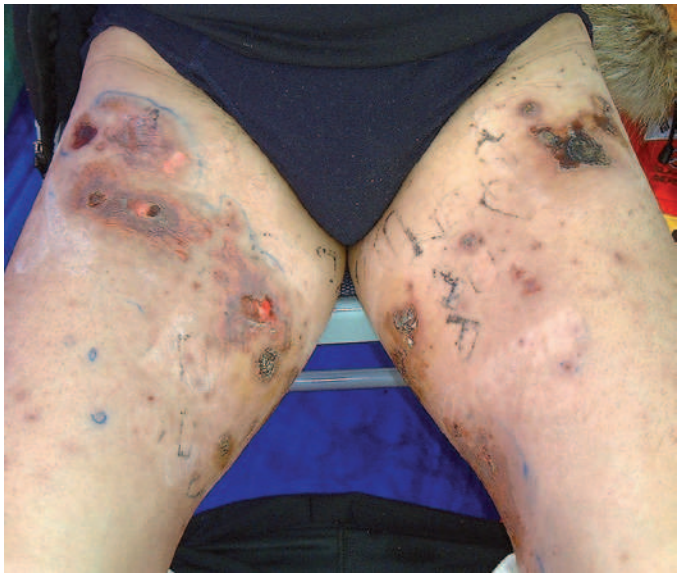


FIGURE 11-17 Polar thigh.

observation that "polar thigh" is also seen where pulk (sledge) pulling harnesses rub, and because it is not seen in the upper arm, which is exposed to the same temperature and winds and is likely to have the same clothing layers as the thighs. It is also neither seen in experienced skiers and guides nor reported in the diaries of early explorers, who were meticulous in recording details of their journey. These groups will have made suitable adjustments to their clothing.

Polar thigh can be prevented by wearing long, silk shorts (or cut-off pajamas) and ensuring liberal use of an emollient or *Aloe vera* gel. In the early stages of the rash, there is usually good response to a topical corticosteroid cream (e.g., betamethasone valerate 0.025% or 0.05%) combined with an emollient or *Aloe vera*. If the skin breaks down, topical corticosteroids should not be applied to ulcerated areas, which should be covered with a hydrocolloid dressing. Granuflex is ideal (www.convatec.com). Antibiotics are not routinely indicated. The key to management is scrupulous wound care and dressing changes. Once out of the field, a plastic surgery or burn unit may well be the appropriate setting for severe cases (Figure 11-18).

### Skier's Thumb

Skier's thumb does not refer to the ruptured ulnar collateral ligament seen in skiers who fall while holding a skipole, but rather refers to frostbite of the terminal phalanx of the thumb (Figure 11-19). This was often seen in returning expeditioners whose thumb was exposed to the cold and wind at the top of the skipole, away from the shared heat of the other digits enclosed in a mitten. Skier's thumb is not seen in persons who use "Pogies," which are neoprene and Velcro gloves (inspired by the handlebar mitts used by motorcycle and snowmobile drivers) fixed to the ski pole that protect the whole hand (Figure 11-20).

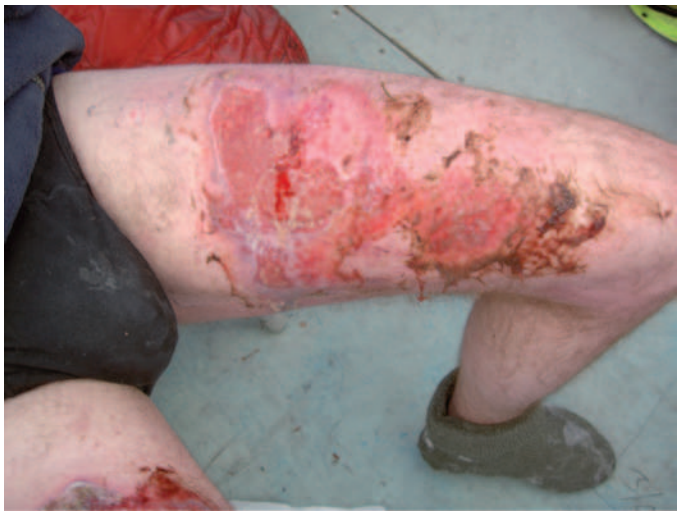


FIGURE 11-18 Severe polar thigh.

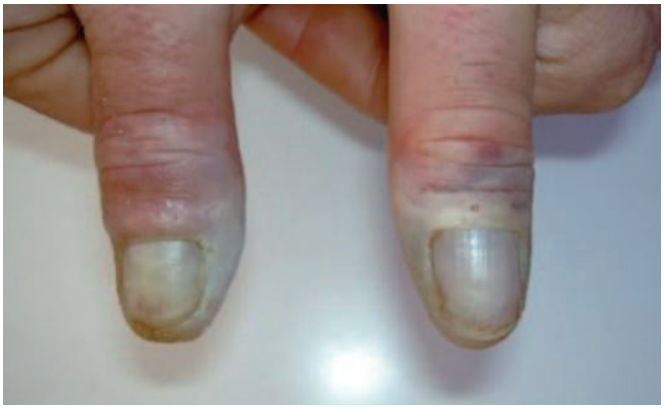


FIGURE 11-19 Skier's thumb.

### Kite Skier's Toe

This condition is frostbite of the downwind hallux in kite skiers, as described in a 2013 case report[114] (Figure 11-21).

## OVERVIEW AND FUTURE DEVELOPMENTS

A point made early in this chapter is the challenge inherent in meaningfully synthesizing Arctic and Antarctic medicine.

FIGURE 11-20 Pogies.

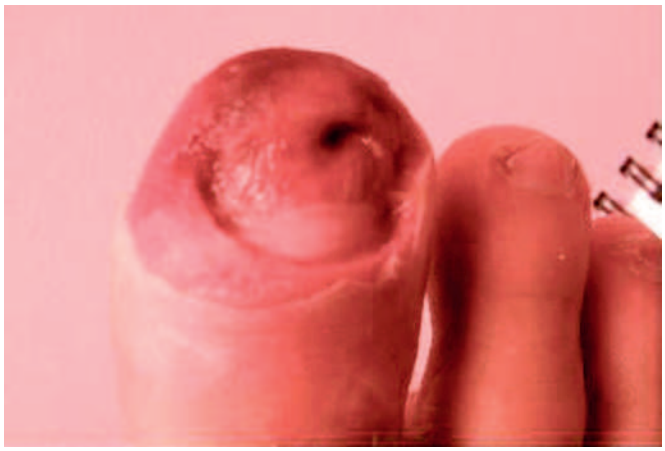


FIGURE 11-21 Kite skier's toe.

Reflection on some of the issues raised previously suggests several common areas of linkage and directions for future work.

## ISSUES OF METHODOLOGY AND MEDICAL EPISTEMOLOGY

The state of knowledge about the human factors involved in living in the Antarctic is still rudimentary, although renewed interest by NASA and ESA in Antarctica as a space analog has led to increased research funding and should lead to better information. Studies in polar settings are often handicapped by extremely difficult research conditions and may never achieve the statistical power and validity expected of counterparts in more forgiving climes. Common methodologic problems most notably include small sample sizes, unknown effect sizes, measurement of proxy variables, and multiple confounders.

## FOURTH WORLD MEDICAL DECISION MAKING

Polar medical lore is replete with stories like that of Leonid Rogozov, the physician of the sixth Soviet Antarctic Expedition at Novolazarevskaya Station, who performed an appendectomy on himself in April 1961 with assistance from the station mechanic (Figure 11-22).[111] Although the basic principles of emergency medicine, epidemiology, occupational health, psychology, and other disciplines still apply in polar settings, the spectrum of health problems and some important aspects of their management are undoubtedly skewed. However, with newer and improved technical communication modalities and transportation, delivery of advanced care in the polar latitudes has improved, and many lessons learned in Antarctica are applicable to space exploration and settlement.

Fourth World medicine requires distillation of medical practice into a compact yet comprehensive package that is sufficiently robust to travel well. Novel constraints and the inherently unpredictable nature of a hostile environment further stretch the usual, already tentative rules and thresholds of medical decision making. Perhaps to a greater extent than in most settings, prevention and preparation are paramount in polar medicine. As might be imagined, cold and its effects on both humans and equipment exacerbate the risks from even minor mishaps, altitude impairs tissue oxygenation and wound healing, and bulky clothing restricts dexterity and vision. Isolation from medical facilities exerts a multiplier effect on these risks. Patient extrication and resuscitation that would be routine in most urban or suburban settings present overwhelming challenges in polar settings.[106]

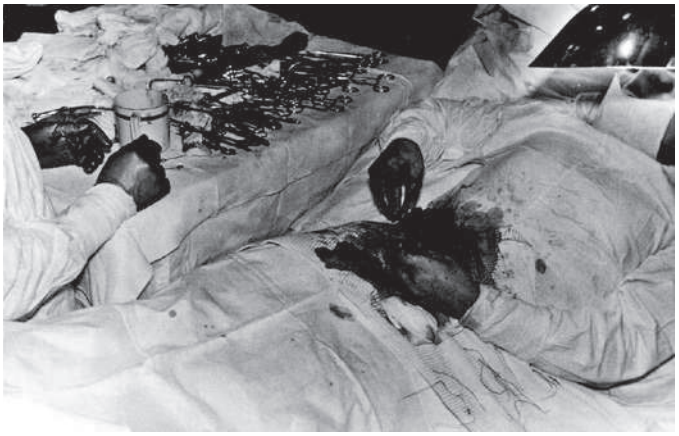


FIGURE 11-22 Leonid Rogozov.

With lives at stake, arguments have been made for planning for worst-case scenarios rather than only for likely situations.[116] On the other hand, a realistic balance point on the cost-versus-utility curve, based on estimated risks, must be set for each situation. Given existing fiscal and logistic constraints, preventive measures should take priority over higher-cost options.[9]

A recurrent medical issue in polar stations involves contingency planning and the optimal level of inventory. This question applies equally to drugs, equipment, training, and personnel and is faced immediately by any incoming physician. "Just in time" principles of inventory management are unlikely to be appropriate.[9,116]

Combined improvements in communications systems, the Internet, and the powerful tool of telemedicine with its many modalities have transformed what was once an extremely isolated practice of medicine. The advantages of rapid access to organized databases and remote consultations for radiology and other specialties via video are realities. Telemedicine is in place and functioning in many northern Arctic regions. The Australian, British, Italian, and U.S. Antarctic Programs and many others have been using it successfully for a number of years.[36,59,67,108] Physiologic, psychological, and occupational health data can be monitored or retrieved, ultimately linking geography and information flow and allowing almost real-time consultation and guidance from multiple specialists. These promising tools are real solutions to the problems of isolation faced by earlier physicians.

## USE OF FROZEN MEDICATIONS

Although the medical literature is relatively sparse on the use of frozen drugs, there is a useful consensus document from the Union of International Alpine Associations (UIAA).[23] Notable points are that glass ampoules may have microscopic cracks when frozen, and that drugs (e.g., insulin) that contain protein or any emulsion should not be used once frozen. They will degrade, and the products could cause a pulmonary embolus. Morphine is a useful drug not covered in this guidance, although it has been used to good effect in our experience after multiple freeze-thaw cycles. A BAS study found that most medications remained stable, even after multiple freeze-thaw cycles.[107a] The exception was hydrocortisone cream, although the investigator also recommended against subjecting eye medications to temperature extremes. Medical devices, such as IV cannulas, worked normally after rewarming, as did all forms of tape and dressings. Frozen IV fluids expanded when frozen, may perforate the bags, and thus leak when rewarmed.

## ACKNOWLEDGMENTS

*The authors would like to acknowledge Betty Carlisle, Lesley J. Ogden, Ian Davis, and Kenneth V. Iserson for their excellent work on this chapter in the previous edition, on which the current chapter is based. Special thanks to Kenneth H. Willer, MLS, Manager–Library Services, Samaritan Health Services, Corvallis, Oregon, kwiller@samhealth.org.*

## REFERENCES

***Complete references used in this text are available online at expertconsult.inkling.com.***

## REFERENCES

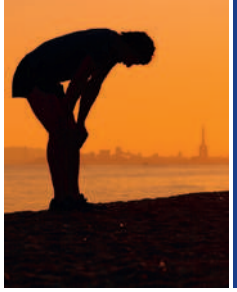

1. Aartsen MG, Ackermann M, Adams J, et al. Observation of high-energy astrophysical neutrinos in three years of IceCube data. IceCube Collaboration. Phys Rev Lett 2014;113:101101.
2. Adams G: Personal communication, July 2005.
3. Adler A. Arctic first aid. N Engl J Med 1992;326:351.

3a. American College of Emergency Physicians. Health care guidelines for cruise ship medical facilities. Reaffirmed by the ACEP Board of Directors. June 2013 <https://www.acep.org/content.aspx?id=29500>.

4. Antarctic Treaty Special Consultative Meeting XXXI, annex 1, Guidelines on contingency planning, insurance and other matters for tourist and other non-governmental activities in the Antarctic treaty area, 2008. <http://www.ats.aq/documents/recatt/Att225_e.pdf>.
5. Antarctic Treaty Summit, November 30–December 03 2009, Smithsonian Institution. <http://www.atsummit50.aq/treaty/members.php>.
6. Arendt J, Skeene DJ. Melatonin as a chronobiotic. Sleep Med Rev 2005;9:25.
7. Ayotte P, Dewailly E, Bruneau S, et al. Arctic air pollution and human health: What effects should be expected? Sci Total Environ 1995;529:160.
8. Ayton J. Polar hands: Spontaneous skin fissures closed with cyanoacrylate (Histoacryl Blue) tissue adhesive in Antarctica. Arctic Med Res 1993;52:126.
9. Ayton J. Report on Australian Antarctic human biology and medicine research. Meeting of SCAR Life Sciences Expert Group on Human Biology and Medicine: SCAR XVIII, Bremen, Germany, 2004. Personal correspondence.
10. Bachelard C. TAAF medicine. Personal communication July 2005.
11. Ballschmite K, Hackenberg R, Jarman WM, et al. Man-made chemicals found in remote areas of the world: The experimental definition for POPs. Environ Sci Pollut Res Int 2002;9:274.
12. BBC News. UK to rebuild Antarctic Lab. Dec 18, 2001. <http://news.bbc.co.uk/2/hi/science/nature/1715922.stm>.
13. Berner J. Health status of the Arctic residents: AMAP assessment 2002: Human health in the Arctic. <http://www.amap.no>.
14. Bhattacharyya M, Pal MS, Sharma YK, et al. Changes in sleep patterns during prolonged stays in Antarctica. Int J Biometeorol 2008; 52:869.
15. Bishop SL. Evaluating teams in extreme environments: From issue to answers. Aviat Space Environ Med 2004;75:1.
16. Bjerregaard P, Bisgaard Kristensen LH, Olesen I, et al.: [Evaluation of the Perinatal Guidelines: A report to the Department of Health], 2012. Center for Sunhedsforskning i Grønland. Statens Institut for Folkesundhed. Syddansk Universitet.
17. Bjerregaard P, Young TK, Dewailly E, et al. Indigenous health in the Arctic: An overview of the circumpolar Inuit population. Scand J Public Health 2004;32:390.
18. Carlisle B. Personal knowledge, McMurdo Station, 2001.
19. Carlisle B. Turnover report McMurdo, 2002-2003.
20. CIA World Fact Book, update May 10, 2010. <https://www.cia.gov/library/publications/the-world-factbook/geos/ay.html>.
21. CNN: Amundsen-Scott Station, Antarctica, April 25, 2001. <http://www.southpolestation.com/news/medevac.html>.
22. Cockell CS, Sherer K, Horneck G, et al. Exposure of Arctic field scientist to ultraviolet radiation evaluated using personal dosimeters. Photochem Photobiol 2001;74:570.
23. Consensus statement of the UIAA Medical Commission. The effect of extremes of temperature on drugs with notes on side effects and use of some other drugs in the mountains intended for doctors, non-medical persons and trekking/expedition operators, 2008, Union of International Alpine Associations.
24. Conway G, Lincoln J, Jorgensen S, et al. Preventing deaths in Alaska's commercial fishing industry. Int J Circumpolar Health 1998; 57:503.
25. Council of Managers of National Antarctic Programs Antarctic Facilities. <http://www.comnap.aq/facilities>.
26. Curry C. Death in Antarctica [letter]. Med J Aust 2002;176:451.
27. Do NV, Mino L, Merriam GR, et al. Elevation in serum thyroglobulin during prolonged Antarctic residence: Effect of thyroxine supplement in polar 3.5.3′-triiodothyronine syndrome. Int J Circumpolar Health 1998;57:388.
28. Dyck R, Osgood N, Lin T, et al. Epidemiology of diabetes mellitus among First Nations and non-First Nations Adults. CMAJ 2010;182:249.
29. Feldman J: Personal communication, Palmer Station, January 10, 2010.
30. Fenge T. Environmental clean-up and sustainable development in the circumpolar Arctic. Northern Perspectives 1993;21:94. <http://www.carc.org/pubs/v21no4/cleanup.htm>.
31. Fenge T, Watt S, Crump J, et al. Persistent organic pollutants: Are we close to a solution? Indigenous peoples and global POPs. Northern Perspectives 2000;26:<http://www.carc.org/pubs/fall2000/Northern_Perspectives_26.pdf>.
32. Francis G, Bishop L, Luke C, et al. Sleep during the Antarctic winter: Preliminary observation on changing the spectral composition of artificial light. J Sleep Res 2008;17:354.
33. Francis JL, Gleeson M, Lugg DJ, et al. Trends in mucosal immunity in Antarctica during six Australian winter expeditions. Immunol Cell Biol 2002;80:382.
34. Freitas CD, Symon L. Bioclimatic index of human survival times in the Antarctic. Polar Rec 1987;23:651.
35. Gander PH, MacDonald JA, Montgomery JC, et al. Adaptation of sleep and circadian rhythms to Antarctic summer: A question of zeitgeber strength. Aviat Space Environ Med 1991;62:1019.
36. Grant IC. Telemedicine in the British Antarctic Survey. Int J Circumpolar Health 2004;63:356.
37. Grant IC. Personal communication, March 2011.
38. Grant I, Ericksen HR, Marquis P, et al. Psychological selection of Antarctic personnel: The "SOAP" instrument. Aviat Space Env Med 2007;78:793.
39. Haggarty JM, Cernovsky Z, Husni M, et al. Seasonal affective disorder in an Arctic community. Acta Psychiatr Scand 2002;105:378.
40. Hall S. The Fourth World: The heritage of the Arctic and its destruction. New York: Vintage Books; 1988.
41. Hansen JC. Environmental contaminants and human health in the Arctic. Toxicol Lett 2000;119:112.
42. Hansen JC, Gilman AP. Exposure of Arctic population to methylmercury from consumption of marine food: An updated risk-benefit assessment. Int J Circumpolar Health 2005;64:121.
43. Hansen V, Jacobsen B, Husby R. Mental distress during winter: An epidemiologic study of the 7759 adults north of the Arctic Circle. Acta Psychiatr Scand 1991;84:137.
44. Harinath K, Malhotra AS, Pal K, et al. Autonomic nervous system and adrenal response to cold in man at Antarctica. Wilderness Environ Med 2005;16:81.
45. Hassi J. Environmental health risks of the Arctic assessed. Int J Circumpolar Health 2002;61:289.
46. Hedblom EE. Polar manual. ed 4. Bethesda, Md: Naval Medical School; 1965.
47. Homler I. Problems with cold work: Proceedings from an international symposium, Stockholm, Arbetslivsinstitutet, 1997, pp 96-8. <http://gupea.ub.gu.se/dspace/bitstream/2077/4185/1/ah1998_18.pdf>.
48. Horwitz S, Jump on the Pole, May 1998. <http://airsports.fai.org/may98/may9804.html>.
49. Hudson S. Risk assessments and casualty evacuation. Expedition Med. <http://www.expeditionmedicine.co.uk/index.php/advice/resource/r-0014.html>.
50. Hughes KA, Blenkharn N. A simple method to reduce discharge of sewage microorganism from Antarctic research station. Mar Pollut Bull 2003;46:353.
51. Human health report, AMAP assessment 2009. Human health in the Arctic. Oslo, Norway: Arctic Monitoring and Assessment Programme (AMAP); 2009.
52. Inspections under Article VII of the Antarctic Treaty. <http://www.state.gov/documents/organization/15274.pdf>.
53. International Association of Antarctic Tour Operators. Tourism overview. <http://www.iaato.org/tourism_stats.html>.
54. Iserson KV. Personal observations, McMurdo Station 2009-2010.
55. Jacobs M, Richardson JI, editors. Arctic life: Challenge to survive. Pittsburgh: Carnegie Institute; 1983.
56. Jenkins AL, Gyorkos TW, Culman KN, et al. An overview of factors influencing the health of Canadian Inuit infants. Int J Circumpolar Health 2003;62:17.
57. Johnson D, Gamble W. Trauma in the Arctic: An incident report. J Trauma 1991;31:1340.
58. Juliano S, Ayton J. Antarctic expeditioners assist bone loss study. Australian Antarctic Magazine 2005;8:29.
59. Karasek M. Melatonin, human aging, and age-related diseases. Exp Gerontol 2004;39:1723.
60. Kennaway D, Van Dorp CF. Free-running rhythms of melatonin, cortisol, electrolytes and sleep in humans in Antarctica. Am J Physiol 1991;260:R1137.
61. Korhonen M. Alcohol problems and approaches: Theories, evidence and northern practice. Med J Aust 2004;180:32.
62. Korhonen M. Helping Inuit clients: Cultural relevance and effective counseling. Int J Circumpolar Health 2004;63:135.
63. Krummel EM. The Circumpolar Inuit Health Summit: A summary. Int J Circumpolar Health 2009;68:509.
64. Lansing A. Endurance: Shackleton's incredible voyage. New York: Carroll & Graff; 1986.
65. Lehti V, Niemelä S, Hoven C, et al. Mental health, substance use and suicidal behaviour among young indigenous people in the Arctic: A systematic review. Soc Sci Med 2009;69:1194.
66. Leon GR, Sandoval GM. Women and couples in isolated extreme environments: Applications for long duration missions. Acta Astronaut 2003;53:259.

67. Levine M, Duffy L, Moore DC, et al. Acclimation of a non-indigenous sub-Arctic population: Seasonal variation in thyroid function in interior Alaska. Comp Biochem Physiol A Physiol 1995;111:209.
68. Lugg DJ. Personal communication 1999.
69. Lugg DJ. Antarctic medicine. JAMA 2000;283:2082.
70. Lugg DJ, Gormerly P, King H. Accidents on Australian Antarctic expeditions. Polar Rec 1999;23:720.
71. Macdonald RW, Bewers JM. Contaminants in the Arctic marine environment: Priorities for protection. I CES J of Marine Science 1996;53:537.
72. Mahar H. Personal communication, January 1999.
73. Marriott BM, Carlson SJ, editors. Committee on Military Nutrition Research: *Nutrition needs in cold and high-altitude environments: Applications for the military personnel in field operations.* Washington, DC: National Academy Press; 1996. p. 198–200.
74. Matheson B, Walker KZ, Taylor DM, et al. Effect on serum lipids of monounsaturated oil and margarine in the diet of an Antarctic expedition. Am J Clin Nutr 1996;63:993.
75. Mawson D. Home of the blizzard. New York: St Martin's Press; 2000.
76. Meinander H, Anttonen H, Bartels V, et al. Manikin measurements versus wear trial of cold protective clothing (SubZero Project). Eur J Appl Physiol 2004;92:619.
77. Meyer-Rochow VB. Coming to grips with a slippery issue: Human waste disposal in cold climates. Int J Circumpolar Health 1999;58:57.
78. Michelen SW, Soborg B. The effectiveness of BCG vaccination in preventing *Mycobacterium tuberculosis* infection and disease in Greenland. Thorax 2014;69(9):851–6.
79. Midwinter M, Arendt J. Adaptation of the melatonin rhythm in human subjects following night shift work in Antarctica. Neurosci Lett 1991;122:195.
80. Montgomery-Andersen R. Adolescent mothers: A challenge for First Nations. Int J Circumpolar Health 2004;63:274.
81. Murray C, Jabour J. Independent expeditions and Antarctic tourism policy. Polar Rec 2004;40:309.
82. Nagaya Y, Shiozaki M, Seto Y. Radioactive contamination of the Indo-Antarctic Ocean water in early parts of 1961 and 1962. J Radiat Res (Jap) 1964;5:206.
83. Natani K, Shurley JT, Pierce CM, et al. Long-term changes in sleep patterns in men on the South Polar Plateau. Arch Intern Med 1970;125:655.
84. National Institute on Polar Research. Proceedings of the International Symposium: Asian collaboration in IPY 2007-2008, Tokyo, Japan.
85. National Science Foundation. Helicopter crash [news release], Antarctic Sun January 19, 2003. <http://antarcticsun.usap.gov/oldissues2002-2003/Sun011903/crash.html>.
86. Neri M, De Jongh R. Medical and trauma evacuations. Clin Occup Environ Med 2004;4:85.
87. New Zealand disasters, aircraft accident. DC 10 ZK-NXP flight 901. <http://christchurchcitylibraries.com/Kids/NZDisasters/Erebus.asp>.
88. NIOSH Safety & Health Topic. Commercial aviation in Alaska (1990-2008). <http://www.cdc.gov/niosh/topics/aviation/>.
89. Occupational Safety and Health Report. In Healthy Alaskans 2010, vol 1, State of Alaska, Health & Social Services. <http://www.hss.state.ak.us/dph/targets/ha2010/PDFs/10_Occupational.pdf>.
90. Oliveri B, Zeni S, Lorenzetti MP, et al. Effect of one year residence in Antarctica on bone mineral metabolism and body composition. Eur J Clin Nutr 1999;53:88.
91. Pääkkönen T, Leppäluoto J, Mäkinen T, et al. Seasonal levels of melatonin, thyroid hormones, mood, and cognition near the Arctic Circle. Aviat Space Environ Med 2008;79:695.
92. Palinkas LA. Going to extremes: the cultural context of stress, illness and coping in Antarctica. Soc Sci Med 1992;35:651.
93. Palinkas LA. The psychology of isolated and confined environments: Understanding human behaviour in Antarctica. Am Psychol 2003;58:353.
94. Palinkas LA, Glogower F, Dembert M, et al. Incidence of psychiatric disorders after extended residence in Antarctica. Int J Circumpolar Health 2004;63:157.
95. Palinkas LA, Houseal M, Miller C, et al. Sleep and mood during a winter in Antarctica. Int J Circumpolar Health 2000;59:63.
96. Palinkas LA, Houseal M, Rosenthal NE. Subsyndromal seasonal affective disorder in Antarctica. J Nerv Ment Dis 1996;184:530.
97. Palinkas LA, Johnson JC, Boster JS, et al. Cross-cultural differences in psychosocial adaptation to isolated and confined environments. Aviat Space Environ Med 2004;75:973.
98. Palinkas LA, Mäkinen TM, Pääkkönen T, et al. Influence of seasonally adjusted exposure to cold and darkness on cognitive performance in circumpolar residents. Scand J Psychol 2005;46:239.
99. Palinkas LA, Reed HC, Reedy KR, et al. Circannual pattern of hypothalamic-pituitary-thyroid (HPT) function and mood during extended Antarctic residence. Psychoneruroendocrinology 2001;26:421.
100. Palinkas LA, Suedfeld P. Psychological effects of Polar expeditions. Lancet 2008;371:153.
101. Parkinson AJ. The International Polar Year 2007-2008: The Arctic human health legacy. Alaska Med 2007;49:43.
102. Parkinson A, Muchmore H, Scott E. Rhinovirus respiratory tract infections during isolation at South Pole Station. Antarctic J US 1984;19:186.
103. Pascoe J. New Zealand Antarctic Programme. Report to SCAR, Sofia, Bulgaria, July 12-15, 2005, Human biology and medicine in the New Zealand Antarctic Programme. Personal communication.
104. Pause B. Development of a new cold protective clothing with phase change material: Problems with cold work. <http://gupea.ub.gu.se/dspace/bitstream/2077/4185/1/ah1998_18.pdf>.
105. Pitson GA, Lugg DJ, Roy CR. Effect of seasonal ultraviolet radiation fluctuations on vitamin D homeostasis during an Antarctic expedition. Eur J Appl Physiol Occup Physiol 1996;72:231.
106. Plowright R. Crevasse fall in the Antarctic: A patient's perspective. Med J Aust 2000;13:576.
107. Pravda. 45th birthday of Russia's Antarctic Station Vostok, April 13, 1982. <http://english.pravda.ru/russia/19216-0>.
107a. Priston MJ, Grant IC, Hughes JM, Marquis PT. Pilot study on potential degradation of drug efficacy resulting from Antarctic storage, transport and field conditions. Int J Circumpolar Health 2005;64:2.
108. Raimer GG, Hermstein SM, Angelo J, et al. Telemedicine at the South Pole. Telemed e-Health 2003;9:67.
109. Reed HL, Reedy KR, Palinkas LA, et al. Impairment in cognitive and exercise performance during prolonged Antarctic residence: Effect of thyroxine supplementation in the polar triiodothyronine syndrome. J Clin Endocrinol Metab 2001;86:110.
110. Risikko T, Anttonen H. Use of personal heaters in cold work. In: Problems with cold work: Proceedings from an international symposium. Stockholm: Arbetslivsinstitutet; 1997. p. 29–30 <http://gupea.ub.gu.se/dspace/bitstream/2077/4185/1/ah1998_18.pdf>.
111. Rogozov V, Bermel N. Auto-appendectomy in the Antarctic: Case report. BMJ 2009;339:b4965.
112. Rosnet E, Jurion S, Bachelard C. Mixed-gender groups: Coping strategies and factors of psychological adaptation in a polar environment. Aviat Space Environ Med 2004;75:C10.
113. Ross JK, Arendt J, Horne J, et al. Nightshift work in Antarctica: Sleep characteristics and bright light treatment. Physiol Behav 1995;57:1169.
114. Russell KW, Imray CH, McIntosh SE, et al. Kite skier's toe: An unusual case of frostbite. Wilderness Environ Med 2013;24(2):136–40.
115. Schmidt LL, Wood J, Lugg DJ. Team climate at Antarctic Research Stations 1996-2000: Leadership matters. Aviat Space Environ Med 2004;75:681.
116. Schweickart R, et al. Safety in Antarctica. Washington, DC: National Science Foundation; 1988.
117. Shephard RJ. Some consequences of polar stress: Data from a transpolar ship-trek. Arctic Med Res 1991;50:25.
118. Smylie J. SOGC Policy Statement #100 2001: Guide for health professionals working with aboriginal peoples: Health issues affecting aboriginal peoples. J Obstet Gynaecol Can 2000;22(1074).
119. Strand P, editor. Radioactivity in the environment (including the Arctic and Antarctica), The International Conference in Nice, France, 2-6 October 2005. J Environ Radioact 2007;96(1).
120. Strand P, Howard BJ, Aarkrog A, et al. Radioactive contamination in the Arctic: Sources, dose assessment and potential risks. J Environ Radioact 2002;60:5.
121. Stroud MA, Jackson AA, Waterlow JC. Protein turnover rates of two human subjects during an unassisted crossing of Antarctica. Br J Nutr 1996;76:165.
122. Stroud MA, Ritz P, Coward WA, et al. Energy expenditure using isotope-labelled water (2H218O), exercise performance, skeletal muscle enzyme activities and plasma biochemical parameters in humans during 95 days of endurance exercise with inadequate energy intake. J Appl Physiol Occup Physiol 1997;76:243.
123. Sugden D. Arctic and Antarctic: A modern geographical synthesis. Totowa, NJ: Barnes & Noble Books; 1982.
124. Syme D. The circumpolar Inuit: Health of population in transition. BMJ 1999;318:133.
125. Taylor A. Professional isolates in New Zealand's Antarctic Research Programme. Int Rev Appl Psychol 1969;18:135.
126. Taylor AJW. Antarctic psychology. In: New Zealand Department of Scientific and Industrial Research Bulletin. Wellington, NZ: Science Information Publishing Centre 244:20; 1987.
127. Tkachev A, Ramenskaya EB, Bojko JR. Dynamics of hormone and metabolic state in polar inhabitants depend on daylight duration. Arctic Med Res 1991;50:152.
128. UNEP/GRID-Arendal. Population distribution in the circumpolar Arctic, by country (including indigenous population). Maps and Graphics Library, 2008. <http://www.maps.grida.no/go/graphic/population

-distribution-in-the-cicumpolar-arctic-by-country-including-indigenous-population1>.
129. United Nations Environment Programme Report. Global environment outlook 2000, The state of the environment—polar regions. <http://www.grida.no/publications/other/geo2000/>.
130. United Nations Environment Programme Report. Global environment outlook 2000, The state of the environment—The Arctic. <http://www.grida.no/publications/other/geo2000/>.
131. Van Do N, Mino L, Merriam GR, et al. Elevation in serum thyroglobulin during prolonged Antarctic residence: Effect of thyroxine supplement in polar $T_3$ syndrome. J Clin Endocrinol Metab 1529;89: 2004.
132. Varynen S. Ergonomic design of machinery for use in the cold: A review based on the literature and original research. Arctic Med Res 1992;51:87.
133. Warman VL, Dijk DJ, Warman GR, et al. Phase advancing human circadian rhythms with short wavelength light. Neurosci Lett 2003; 15:37.
134. Wintrhereik M. The spread of HIV in Greenland: Heterosexual epidemic-risk or reality? A 10 year review of HIV transmission and preventive care. Ugesker Laeger 1998;160:2851.
135. Wood J, Schmidt L, Lugg D, et al. Life, survival, and behavioral health in small closed communities: Studying isolated Antarctic groups. Aviat Space Environ Med 2005;76:B89.
136. Working Paper No 173. C Tisdell, School of Economics, University of Queensland, 2010.
137. Yablokov AV, Nesterenko VB, Nesterenko AV. Consequences of the Chernobyl catastrophe for public health and the environment 23 years later. Ann NY Acad Sci 2009;1181:318.
138. Zerath E, Holy X, Gaud R, et al. Decreased serum levels of 1,25-(OH)2 vitamin D during 1 year sunlight deprivation in the Antarctic. Eur J Appl Physiol Occup Physiol 1999;79:141.



CHAPTER 12

# Pathophysiology of Heat-Related Illnesses

LISA R. LEON AND ROBERT W. KENEFICK*

Heat illnesses exist along a continuum, transitioning from heat exhaustion to heat injury and the life-threatening condition of heatstroke. Environmental heat exposure is one of the most deadly natural hazards in the United States, with about 200 heatstroke deaths per year. The majority of heatstroke deaths are observed in the very young and elderly populations during annual heat waves, whereas fit, young athletes typically succumb to heatstroke during strenuous exertion in hot or temperate environments. Multiorgan system failure is the ultimate cause of heatstroke death as a result of complex interplay among the physiologic and environmental factors that compromise an individual's ability to respond adequately to heat stress. The pathophysiology of heatstroke is thought to be caused by a systemic inflammatory response to endotoxin leakage across ischemic, damaged gut membranes, although our understanding of the mechanisms causing morbidity and mortality remains limited.

This chapter provides an overview of the pathophysiologic responses observed in patients and experimental animal models at the time of heatstroke collapse and during long-term recovery. A brief discussion is provided on current clinical heatstroke treatments as well as promising avenues of research that may aid in the development of more effective interventions and treatments to prevent this debilitating illness.

## HEAT STRESS AND THERMOREGULATION

### FOUR AVENUES OF HEAT EXCHANGE

Mammals and other homeotherms are capable of maintaining body temperature within a fairly narrow range, approximately 35° to 41°C (95° to 105.8°F), despite large fluctuations in environmental temperature. Environmental variables that have the largest impact on heat exchange are temperature; humidity; radiation from the air, water, or land; and air or water motion.[98] To maintain stable body temperature, organisms rely on four avenues of heat exchange: conduction, convection, radiation, and evaporation.

Dry heat exchange is achieved by conduction, convection, and radiation. Effectiveness of these mechanisms depends on differences between the skin and environmental temperature. Dry heat loss occurs when skin temperature exceeds that of the environment, and dry heat gain occurs when environmental temperature exceeds that of the body. *Conduction* occurs when the body surface is in direct contact with a solid object and depends on thermal conductivity of the object and the amount of surface area in contact with the object. Conduction is typically an ineffective mechanism of heat exchange because of behavioral adjustments that minimize contact with an object. For example, wearing shoes is an effective behavioral adjustment that minimizes conduction of heat from a hot or cold surface (e.g., desert sand to the foot). Within the body, conductive heat transfer occurs between tissues in direct contact with one another but is limited by poor conductivity of the tissues. For example, subcutaneous fat has approximately 60% lower conductivity than the dermis and impedes conductive heat loss.[329] *Convection* is a mechanism of dry heat transfer that occurs as air or water moves over the skin surface. The windchill index is an example of the convective cooling effect of wind velocity. The rate of convective heat transfer depends on the temperature gradient between the body and environment, thermal currents, bodily movements, and body surface area exposed to the environment, which can vary dramatically with different clothing ensembles. Within the body, convective heat transfer occurs between blood vessels and tissues and is most efficient at the capillary beds, which are thin-walled and provide a large surface area for heat exchange. Radiative heat transfer is electromagnetic energy exchanged between the body and surrounding objects and occurs independently of air velocity or temperature. *Radiation* is effective even when air temperature is below that of the body. All objects within our environment absorb and emit thermal radiation, but clothing can reduce radiant heat impinging on the skin from various environmental sources.

*Evaporation* represents a major avenue of heat loss when environmental temperature is equal to or above skin temperature or when body temperature is increased by vigorous physical activity. In humans, evaporative cooling is achieved as sweat is vaporized and removes heat from the skin surface, with approximately 580 kilocalories (kcal) of heat lost for each liter (L) of evaporated sweat.[104] The most important environmental variables affecting evaporative cooling are ambient humidity and wind velocity. Sweat is converted to water vapor and readily evaporates from the skin in dry air with wind, whereas the conversion of sweat to water vapor is limited in still or moist air. If sweat accumulates and fails to evaporate, sweat secretion is inhibited and the cooling benefit is negated. Small mammals, such as rodents, do not possess sweat glands but achieve evaporative cooling by grooming nonfurred and highly vascularized skin surfaces, such as the ears, paw pads, and tail, with saliva that evaporates in a manner similar to that of sweat in humans.[114,295]

### BODY TEMPERATURE CONTROL

Regulation of a relatively constant internal temperature is critical for normal physiologic functioning of tissues and cells. For example, membrane fluidity, electrical conductance, and enzyme functions are most efficient within a narrow temperature range. By convention, thermal physiologists describe body temperature control with a two-compartment model that consists of an internal core (viscera and brain) and an outer shell (subcutaneous fat and skin) (Figure 12-1).[81]

The skin is the final barrier between the body and the environment and functions as a conductive pathway for heat transfer, while also serving as the primary site to sense changes in environmental temperature. Skin temperature may fluctuate because of changes in environmental temperature, relative humidity, wind velocity, and radiation. Heat transfer mechanisms are evoked in response to changes in body heat storage (S), which depends on metabolic rate, work, and the four avenues of heat exchange, as follows:

$$S = M - (W) - (E) - (C) - (K) - (R)$$

*The opinions or assertions in this chapter are the primary views of the authors and are not to be construed as official or reflecting the views of the U.S. Army or Department of Defense. Any citations or trade names do not constitute an official endorsement of approval of the products or services or these organizations.

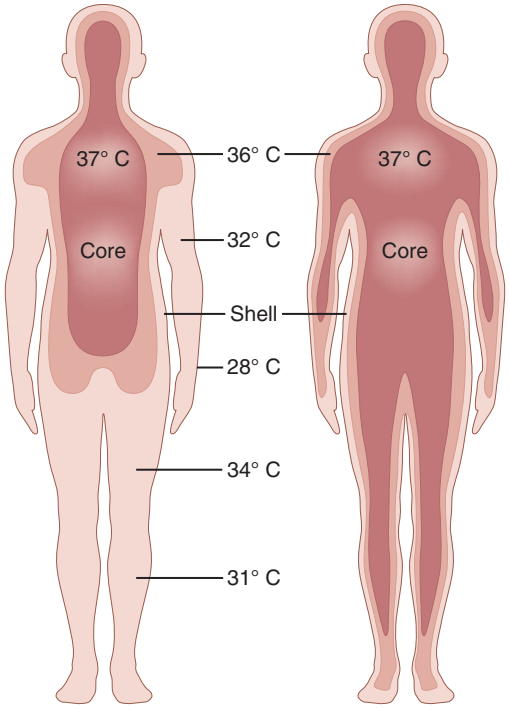



**FIGURE 12-1** Distribution of temperatures within the human body into core and shell during exposure to cold and warm environments. The temperatures of the surface and thickness of the shell depend on the environmental temperature: the shell is thicker in the cold and thinner in the heat. *(From Elizondo RS: Human adaptation to hot environments. In Rhoades RA, Pflanger RG, editors:* Human physiology, *ed 3, Philadelphia, 1996, Saunders. Reprinted with permission of Brooks/Cole, a division of Thomson Learning.)*

where M is metabolic rate, W is work, and E, C, K, and R are evaporative, convective, conductive, and radiant heat transfer, respectively.[141] The impact of the four avenues of heat exchange on total body storage depends on a variety of organismal (e.g., age, gender, adiposity), environmental (e.g., humidity, wind velocity), and occupational (e.g., protective clothing, work intensity) variables. Under conditions in which heat production and/or heat gain exceeds heat loss, such as during exercise or heat exposure, positive heat storage occurs (S >0) and body temperature increases. When heat loss exceeds heat production and/or heat gain, such as during prolonged cold exposure, negative heat storage occurs (S <0) and body temperature decreases.[98]

Endothermic animals use both autonomic and behavioral thermoeffector mechanisms to regulate body temperature. Autonomic thermoeffector responses are often referred to as "involuntary" and include sweating, vasodilation, vasoconstriction, piloerection (furred mammals), shivering, and nonshivering thermogenesis (brown fat heat production). Behavioral thermoeffector mechanisms are considered "voluntary" and include clothing changes, use of heat or air-conditioning systems, huddling or use of blankets, fan cooling, and seeking of shade or shelter. Rather than working independently of one another, autonomic and behavioral thermoeffector mechanisms typically function in concert to maintain temperature control. For example, evaporative cooling in rodents requires autonomic stimulation of salivation and behavioral spreading of saliva onto nonfurred surfaces.[114,295] Many large species in the wild use natural water sources to facilitate cooling. Elephants spray water onto their skin surface, and hippopotami and other species are often observed near or in watering holes. Water is a more effective medium to facilitate convective heat transfer because of its high heat transfer coefficient, approximately 25 times greater than air,[308] even if the water temperature is tepid. However, voluntary suppression of behavioral mechanisms of cooling in humans can increase the risk for thermal injury. This is illustrated by older adults who refuse to use air-conditioning systems or leave their residences during heat waves, and highly motivated athletes and military personnel who voluntarily dehydrate and sustain a high rate of work in hot weather.

Regulation of body temperature is best conceptualized as a negative feedback system consisting of sensors, integrators, and effectors. In vertebrates, neurons in the skin, spinal cord, and abdomen sense thermal stimuli and convert those signals to action potentials that are transmitted by afferent sensory neurons to the preoptic area of the anterior hypothalamus (POAH). The POAH is considered the main central nervous system (CNS) site for thermoregulatory control because it receives and integrates synaptic afferent inputs and evokes corrective autonomic and behavioral thermoeffector responses for body temperature regulation.[38] This negative feedback loop is diagrammed in Figure 12-2.

The concept of a temperature set point was developed as a theoretical framework to examine regulated and unregulated changes in body temperature.[28] The temperature set point is analogous to a thermostat that controls a mechanical heating device; under homeostatic conditions, body temperature is approximately equal and oscillates around the temperature set point. Environmental perturbations, such as heat and exercise, cause body temperature to deviate from the set-point temperature as heat gain and/or production exceeds heat loss and the organism becomes hyperthermic (S >0). During prolonged cold exposure, heat loss exceeds heat gain and/or production and the organism becomes hypothermic (S <0) (Figure 12-3).

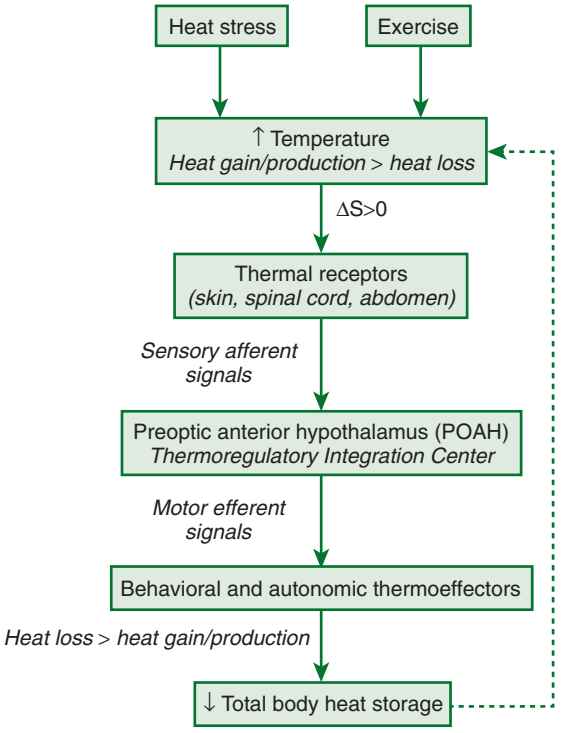



**FIGURE 12-2** Diagrammatic representation of the negative feedback pathway regulating core temperature in homeotherms. Climatic heat stress and exercise (metabolic work) cause heat gain/heat production to exceed heat loss (ΔS >0) and increase body temperature above baseline. Increase in total body heat storage is sensed by thermal receptors in the skin, spinal cord, and abdomen, which transmit action potentials via sensory afferent nerves to the preoptic area of the anterior hypothalamus (POAH). The POAH receives and integrates synaptic afferent inputs and evokes corrective behavioral (e.g., fanning, removal of clothing) and autonomic (e.g., vasodilation, sweating) thermoeffector responses to decrease total body heat storage and return body temperature to baseline. *Solid line* indicates stimulatory pathway; *dashed line* indicates inhibitory pathway.

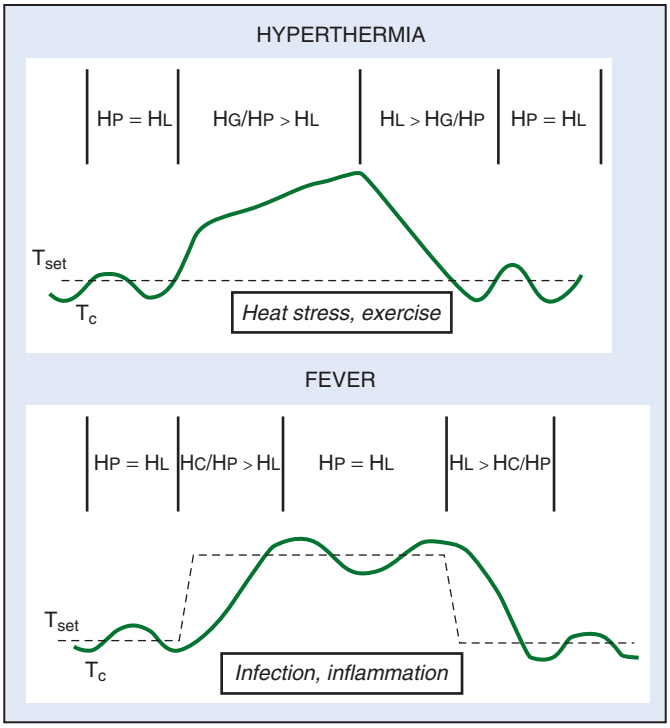



**FIGURE 12-3** Theoretical concept of core temperature ($T_c$) changes mediated by a change in the temperature set point ($T_{set}$). Hyperthermia represents an increase in $T_c$ in the absence of a change in $T_{set}$. In response to climatic heat stress, exercise, or the combination of these factors, heat gain (*HG*) and/or heat production (*HP*) exceed heat loss (*HL*) and $T_c$ rises above $T_{set}$ as the organism becomes hyperthermic. In response to removal from the heat, cooling, or cessation of exercise, HL exceeds HG/HP and $T_c$ returns to baseline. Fever is defined as a regulated increase in body temperature that is actively established and defended by behavioral and autonomic thermoeffector responses that increase heat conservation (*HC*) and/or HG, and decrease HL, to increase $T_c$ to a new elevated level. The rising phase of fever is associated with shivering (increases HP) and the donning of blankets (increases HC). The individual feels "cold" until a new elevated level of $T_c$ is attained. Note that while fever is maintained, $T_c$ oscillates around $T_{set}$ and the individual is considered normothermic with HP = HL. Once fever breaks, HL exceeds HC/HP as the individual sweats, removes clothing, and so forth, to return $T_c$ to the baseline level.

Regulated increases and decreases in the temperature set point are referred to as fever and regulated hypothermia (also called *anapyrexia*), respectively, and are protective immune responses to infection, inflammation, or trauma. *Fever* is defined as a regulated increase in the temperature set point and is actively established and defended by heat-producing (e.g., shivering and nonshivering thermogenesis) and heat-conserving (e.g., peripheral vasoconstriction, huddling to reduce exposed body surface area) thermoeffectors (Figure 12-3).[141] An individual is considered normothermic (S = 0) once fever is established and body temperature oscillates around the new, elevated temperature set point. The highly regulated nature of fever was first suggested by Liebermeister in the 1800s when it was observed that individuals actively reestablished an increase in body temperature after experimental warming or cooling.[185,287] Fever is a protective immune response used by invertebrates, fish, amphibians, reptiles, and mammals to survive infection or injury.[163] The protective effects of fever are mediated by increased mobility and activity of white blood cells,[215,308] increased production of interferon (IFN; antiviral and antibacterial agent) antibodies,[75] and reduced plasma iron concentrations; all these effects inhibit the growth of pathogens.[98,160] In mammals, inhibition of fever with nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., aspirin) increases mortality from bacterial and viral infections, emphasizing the importance of fever as an immune response.[134,310]

Many species exploit regulated hypothermia as a means of surviving severe environmental insults. *Regulated hypothermia* is elicited in response to a decrease in the temperature set point and is actively established and defended by behavioral and autonomic heat loss mechanisms.[137] The $Q_{10}$ effect states that each 10°C (18°F) change in body temperature is associated with a twofold to threefold change in enzymatic reaction rates. Based on this relationship, a regulated decrease in body temperature is thought to protect against injury and inflammation by reducing production of reactive oxygen species that compromise tissue function under conditions of low oxygen supply. In bumblebees, infected worker bees spend significantly more time in cooler temperatures outside the nest than healthy worker bees; this cold-seeking behavior is associated with increased survival from parasitic infection.[128] Mice inoculated with influenza virus also show cold-seeking behavior and develop regulated hypothermia, which is associated with improved infection outcome.[162] Other environmental insults that induce regulated hypothermia in small rodents include hypoglycemia,[43,109] hypoxia,[199,255] hemorrhage,[129] dehydration,[138] infection,[162,181,260] and heatstroke.[180]

### Mechanisms of Heat Dissipation during Thermal Stress

Cardiovascular mechanisms have evolved to shunt warm blood from the body core to the skin surface to facilitate an increase in heat loss during thermal stress. Arteriovenous anastomoses (AVAs) are collateral connections between adjacent blood vessels that increase the volume of blood delivered to a particular tissue. Mean skin blood flow can vary approximately 10-fold in humans, depending on the thermal environment. The hands and feet are concentrated with AVAs that serve as effective areas for dry heat loss. The nonfurred surfaces of small rodents, such as the ears, tail, and paw pads, also have an abundance of AVAs and a large surface area to facilitate convective heat transfer.[101] During exercise heat stress, increased blood flow to the skin surface is accompanied by sweat secretion. The density, secretion rate, and activation threshold of regional sweat glands determine the volume of sweat loss at a body site. In humans, the back and chest have the highest sweat rates for a given body temperature change, whereas only about 25% of total sweat is produced by the lower limbs.[218] Additional factors affecting sweat rate include clothing characteristics, environmental conditions, and rate of metabolic heat production. Panting is an effective method of evaporative heat dissipation in animals, such as birds, dogs, sheep, and rabbits, and occurs at a resonant ventilation frequency that requires minimal energy expenditure.[116,261] Humans and rodents do not pant, but breathing frequency and minute volume increase during severe heat exposure to facilitate evaporative cooling from the respiratory surfaces. In humans, the contribution of respiratory evaporative cooling is small compared with skin evaporative cooling (Figure 12-4).

## DEHYDRATION AND ELECTROLYTE IMBALANCE

Water requirements during heat exposure are primarily determined by a person's sweat losses. Water depletion dehydration develops when the rate of water replacement is not adequate, which can result from a mismatch between fluid intake and sweat loss, lack of water availability, or use of diuretic medications. Sweat rates may range from 0.3 to about 3 L/hr during athletic or occupational activities, depending on the environmental conditions and type, duration, and intensity of work.[57,150] If high sweat rates are maintained without adequate replenishment of lost water, this can cause electrolyte imbalances that impede the efficiency of autonomic mechanisms of thermoregulatory control. For example, hyperosmolarity alters heat responsiveness of warm-sensitive neurons in the POAH and limits the effectiveness of evaporative heat loss.[303,304,335] Severe hypernatremic dehydration is associated with brain edema, intracranial hemorrhage, hemorrhagic infarcts, and permanent brain damage (Figure 12-5).[214]

Severe reductions in electrolytes can have a profound impact on heatstroke outcome. Symptomatic hyponatremia (decreased serum sodium concentration) is a relatively rare condition but has been observed during marathon running and military training

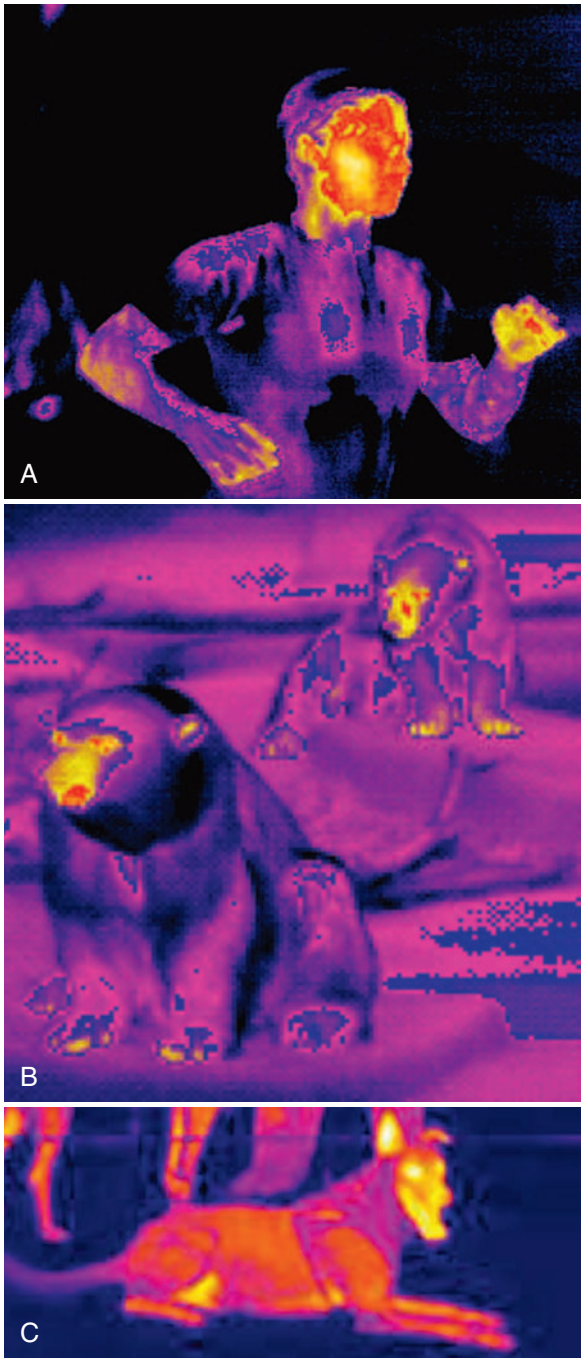



**FIGURE 12-4** Infrared images of various surface regions; the brighter the color, the warmer the surface temperature. **A,** Female runner after 45 minutes of exercise in a 23°C (73.4°F) environment. Note that the palms of the hands and the face are substantially warmer than the rest of the body surface. **B,** Two polar bears. Note that only the snout, eyes, ears, and footpads are noticeably different from the surroundings. **C,** Sled dog relaxing shortly after completing the 17.7-km (11-mile) ceremonial starting leg of the 2005 Iditarod Trail Sled Dog Race. The course of the Iditarod is greater than 1850.7 km (1150 miles) from Anchorage to Nome, Alaska. Ambient conditions were 0°C (32°F), with a lightly overcast sky and no wind. The infrared shot shows that the dog's entire snout is white, meaning it is the hottest part of the body surface. The armpits and ears also are warmer. This may explain why dogs roll around in the snow, face first, on a warm day. (***A*** *and* ***B*** *from Grahn D, Heller HC: The physiology of mammalian temperature homeostasis,* Trauma Care *14:52, 2004, with permission;* ***C*** *courtesy D. Grahn; photo by Matthew Grahn.)*

due to overconsumption of hypotonic fluids without adequate replacement of sodium losses.[214,227] Hyponatremia is associated with intracellular swelling that can lead to CNS dysfunction. Hypokalemia (decreased serum potassium concentration) may be caused by overproduction of aldosterone, excessive sweating, or respiratory alkalosis. Any cause of overproduction of urine (polyuria) potentially causes urinary potassium loss. Potassium is a potent vasodilator of blood vessels to the skeletal and cardiac muscles. Excessive loss of this electrolyte can have detrimental effects, such as decreased sweat volume, cardiovascular instability, and reductions in muscle blood flow that predispose to skeletal muscle injury (i.e., rhabdomyolysis).[164,278]

## HEAT ILLNESSES

Heat illnesses are best viewed as existing along a continuum transitioning from the mild condition of heat exhaustion to heat injury and the life-threatening condition of heatstroke (Table 12-1). *Heat cramps* are often mistaken as a form of heat illness because they occur during or in response to physical activity in warm environments. However, the muscle soreness associated with heat cramps is transient and rapidly resolves with no permanent disability, so this condition is not regarded as a true heat illness. Cramps may be recurrent but are typically confined to the skeletal muscles that are involved in vigorous exercise in the heat. Skeletal muscle spasms in the extremities may be sporadic but are painful and develop most frequently in persons who are not acclimatized to physical exertion. However, heat cramps may also occur in fit athletes who are salt depleted. Although their cause is not fully understood, heat cramps are thought to occur in response to increased intracellular calcium release that stimulates actin-myosin filaments and muscle contraction. Current treatments include rest and replacement of electrolytes with fluids or salted food. Salt tablets should be avoided because they can cause gastrointestinal irritation and may stimulate excess potassium loss in the distal tubules of the kidneys.

*Heat exhaustion* is characterized by elevation in body temperature and the potential for collapse because of an inability to maintain adequate cardiac output.[333] The signs and symptoms of heat exhaustion include fatigue, dizziness, headache, nausea, vomiting, malaise, hypotension, and tachycardia with possible collapse. Heat exhaustion can occur with or without exercise in hot environments and may progress to a moderately severe condition without associated organ damage. Heat exhaustion is often observed in older adults as a result of medications (e.g., diuretics), inadequate water intake that leads to dehydration, or preexisting cardiovascular insufficiency that predisposes to collapse. Treatment should consist of placing the individual in a recumbent position in a cool environment to normalize blood pressure. Oral fluid ingestion with electrolytes is often adequate for recovery, whereas intravenous (IV) fluid administration may be warranted in severely dehydrated individuals.

*Heat injury* is a more recent classification of heat illness characterized by an elevation in body temperature in the presence of organ (e.g., kidney, liver) or tissue (e.g., gut, skeletal muscle) dysfunction that resolves with proper treatment.[333] Heat injury may be difficult to distinguish from heat exhaustion during the early time course of heat exposure and can progress to heatstroke if not properly diagnosed and treated. A lack of mental status changes distinguishes heat injury from heatstroke. Rapid cooling is the most effective treatment because the reduction in body temperature mitigates organ injury, although it does not prevent dysfunction in all victims.

*Heatstroke* is clinically recognized by a triad of symptoms that include (1) a severe elevation in body temperature (typically, but not always, >40°C [104°F]); (2) CNS dysfunction that may include combativeness, delirium, seizures, and coma; and (3) a history of exposure to hot and humid weather or vigorous physical exertion.[333] The onset of heatstroke may be gradual (over hours or sometimes days) with nonspecific symptoms that are similar to heat exhaustion (e.g., weakness, dizziness, nausea, headache) but may also occur rapidly with no warning signs. CNS dysfunction is the hallmark clinical sign of heatstroke that requires immediate medical intervention to prevent permanent neurologic

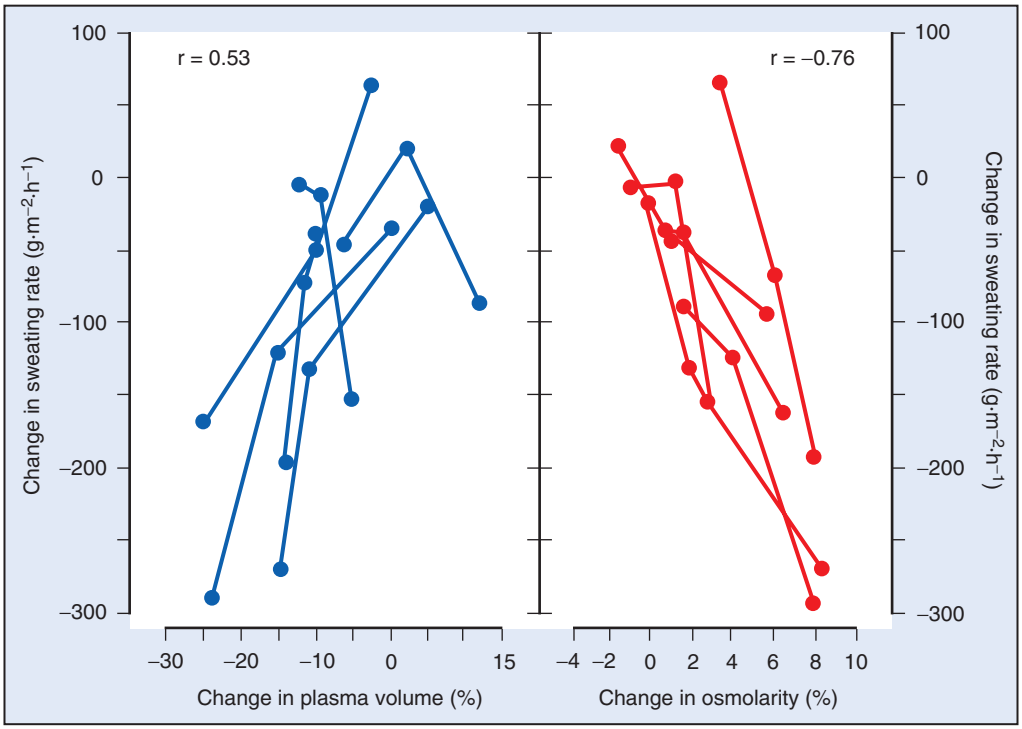



**FIGURE 12-5** Effect of reduced plasma volume or increased osmolality on the sweat rates of six individuals. *(Modified from Sawka MN, Young AJ, Francesconi RP, et al: Thermoregulatory and blood responses during exercise at graded hypohydration levels,* J Appl Physiol *59:1394, 1985.)*

damage. However, CNS dysfunction is not the sole determinant of heatstroke severity; injury to the gut, kidney, lung, spleen, liver, and skeletal muscle (specific to exertion) often occurs within days or weeks of clinical presentation.

Heatstroke may be classified as "classic" or "exertional" depending on the etiology of the condition. *Classic heatstroke* is observed in very young or elderly persons who are often immunocompromised before heat exposure and experience high mortality during annual summer heat waves. Classic heatstroke occurs at rest during exposure to high environmental temperature, with patients often presenting with hot, dry skin caused by failure of the normal sweating response (e.g., anhydrosis). Up to 60% of patients with classic heatstroke are hospitalized or found dead within 1 day of the reported onset of illness, underlying the life-threatening nature of this condition.[145] Several intrinsic factors may predispose infants to heatstroke death, including increased surface area–to–body mass ratio (accelerates heat gain), limited effective mechanisms of thermoregulation (e.g., suppressed behavioral adjustments), increased risk for dehydration (e.g., lack of water availability), and preexisting respiratory infections. On the other hand, older individuals have preexisting conditions, such as mental illness, prescription drug use (e.g., diuretics, anticholinergics), or infections, that predispose to passive heatstroke[10,69,315] (Box 12-1).

*Exertional heatstroke* (EHS) occurs primarily in young, physically fit individuals who collapse during exercise from heat stress.[333] Physical effort unmatched to physical fitness is a significant risk factor for EHS.[256] Anhydrosis is an uncommon finding in these patients; rather, continuation of sweating after cessation of exercise facilitates spontaneously cooling of EHS patients after collapse. Behavioral influences may increase the risk for EHS; highly motivated individuals may ignore the physiologic signs of

**TABLE 12-1** Heat Illness Symptoms and Management

| Condition | Symptoms | Management |
|---|---|---|
| Heat cramps | Brief, painful skeletal muscle spasms | Rest; replacement of electrolytes; avoid salt tablets. |
| Heat rash (miliaria rubra) | Blocked eccrine sweat glands | Cool, dry affected skin area; topical corticosteroids, aspirin |
| Heat exhaustion | Mild to moderate illness with inability to sustain cardiac output; moderate (>38.5° C [101.3° F]) to high (>40° C [104° F]) body temperature; often accompanied by dehydration | Move supine individual to cool, shaded environment, and elevate legs; loosen or remove clothing, and actively cool skin; administer oral fluids. |
| Heatstroke | Profound CNS abnormalities (agitation, delirium, stupor, coma) with severe hyperthermia (>40° C [104° F]) | Ensure an open airway, and move to a cool environment. Immediately cool to <39° C (102.2° F) using ice packs, water bath, wetting with water and continuous fanning; IV fluid administration; reestablish normal CNS function; avoid antipyretics or drugs with liver toxicity. |

Data from Bouchama A, Knochel JP: Heat stroke. *N Engl J Med* 346:1978, 2002; and Winkenwerder W, Sawka MN: Disorders due to heat and cold. In Goldman L, Ausiello DA, Arend W, et al, editors: *Cecil textbook of medicine,* ed 23, Philadelphia, 2007, Saunders, pp 763-767.
*CNS,* Central nervous system; *IV,* intravenous.

**BOX 12-1 Predisposing Risk Factors for Serious Heat Illness**

**Environmental Factors**
High ambient temperature
High humidity
Lack of air movement
Trees and shrubbery
Access to air-conditioning
Lack of shelter
Heat wave (≥3 days of temperatures >32.2°C [90°F])

**Individual Factors**
Age (small children, older adults)
Obesity
Poor physical fitness level
Lack of acclimatization
Dehydration

**Drug Use**
Diuretics
Anticholinergics (e.g., atropine)
β-Adrenergic blockers (e.g., propranolol)
Antihistamines
Amphetamines (e.g., Ecstasy)
Ergogenic aids (e.g., ephedra)
Antidepressants
Alcohol consumption

**Compromised Health Status**
Viral infection (e.g., pneumonia, mononucleosis)
Inflammation (e.g., fever)
Skin disorders (e.g., miliaria rubra, burns)
Cardiovascular disease
Diabetes mellitus
Malignant hyperthermia
Sickle cell trait

fatigue that would normally cause them to stop exercising.[2] EHS may occur in temperate conditions because of high physical demand or clothing that inhibits cooling (e.g., firefighter uniforms). Mortality from EHS is relatively low (~3% to 5%) compared with classic heatstroke (~10% to 65%), which is likely a consequence of preexisting medical conditions and chronic use of medications in the classic form that increase thermoregulatory and cardiovascular strain.[49,281,284,286]

## COMPENSABLE VERSUS UNCOMPENSABLE HEAT STRESS

*Heat stress* refers to conditions that increase body temperature, whereas *heat strain* refers to the physiologic consequences of heat exposure. Heat stress is typically described as *compensable* heat stress (CHS) or *uncompensable* heat stress (UCHS), with both these conditions affected by biophysical (environment, clothing) as well as biologic (hydration status, acclimatization) factors. CHS occurs when the rate of heat loss maintains balance with heat production, and steady-state body temperature can be sustained during physical activity or heat exposure. A physically fit individual wearing light clothing while exercising in moderate heat and low humidity would typically experience CHS. Under these conditions, elevated body temperature (<40°C [104°F]) can be sustained for a relatively long period until dehydration or energy depletion occurs.

Uncompensable heat stress is a consequence of an individual's evaporative cooling requirements being ineffective because of environmental or other conditions that impede cooling. For example, an individual wearing heavy protective clothing while exercising in a hot, humid environment would be expected to experience UCHS. Under UCHS conditions, body temperature will increase to the point of exhaustion. Even for individuals at low risk for UCHS, the physiologic demands for increased heat dissipation during prolonged exercise and heat stress cannot be endured indefinitely and often lead to circulatory insufficiency and collapse at relatively mild temperatures.

## HEATSTROKE EPIDEMIOLOGY AND RISK FACTORS

The ability to perform strenuous work in a hot environment is inversely related to the heat stress level, which can be assessed using the wet bulb globe temperature (WBGT) index. The WBGT for indoor or outdoor environments is determined as follows:

$$\text{Indoor WBGT} = 0.7T_w + 0.3T_{amb}$$

$$\text{Outdoor WBGT} = 0.7T_w + 0.2T_{bg} + 0.1T_{amb}$$

where $T_w$ is the natural wet bulb temperature, $T_{bg}$ is the black globe temperature, and $T_{amb}$ is the dry bulb temperature. $T_{bg}$ determines the radiant heat load with a specialized thermometer that is surrounded by a 15-cm (6-inch)–diameter blackened sphere. The WBGT is the most widely used index to determine safe limits of physical activity and establish strategies that will minimize the incidence of heat illness during military, athletic, or occupational tasks. The WBGT index does not take into consideration different clothing ensembles or exercise intensities, so the most practical and safe application of this measurement requires adjustment for these factors.

Heat waves are defined as three or more consecutive days during which the environmental temperature exceeds 32.2°C (90°F).[50] In summer 2003, Europe experienced 22,000 to 45,000 heat-related deaths during a 2-week period in which the average temperature was 3.5°C (6.3°F) above normal.[59,274] The European continent has experienced an increase in minimum daily temperatures over the last 30 years, and this trend will likely increase if average global temperatures continue to rise. A 1.4° to 5.8°C (2.5° to 10.4°F) increase in minimum daily temperatures in Europe is predicted over the next century.[59] Most prediction models suggest more severe and longer-duration heat waves, suggesting that the incidence of heatstroke will increase in future decades. Predictions based on climate variability data from the 1995 Chicago and 2003 Europe heat waves suggest that by 2090, heat waves in these cities will be 25% to 31% more frequent and last 3 to 4 days longer.[204] Another prediction model suggests a 253% increase in annual heatstroke deaths in the United Kingdom by 2050.[74]

The impact of climate change is not equally distributed across the globe because of regional variability in thermal tolerance that influences the incidence of heatstroke mortality. A study of 11 U.S. cities showed that threshold temperatures for heatstroke mortality are higher in warmer southern cities than in cooler northern cities.[63] A comparison of temperature-mortality relationships in southern Finland, southeastern New England, and North Carolina indicated that lower temperature thresholds in cooler climates are coupled with steeper temperature-mortality relationships.[73] Similarly, the upper safety limit of environmental temperatures in The Netherlands, London, and Taiwan are 16.5°, 19°, and 29°C (61.7°, 66.2°, 84.2°F), respectively.[193] A case study of 15 Marine Corps recruits who collapsed from heatstroke during training exercises in South Carolina showed that 73% previously resided in northern states and that 60% of cases occurred during the second week of training during the hottest summer months.[229] From 1980 to 2002, the highest EHS incidence in military recruits was in unacclimatized individuals from northern, cold-climate states who were enlisted for less than 12 months.[49] During July, many regions of the world have a WBGT index that is greater than 29°C (84.2°F), and military training often occurs in environments with a WBGT index that is greater than 35°C (95°F). During peacetime exercises, approximately 25% of fatal military EHS cases occur during the hottest summer months in recruits who have been in training camp less than 2 weeks.[197] Individuals from northern states are expected to be less acclimatized to hot, humid summer conditions than those from southern states. Heat acclimatization improves thermotolerance but requires several days to weeks of exposure to similar heat stress and exercise conditions to be fully effective. This likely accounts for hot days early in the summer showing a greater impact on heatstroke morbidity and mortality than those cases occurring later in the training process, after the protective effects of heat acclimatization have been realized.[115]

Humanity's impact on the landscape in conjunction with increased production of greenhouse gases may be creating the largest climate change. Urban heat islands are created in cities when vegetation is removed and blacktop roads and concrete buildings are erected. Temperatures may be 30° to 40°C (54° to 72°F) higher on asphalt roads and rooftops compared with those of the surrounding air.[95] Since 1978, urban sprawl has accounted for an increase in city temperatures in southeastern Asia of approximately 0.05°C (0.09°F) per decade.[147] Across the entire land mass of the United States, the surface temperature has increased approximately 0.27°C (0.49°F) per century because of changes in the land cover arising from agricultural and urban development.[147] Concrete and asphalt surfaces cool slowly at night when air temperature decreases, and this increase in urban heat storage magnifies the intensity of heat exposure experienced by individuals living in concrete urban structures.[57,171]

Several social factors predispose older adults to heatstroke mortality, including living alone, inability or unwillingness to leave one's home, residing on the top floor of buildings (heat rises), and annual income of less than $10,000.[32,219] Most heat wave early-warning systems emphasize use of air-conditioning, but availability and use of the units are limited by socioeconomic status because they are expensive to operate. A working air conditioner was the strongest protective factor against mortality during the 1999 heat wave in Chicago; fan cooling did not afford protection.[219] High mortality rates were recorded in Chicago despite extensive programs to educate high-risk populations, such as advising older adults to seek cool shelters or use air-conditioning. Approximately 10,000 elderly persons died during the France heat wave of 2003 primarily because of lack of air-conditioning units in residences and hospitals.[75,315] In 2005, Hurricane Katrina ravaged the U.S. Gulf Coast, and electrical failures caused high heatstroke mortality of older adults confined to residences, retirement homes, and hospitals because local temperatures exceeded 43°C (109.4°F). Increases in the average human life span, global climate change, and use of medications that compromise cardiovascular adjustments to heat stress will necessitate increased reliance on artificial cooling systems and education programs to prevent heatstroke deaths in vulnerable populations such as older adults.

The death toll of older adults from excessive heat may be small compared with that caused by aggravation of a preexisting illness. Heat strain imposes large cardiovascular demands on the body. Blood flow is shunted from the viscera to the skin to dissipate excess heat to the environment, making cardiovascular fitness a more important factor than age in determining an individual's susceptibility to heatstroke. Austin and Berry[14] examined 100 cases of heatstroke during three summer heat waves in St. Louis and reported cardiovascular illness in 84% of patients. Levine[183] found that heatstroke deaths are associated with arteriosclerotic heart disease (72%) and hypertension (12%). Cardiovascular deficiency impedes heat loss and compromises the ability to maintain cardiac output during prolonged heat exposure, leading to circulatory collapse and death. Older individuals may have impaired baroreceptor reflex modulation, lower sweat rates, longer time to onset of sweating, and diminished sympathetic nerve discharge, all of which increase the risk for heatstroke morbidity and mortality.[139,151,293] Minson and colleagues[212] demonstrated reliance on a higher percentage of cardiac chronotropic reserve in older than in younger men.

Preexisting illness is thought to compromise an individual's ability to respond appropriately to heat stress and can be a complicating factor, regardless of age. During a Chicago heat wave in 1995, 57% of heatstroke patients older than 65 had evidence of infection on clinical admission.[69] In Singapore, a young EHS victim had been ill for 3 days before heatstroke collapse.[53] It has been proposed that acute illness causes transient susceptibility to heatstroke in young, fit individuals exercising in the heat. For example, idiosyncratic episodes of hyperthermia were associated with acute cellulitis and gastroenteritis in soldiers exercising in the heat.[48,154] Four male Marine recruits presented with viral illness (mononucleosis, pneumonia) before collapse from exertional heat illness (EHI) during training exercises associated with "the Crucible" at Parris Island, South Carolina.[290] Peripheral blood mononuclear cells (PBMCs) from these recruits expressed higher levels of IFN-inducible genes than did those from controls who participated in the training event but did not collapse.[290] High plasma levels of IFN-α and IFN-γ mediate flulike symptoms during viral infection and are often associated with EHI/EHS.[29,290] In rats, exposure to lipopolysaccharide (LPS), a cell wall component of gram-negative bacteria, exacerbated inflammation, coagulation, and multiorgan system dysfunction from heat exposure.[187]

Several mechanisms may account for increased heatstroke risk in individuals who recently experienced a mild illness. Respiratory or gastrointestinal illness may cause mild dehydration, which is known to compromise reflexive thermoregulatory control mechanisms. However, euhydrated individuals also experience exacerbated hyperthermia, indicating that other factors are affecting body temperature control.[48] Fever is a common response to infection that may contribute to the rise in body temperature during heat exposure. Rapid development of hyperthermia leading to heatstroke in otherwise low- to medium-risk individuals is caused by activation of neuronal pathways of fever in the liver after pathogen exposure.[27] The liver reticuloendothelial system (RES) is composed of monocytes, macrophages, and Kupffer cells that detect pathogens and stimulate the complement cascade for rapid, local production of prostaglandin $E_2$ ($PGE_2$, a main fever inducer[27]). Binding of locally produced $PGE_2$ to receptors on afferent (vagal) neurons projecting to the POAH evokes behavioral and autonomic mechanisms of heat production/heat conservation and inhibits mechanisms of heat loss for rapid generation of fever.[27] Neuronal thermogenesis is an effective mechanism for rapid fever development during infection and could rapidly increase body temperature during heat exposure with mild illness. Regardless of the mechanism(s) for increased vulnerability, use of NSAIDs is contraindicated for alleviation of fever because of toxic organ effects. This suggests that monitoring of sickness symptoms and medication use before a predicted heat wave or an athletic or other physical event may be an effective method to identify individuals at high risk for both classic heatstroke and EHS.

The annual Muslim pilgrimage to Mecca (the Hajj) is associated with high heatstroke incidence each year and provides many lessons regarding etiologic factors that increase susceptibility. The Hajj takes place in the hot desert environment of Saudi Arabia during the extreme-weather months of May to September, with temperatures ranging from 38° to 50°C (100.4° to 122°F).[156] Hot weather combined with physical exertion (first day consists of a 3.5-km [2.2-mile] jog), heavy clothing that is traditional to the region (limits heat dissipation), and an older population (~50 years is an advanced age for this region) predispose many individuals to heatstroke. Clothing has a significant impact on Muslim women because they are required to wear darker clothing that covers a larger body surface area than clothing worn by men.[122] Medical conditions such as diabetes, cardiovascular abnormalities, and parasitic disease are common.[122] Heatstroke is a major concern, but heat exhaustion with water or salt depletion is also prevalent. Overcrowding and congestion impose large demands on sanitation services, as exemplified in the 1980s, when approximately 2 million people participated in the Hajj. Advances in modern technologies, such as more rapid transport, will likely introduce additional factors (e.g., lack of acclimatization, increased greenhouse gas production, increased congestion) to this already complex situation.

Protective clothing is a significant predisposing factor to EHS during athletic (heavy uniforms), military (chemical protective clothing), or occupational activities (e.g., pesticide application, firefighting, race car driving). Protective clothing often consists of multiple layers that insulate anatomic sites from heat exchange, including the skin and head.[254] Protective clothing in combination with strenuous work can cause rapid elevation in body temperature. Fifty-one cases of EHI were observed in military trainees in San Antonio, Texas, during participation in a 9.3-km (5.8-mile) march in full battle dress uniform and boots.[286] Lack of acclimatization to athletic uniforms and high environmental temperatures result in the majority of EHS cases in athletes occurring on the second or third day of exposure to hot weather before these

individuals are acclimatized to uniforms and environmental temperatures.[108,263]

## SKIN DISORDERS

*Miliaria rubra* (also known as "prickly heat" or "heat rash") occurs when the sweat gland ducts become blocked with dead skin cells or bacteria. Obstruction of the sweat glands causes eccrine secretions to accumulate in the ducts or leak into the deeper layers of the epidermis, causing a local inflammatory reaction consisting of redness and blister-like lesions. Miliaria rubra can increase body heat storage, reduce exercise performance in the heat (with as little as 20% of the body surface affected), and persist for up to 3 weeks after the rash appears to have resolved.[241,242] If heat illness is expected, the affected area of the skin should be cooled and dried to control infection. Topical corticosteroids or aspirin may be effective in reducing swelling and irritation.

*Sunburn* is a common reaction to ultraviolet (UV) radiation that causes epidermal and dermal injury and limits efficiency of the sweating response.[105] Sweating sensitivity as well as sweat rates on the forearm and back were significantly reduced 24 hours after artificial sunburn compared to responses observed in body regions that were protected from UV exposure.[240] Severe sunburn to major portions of the body can cause systemic toxicity that manifests as chills, fever, nausea, and delirium.[132] Sunburn effects on sweating are locally mediated at the sweat glands and dermal vasculature and can persist after the skin appears to be completely healed.[240] If the sunburn covers more than 5% of the body, heat exposure should be avoided until the skin has healed. Sunburn is a preventable disorder with the use of sun-blocking lotions, protective clothing, and shelter from sun exposure.

In the past decade, burn-related injuries requiring extensive skin grafts affected about 180,000 individuals in the United States.[7] Split-thickness skin grafts require transplantation of the entire epidermis as well as a portion of the dermis from a non-injured body site to the burned area. Because most split-thickness grafts do not contain functional sweat glands, revascularization and neural control of blood flow must be reestablished at the grafted site to support thermoregulatory control. Higher rectal temperature and a diminished tolerance for heat were observed in patients with healed burns over 40% of the body.[20,269,279,280] Interestingly, grafted burn patients showed diminished cutaneous vasodilation during heat exposure for more than 4 years after surgery, whereas the vasoconstrictor responses to cooling remained intact.[64,65] These findings suggest that grafted skin loses vasodilator control of body temperature while the vasoconstrictor response remains intact. A comprehensive review of the cutaneous vascular and sudomotor responses in human skin grafts is available.[62]

# PATHOPHYSIOLOGY OF HEATSTROKE

The pathophysiologic responses to heatstroke range from conditions experienced immediately after collapse to long-term changes that persist for several weeks, months, or years after hospital treatment and release. Clinical records documenting the immediate symptoms of heatstroke have provided most information regarding the severity of this syndrome. Case reports and epidemiologic studies from major heat events highlight the long-term outcomes, although the mechanisms mediating permanent organ dysfunction, which often leads to death, remain poorly understood. It is now believed that the long-term pathophysiologic responses to heatstroke are caused by a systemic inflammatory response syndrome (SIRS) that ensues after heat-induced damage to the gut and other organs.[34] Following damage to the epithelial membrane of the gut, endotoxin normally confined to the gut lumen is able to "leak" into the systemic circulation and elicit immune responses that cause tissue injury. The thermoregulatory, immune, coagulation, and tissue injury responses that ensue during long-term progression of heatstroke closely resemble those observed during clinical sepsis and are likely mediated by similar cellular mechanisms. Figure 12-6 provides an overview of the current understanding of the pathophysiologic responses that are thought to initiate and mediate heat-induced SIRS, as discussed in detail here.

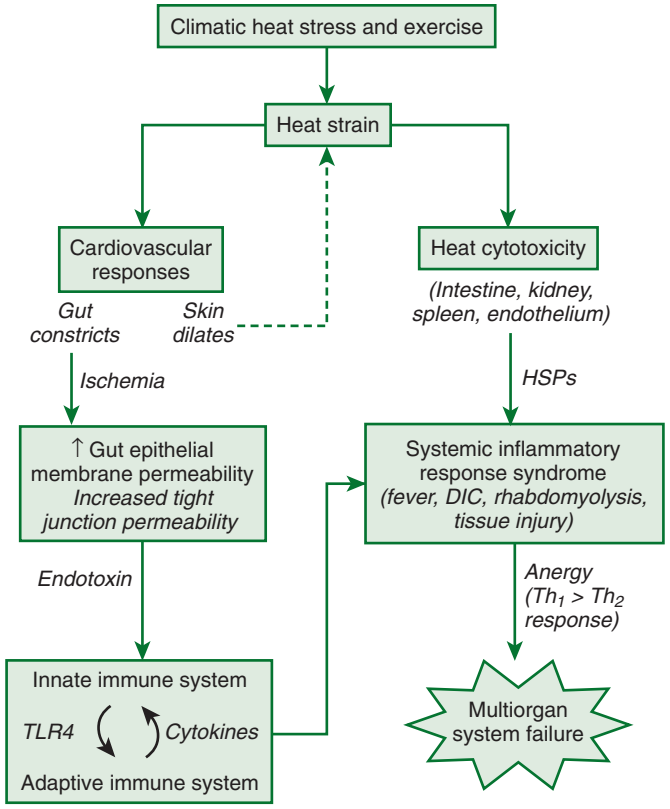



**FIGURE 12-6** Summary of heatstroke pathophysiologic responses that culminate in multiorgan system failure. An increase in heat strain stimulates a reflexive increase in cutaneous blood flow and decrease in splanchnic blood flow to facilitate heat dissipation to the environment. Gut ischemia causes increased epithelial membrane permeability and leakage of endotoxin into the systemic and portal circulation. Toll-like receptors (e.g., TLR4) detect pattern-associated molecular patterns on the cell membrane of endotoxin and stimulate proinflammatory and antiinflammatory cytokine production. Heat is toxic to several organs and stimulates secretion of heat shock proteins (*HSPs*) that interact with cytokines and other proteins to mediate the systemic inflammatory response syndrome (SIRS) of the host. Peripheral and central nervous system actions of cytokines and other mediators of SIRS are thought to mediate many of the adverse consequences of the heatstroke syndrome that lead to multiorgan system failure and death. *DIC,* Disseminated intravascular coagulation.

## BODY TEMPERATURE RESPONSES

The severity of hyperthermia varies widely between heatstroke patients at the time of collapse with values ranging from approximately 41°C (105.8°F) to 47°C (116.6°F).[36,51,118,285] During a summer heat wave in St. Louis in 1954, the core temperature of 100 heatstroke patients ranged from 38.5° to 44°C (101.3° to 111.2°F), with 10% of fatalities occurring below 41.1°C (106°F).[14] In some cases, individuals may tolerate hyperthermia without adverse side effects. During a competitive marathon race in California, a 26-year-old man maintained a rectal temperature of 41.9°C (107.4°F) for approximately 45 minutes without clinical signs of heat illness.[202] However, there are several reports of athletic, military, and occupational workers with core temperatures below 41.9°C who were hospitalized, experienced permanent CNS impairment, or died from EHS (Table 12-2).

Hypothermia and fever are often observed in patients and experimental animal models during heatstroke recovery. Hypothermia is not a universal heatstroke recovery response in humans, but it has been anecdotally observed following aggressive cooling treatment. Hypothermia manifests as a rapid

**TABLE 12-2** Clinical Characteristics of Exertional Heat Illness Cases

| Activity | Body Temperature °C (°F) | Age (Years) | Duration of Symptoms | Outcome |
|---|---|---|---|---|
| **Military Training** | | | | |
| Army (aviation) | >39.0 (102.2) | 18-59 | 10 min | CNS dysfunction* |
| Army (basic) | 40-41.1 (104-106) | 18-41 | 24 hr to 12 d | Death |
| Army (basic) | 41.1 (106) | 20 | 5 d | Recovery |
| Army (Singapore) | 40-42 (104-107.6)† | 18-29 | 45 min to 99 hr | Death |
| Marine Corps | <38.9-40.0 (102-104) | 17-30 | None | Recovery |
| Marine Corps | 39-42.5 (102.2-108.5)†‡ | 17-19 | >1 d | Recovery |
| Marine Corps | 41.1 (106) | NR | ≤12 hr | Hospitalization |
| NBC | 41.3 (106.3) | 25 | 12 d | Recovery |
| **Athletic Events** | | | | |
| 6-mile run | 39.2 (102.6)§ | 29 | 10 d | Death |
| Marathon run | 40.7 (105.3)‡ | Late 30s | 5 d | Recovery |
| Marathon run | 41.9 (107.4) | 26 | None | Recovery |
| Hajj rituals | <42 (107.6) | 32-80 | NR | Ataxia, infarction, death |
| | ≥42 (107.6) | NR | NR | Death |
| | 43.9 (111) | NR | NR | Recovery |
| Migrant farming | 42.2 (108) | 44 | None | Death |
| Firefighter training | 42.6 (108.7) | 22 | 9 d | Death |

*CNS,* Central nervous system; *d,* day(s); *NR,* not reported; *NBC,* nuclear, biologic, and chemical protective clothing.
*CNS dysfunction includes agitation, confusion, disorientation, delirium, poor memory, convulsions, and/or coma.
†Indicates patient cohorts with documented prodromal illness before heatstroke collapse.
‡Body temperature measured several minutes after collapse or cooling.
§Patient temperature increased to 41°C (105.8°F) on day 10 of hospitalization before death.

undershoot of body temperature below 37°C (98.6°F) and is thought to represent a loss of thermoregulatory control after heat-induced damage to the POAH. However, evidence in support of this hypothesis is lacking. That is, histology and magnetic resonance imaging (MRI) studies have failed to detect damage to the POAH despite extensive damage in other organs.[5,180,197,235,298,340] In experimental animals, hypothermia is a natural heatstroke recovery response associated with behavioral and autonomic thermoeffector responses that support a decrease in core temperature. Mud puppies are ectothermic species that rely on behavioral adjustments, such as the selection of different microclimates, to control body temperature. Mud puppies heat-shocked to about 34°C (93.2°F) behaviorally selected a cooler microclimate and maintained a significantly lower body temperature than did nonheated controls during 3 days of recovery.[137] This study did not determine the impact of hypothermia on survival, but the association of decreased body temperature with the selection of cool microclimates indicated this was a regulated response to a decrease in the temperature set point. Small rodents, such as mice, rats, and guinea pigs, showed reductions greater than 1.0°C (1.8°F) in body temperature that were associated with improved survival after passive heatstroke. In mice, hypothermia was associated with a 35% decrease in metabolic heat production and with the behavioral selection of microclimates that precisely regulated the depth and duration of this response.[180] Exposure of mice to warm ambient temperatures that prevented heat-induced hypothermia caused increased intestinal damage and mortality.[179,331] Hypothermia likely provides protection against heat-induced tissue injury in a manner similar to that shown for protection against other extreme environmental insults based on the temperature coefficient ($Q_{10}$) effect.

A common heatstroke recovery response observed in patients and animal models is recurrent fever during the days and weeks of recovery.[14,179,197,210] In mice, fever was observed within a day after passive heatstroke collapse and was associated with a 20% increase in metabolic heat production and increased plasma levels of the proinflammatory cytokine interleukin-6.[177,179,180] IL-6 is an important regulator of fever during infection and inflammation and may regulate fever during heatstroke recovery, although this hypothesis remains to be experimentally tested.[175] In patients, fever is reestablished after clinical cooling.[197] This is reminiscent of Liebermeister's experimental observations of the recurrence of fever after experimental cooling of the POAH of rats.[185] This suggests that fever may provide protection against some aspect of the SIRS and development of multiorgan dysfunction. The argument against this hypothesis is that recurrent hyperthermia in heatstroke patients has been anecdotally associated with poor outcome.[197,210,285] For example, an amateur long-distance runner was hospitalized for 10 days after collapsing from EHS during a 9.6-km (6-mile) foot race. This patient displayed moderate fever (>38°C [100.4°F]) during the first 4 days of hospitalization, but on the 10th day, convulsions induced a rapid increase of body temperature to 41°C (105.8°F). Rapid cooling and aspirin therapy were ineffective in reducing body temperature, and the patient died.[210] NSAIDs are potent inhibitors of prostaglandin production within the POAH, which is the mechanism by which these drugs normally inhibit fever during infection. Lack of an effect of aspirin on recurrent hyperthermia suggests this was not a true fever response, but rather a pathologic response to increased metabolic heat production induced by convulsions. Indomethacin is an NSAID with potent antipyretic actions in mice, but it failed to reduce fever during heatstroke recovery.[24] Unfortunately, prostaglandin production within the POAH has never been examined in animal heatstroke models, so it remains unknown if activation of these signaling pathways is associated with development of recurrent hyperthermia during heatstroke recovery. Physicians may attempt to treat recurrent hyperthermia episodes with NSAIDs, but these drugs are toxic to the liver and have been associated with the need for liver transplantation.[102,123,124,271,318]

## IMMUNE RESPONSES

During heat stress, blood flow to the skin is increased to facilitate heat loss to the environment and reduce the rate of total body heat storage. Increased skin blood flow is accompanied by a fall in splanchnic (i.e., visceral organ) blood flow as a compensatory mechanism to sustain blood pressure. Endotoxin is normally confined to the gut lumen by tight junctions of the epithelial membrane, but these junctions can become "leaky" following prolonged reductions in blood flow that cause ischemic stress.[117,170] Several lines of evidence support the hypothesis that endotoxin leakage from the gut lumen into the systemic circulation is the

initiating stimulus for heat-induced SIRS. First, systemic injection of LPS into experimental animals induces symptoms similar to those observed in heatstroke, including hyperthermia, hypothermia, fever, hypotension, cytokine production, coagulation, and tissue injury.[166,265,266] Second, increased portal or systemic endotoxin levels are observed in heatstroke patients and animal models. In primates, circulating endotoxin was detected at rectal temperatures above 41.5°C (106.7°F), with a precipitous increase at approximately 43.0°C (109.4°F).[99] Splanchnic blood flow shows an initial decrease at 40°C (104°F); the liver, which is an important clearance organ for endotoxin, shows damage at body temperatures of approximately 42° to 43°C (107.6° to 109.4°F).[39,40,53,117,223] In a young athlete with a body temperature of 40.6°C (105.1°F) on the second day of football practice, high circulating levels of endotoxin were associated with hemorrhagic necrosis of the liver.[108] In heatstroke patients, endotoxin was detected at approximately 42.1°C (107.8°F) and remained elevated despite cooling.[36] Third, rats rendered endotoxin tolerant after systemic injection of LPS are protected from heatstroke mortality. The protective effect of endotoxin tolerance is related to enhanced stimulation of the liver RES, which is composed of monocytes, macrophages, and Kupffer cells that are important for endotoxin clearance.[77,78] RES stimulation reduced and RES blockade increased mortality of heat-stressed rats.[78] Fourth, antibiotic therapy protects against heatstroke in several species. In dogs, antibiotics reduced gut flora levels and improved 18-hour survival by more than threefold when provided before heat exposure.[46] In rabbits with heatstroke, hyperthermia and endotoxemia were reduced after administration of oral antibiotics.[45] Anti-LPS hyperimmune serum reversed the heatstroke mortality of primates and returned plasma LPS levels to baseline, but it was ineffective at the highest body temperature of 43.8°C (110.8°F), indicating hyperthermia alone may cause irreversible organ damage and death.[100]

The heat-induced SIRS is initiated by the innate and adaptive immune systems, which interact to sense the presence of endotoxin and orchestrate an immunologic response. The innate immune system comprises monocytes, macrophages, and neutrophils that use pattern recognition receptors (PRRs) on their cell surfaces to recognize pattern-associated molecular patterns (PAMPs) on the cell surface of endotoxin and other invading pathogens.[144,310] Toll-like receptors (TLRs) are a class of PRRs that have been widely studied in the immune response to infection.[209,310] Ten mammalian TLRs have been identified, and the specific pathogenic ligands that activate these PRRs are known (Table 12-3).

Toll-like receptor 4 (TLR4) is the principal receptor for LPS that stimulates gene transcription factors, such as nuclear factor (NF)–κB, to increase the synthesis of a variety of immune modulators in response to endotoxin. Endotoxin infection (i.e., sepsis) is associated with increased expression of TLR4 on circulating human PBMCs, as well as on mouse liver and spleen macrophages.[310,311] In the 1960s, a spontaneous mutation in the *TLR4* gene was discovered in C3H/HeJ mice, which has been an important animal model to determine the role of TLR4 in endotoxin and heatstroke responsiveness. C3H/HeJ mice experienced mortality during the SIRS to bacterial infection, which was caused by inability to induce the full complement of immune responses.[113] These mice also experienced more severe classic heatstroke responses than did wild-type mice. These included profound and sustained hypothermia, rapid induction of circulating IL-1β, IL-6, tumor necrosis factor (TNF)–α, high-mobility group box 1 (HMGB1), more severe liver damage, and increased mortality through 3 days of recovery.[67] HMGB1 is a classic alarmin that binds a wide range of molecules to dictate the resulting immune response. On binding LPS, HMGB1 induces a SIRS composed of elevated IL-1β and IL-6 secretion.[135] Given that TLR4 polymorphisms exist in humans, this may be one of several genetic factors that predispose to mortality during the SIRS to heatstroke.[7,85]

Specificity of immune responses is provided by B and T cells of the adaptive immune system. These cells respond to antigens by secreting cytokines, which are intercellular immune signals that elicit proinflammatory (T helper type 1 [$Th_1$]) and antiinflammatory (T helper type 2 [$Th_2$]) actions during the progression of the SIRS. The actions of cytokines depend on the nature of the danger signal, the target cells with which they interact, and the cytokine "milieu" in which they function. $Th_1$ and $Th_2$ cytokines function in a negative feedback pathway to regulate each other's production and maintain a delicate balance of inflammatory reactions. Anergy is thought to be a consequence of inadequate $Th_2$ cytokine production late in the SIRS. For example, increased patient mortality from peritonitis is associated with the inability to mount a $Th_2$ cytokine response[127] (see Figure 12-6).

*Alarmins* are endogenous PAMPs released from stressed or injured tissues that initiate restoration of homeostasis after an infectious or inflammatory insult.[23] HMGB1 is a highly conserved nuclear protein that functions as an alarmin after release from necrotic (but not apoptotic) cells.[273] *Necrosis* is premature death of cells in a tissue or organ in response to external factors, such as pathogens and toxins. Because necrosis is detrimental to the host, it is associated with an inflammatory response. *Apoptosis* refers to genetically programmed cell death that does not elicit an inflammatory response because it is beneficial to the host.

**TABLE 12-3 Toll-Like Receptors of the Innate Immune System**

| Toll-Like Receptor | Ligand | Cell/Tissue Types |
|---|---|---|
| TLR1 | Triacyl lipopeptide | Monocytes, macrophages, DCs, polymorphonuclear leukocytes, B and T cells, NK cells |
| TLR2 | Lipopolysaccharide<br>Peptidoglycan<br>Lipoteichoic acid<br>Measles virus<br>Human cytomegalovirus<br>Hepatitis C virus<br>Zymosan<br>Necrotic cells | Monocytes, granulocytes<br>Brain, heart, lung, spleen |
| TLR3 | Viral double-stranded RNA | DCs, T cells, NK cells, monocytes, granulocytes<br>Placenta, pancreas |
| TLR4 | Lipopolysaccharide<br>Fibrinogen<br>Heat shock proteins<br>High-mobility group box 1 | B cells, DCs, monocytes, macrophages, granulocytes, T cells<br>Spleen |
| TLR5 | Flagellated bacteria | Monocytes<br>Ovary, prostate |
| TLR6 | Diacyl lipopeptide | B cells, monocytes<br>Thymus, spleen, lung |
| TLR7 | Single-stranded RNA | Monocytes, B cells, DCs<br>Lung, placenta, spleen, lymph node, tonsil |
| TLR8 | Single-stranded RNA | Monocytes<br>Lung, placenta, spleen, lymph node, bone marrow, PBLs |
| TLR9 | CpG DNA | B cells, DCs<br>Spleen, lymph node, bone marrow, PBLs |
| TLR10 | Unknown | B cells<br>Spleen, lymph node, thymus, tonsil |

Data from Medvedev AE, Sabroe I, Hasday JD, et al: Tolerance to microbial TLR ligands: Molecular mechanisms and relevance to disease, *J Endotoxin Res* 12:133, 2006; and Tsujimoto H, Ono S, Efron PA, et al: Role of Toll-like receptors in the development of sepsis, *Shock* 29:315, 2008.
*CpG*, Deoxycytidylate-phosphate-deoxyguanylate; *DC*, dendritic cell; *DNA*, deoxyribonucleic acid; *NK*, natural killer; *PBL*, peripheral blood leukocyte; *RNA*, ribonucleic acid.

Release of HMGB1 from necrotic cells stimulates $Th_1$ cytokine production late in the sepsis syndrome and is a purported mediator of lethality; this shift in the balance of cytokines from a $Th_2$ to $Th_1$ phenotype is a potential mechanism of sepsis lethality. In human PBMCs, HMGB1 interacts with TLR2 and TLR4 to enhance $Th_1$ cytokine production in synergy with LPS.[135] Elevated serum HMGB1 levels are observed 8 to 32 hours after LPS injection in mice. Anti-HMGB1 antibodies did not protect against LPS-induced mortality unless the antibodies were provided 12 and 36 hours after LPS exposure.[323] The delayed kinetics of HMGB1 and the association of elevated serum levels of this protein with poor outcome in sepsis patients suggest that HMGB1 detection late in the SIRS may be a sensitive clinical marker of disease severity.[125,299,323]

## COAGULATION

Disseminated intravascular coagulation (DIC) is a common clinical symptom of heatstroke that manifests as two distinct forms (Figure 12-7). Microvascular thrombosis is a form of DIC characterized by fibrin deposition and/or platelet aggregation that occludes arterioles and capillaries and predisposes to multiorgan system dysfunction.[182] Microvascular thrombosis is frequently observed in response to sepsis or trauma. DIC associated with consumptive coagulation is characterized by excessive blood loss when platelets and coagulation proteins are consumed faster than they are produced.[13,16] Hemorrhagic complications in heatstroke patients include prolonged bleeding from venipuncture sites or other areas (e.g., gums), which can have a fatal outcome.[156] The primary event that initiates coagulation in heatstroke patients is thermal injury to the vascular endothelium.[30,34,217] In vitro studies have shown the ability of heat (43° to 44°C [109.4° to 111.2°F]) to directly activate platelet aggregation and cause irreversible hyperaggregation despite cooling.[97,330] Cancer patients treated with whole-body hyperthermia (41.8°C [107.2°F] for 2 hours) showed decreased fibrinogen and plasminogen at body temperatures as low as 39°C (102.2°F), alterations in factor VII activity at 41.8°C (107.2°F), and decreased platelet concentrations from the time of maximum body temperature through 18 hours of recovery.[296]

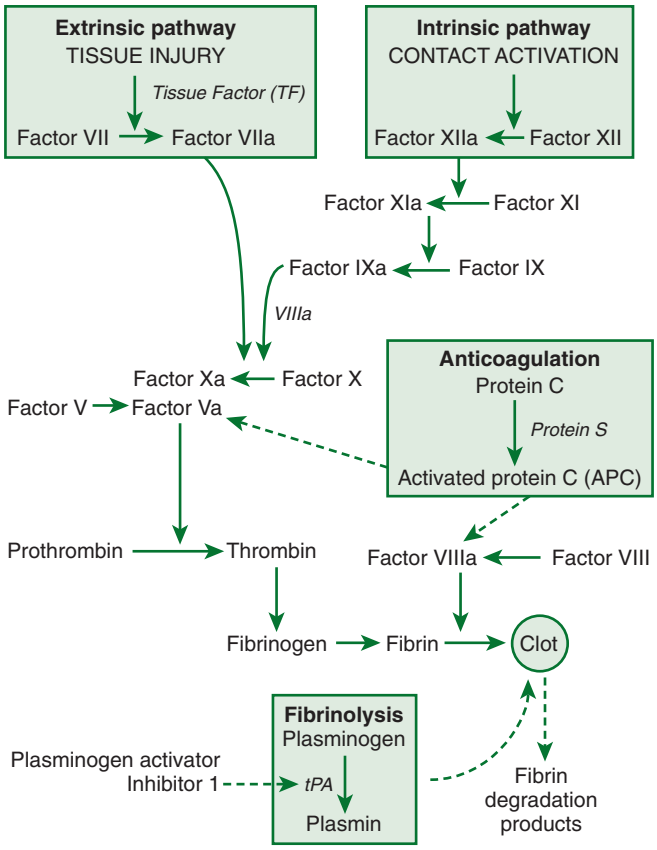



**FIGURE 12-7** Pathways of disseminated intravascular coagulation (DIC). The coagulation cascade is stimulated by the extrinsic pathway (also known as the tissue factor [TF] pathway) and the intrinsic pathway (also known as the contact activation pathway). Both pathways represent a series of enzymatic reactions that result in formation of a fibrin clot. Fibrinolysis represents the pathway by which the fibrin clot is resorbed through the actions of plasmin. The major physiologic anticoagulant is protein C, which is activated by protein S and inactivates factors Va and VIIIa to inhibit clot formation. Lipopolysaccharide, interleukin-1, and tumor necrosis factor affect DIC by stimulating TF formation and inhibiting the inactivation of factors Va and VIIIa, which prolong clot formation.

Several proteins, including HMGB1, IL-1, TNF, and activated protein C (APC), affect the coagulation, anticoagulation, and fibrinolytic pathways. In rats, HMGB1 in combination with thrombin caused excess fibrin deposition in glomeruli, prolonged clotting times, and increased sepsis mortality compared with thrombin alone.[140] As demonstrated in vitro, the effect of HMGB1 protein is caused by inhibition of the APC pathway and stimulation of tissue factor expression on monocytes.[140] Cytokines stimulate microvascular thrombosis by interacting with neutrophils, macrophages, platelets, and endothelium to increase expression of intracellular adhesion molecules. Increased expression of cell adhesion molecules, neutrophil adhesion, and release of reactive oxygen species cause endothelial activation and injury.[207] APC is an important component of the anticoagulation pathway that inactivates factors Va and VIIIa to inhibit fibrin clot formation. In septic patients, reduced APC production was associated with increased risk of mortality from systemic inflammation and DIC.[88,184] In addition to its anticoagulation properties, APC possessed antiinflammatory and antiapoptotic properties that protected against experimental sepsis and heatstroke.[54,305]

Typical clinical measures of coagulation include prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen. PT in combination with aPTT assesses the time for plasma clot formation to occur in response to exogenous tissue factor and is a sensitive measure of responsiveness of the coagulation pathway. The reference range for PT is approximately 12 to 15 seconds and may be prolonged several-fold in heatstroke patients. The aPTT normally ranges from 30 to 40 seconds and is used clinically to monitor treatment effects of anticoagulants such as heparin. Fibrinogen is an acute-phase protein synthesized by the liver that is normally in the range of 2 to 4 g/L. Low fibrinogen levels indicate liver damage or DIC, whereas elevated levels are a clinical sign of systemic inflammation. DIC can be difficult to diagnose, but low fibrinogen levels and prolonged PT or aPTT are strong clinical indicators in critically ill patients.

## TISSUE INJURY

Multiorgan system failure is the ultimate cause of heatstroke mortality and is a result of SIRS, which ensues after heat-induced damage to the gut and other tissues.[34] A variety of noninfectious and infectious clinical conditions are associated with SIRS, and similar physiologic mechanisms are thought to mediate the pathogenesis of these conditions (Box 12-2).

The term *sepsis* refers to SIRS associated with the presence of infection. Much of the understanding of pathophysiologic mechanisms mediating heat-induced SIRS has been obtained from sepsis studies. This section provides an overview of the responses that constitute heat-induced SIRS and our current understanding of the pathophysiologic mechanisms that mediate the adverse events of this syndrome.

The severity of heatstroke is primarily related to the extent of damage to the brain, liver, and kidneys and is clinically identified by elevations in serum biomarkers, such as creatine kinase (CK), blood urea nitrogen (BUN), aspartate aminotransferase/transaminase (AST), and alanine aminotransferase/transaminase (ALT). CK is released from muscle and is a marker of skeletal muscle injury (also known as rhabdomyolysis), myocardial

**BOX 12-2 Predisposing Risk Factors for Serious Heat Illness**

**Clinical**

Neurologic symptoms (fatigue, weakness, confusion, stupor, coma, dizziness, delirium)
Tachycardia
Nausea, vomiting, diarrhea
Headache
Hypotension
Oliguria, multiorgan system failure
Hyperventilation
Shock

**Laboratory**

Metabolic acidosis
Elevated hematocrit
Elevated blood urea nitrogen (BUN), aspartate transaminase (AST), and alanine transaminase (ALT)
Elevated lactate
Disseminated intravascular coagulation
Elevated cytokines
Circulating endotoxin

infarction, muscular dystrophy, and acute renal failure. BUN is a measure of the amount of nitrogen in the blood in the form of urea, which is secreted by the liver and removed from the blood by the kidneys. A high BUN concentration is typically regarded as an indication of impaired renal function, although BUN levels may be altered by conditions unrelated to heat illness, including malnutrition, high-protein diets, burns, fever, and pregnancy.[2,270,321] AST is released by the liver and skeletal muscle and may be a clinical sign of congestive heart failure, viral hepatitis, mononucleosis, or muscle injury. ALT is released by the liver, red blood cells, cardiac muscle, skeletal muscle, kidneys, and brain tissue. AST and ALT are common clinical markers of liver function in heatstroke patients despite multiple tissue sources of these enzymes and occasional false-negative results that complicate interpretation. Unfortunately, all these biomarkers are released by a variety of tissues and altered by heat-exhaustive exercise and thus do not always provide a precise measure of the extent of tissue injury.[106,112,283] The extent and time course of organ injury vary widely between individuals. Tissue injury manifests as primary and/or secondary multiorgan dysfunction, depending on whether heat toxicity alone or in combination with a SIRS causes cellular damage.[8] Gut epithelial barrier disruption is an example of primary organ dysfunction evident at the time of heatstroke collapse. Hyperthermia degrades epithelial membrane integrity and causes microhemorrhages, dilation of the central lacteals of the microvilli, and blood clots within the stomach and small intestine[37,117,177,234] (Figure 12-8).

It is often difficult to determine if organ injury is caused by primary or secondary factors.[30,69,108,177,197] For example, protein clumping in kidney tubular epithelial cells may be a result of heat toxicity, elevated myoglobin levels, or DIC.[37,53,108,177,252,322] A conscious mouse model has shown that kidney damage is present within approximately 2 hours following heatstroke collapse and remains elevated through 24 hours of recovery.[177] In heatstroke patients, acute renal failure is a nearly universal finding that is accompanied by decrements in function within 24 hours of admission to the intensive care unit.[246] In patients who survive more than 24 hours, severe hypotension, dehydration, BUN, and oliguria are associated with tubular necrosis or intertubular edema.[197] Primary changes in the spleen are even less well understood, but cytoplasmic protein clumping is thought to be a consequence of this organ being "simply cooked and coagulated."[53]

A hallmark of heatstroke, CNS dysfunction is dominant early in the disorder. Patients are often confused, delirious, combative, or comatose at clinical presentation. Hyperthermia with exercise is also associated with reduced cerebral blood flow, which may account for these CNS abnormalities.[226] Despite rapid treatment, about 30% of heatstroke survivors experience permanent decrements in neurologic function.[10,34,69] CNS dysfunction is often associated with cerebral edema and microhemorrhages at autopsy in heatstroke patients.[5,53,197,301] The blood-brain barrier (BBB) is a semipermeable membrane that allows selective entry of substances (e.g., glucose) into the brain while blocking entry of other substances (e.g., bacteria). Hyperthermia increases BBB permeability in experimental animal models, which permits leakage of proteins and pathogens from the systemic circulation into the brain. Computed tomography (CT) scans have been used to examine CNS changes in heatstroke patients. In the 1995 Chicago heat wave, atrophy, infarcts of the cerebellum, and edema were evident in older adult victims. CT scans also revealed severe loss of gray-white matter discrimination (GWMD), which was associated with headache, coma, absence of normal reflexive responses, and multiorgan dysfunction.[301] Loss of GWMD is a result of increased brain water content, which is in line with occurrence of edema in heatstroke victims. If GWMD provides an early, sensitive measure of brain injury, it will be a powerful prognostic indicator of outcome for heatstroke patients.

Exertional heatstroke is often associated with rhabdomyolysis, which is a form of skeletal muscle injury caused by leakage of muscle cell contents into the circulation or extracellular fluid. Myoglobin released from damaged muscle cells is filtered and metabolized by the kidneys. When severe muscle damage occurs, the renal threshold for filtration of myoglobin is exceeded, and this protein appears in the urine in a reddish brown color.[96] Myoglobin is toxic to nephrons and causes overproduction of uric acid, which precipitates in the kidney tubules to cause acute renal failure, coagulopathy, and death if not rapidly detected and treated.[15,96,190,244,322] Not all cases of rhabdomyolysis are associated with myoglobinuria; many patients can be asymptomatic. Clinical markers of rhabdomyolysis include elevated myoglobin, CK, aldolase, lactate dehydrogenase, ALT, and AST, which are influenced by a variety of factors (type, intensity, and duration of exercise; gender; temperature; altitude) and released by more than one organ or tissue.[58,211,270] If a clinical diagnosis of rhabdomyolysis is confirmed, immediate medical attention is imperative

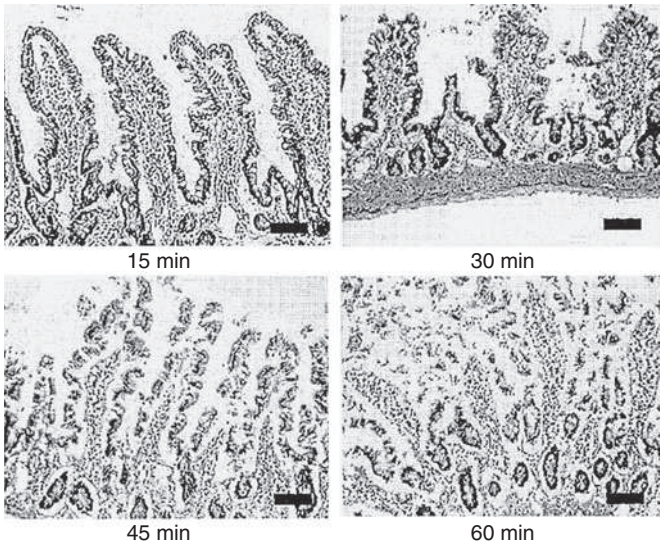



**FIGURE 12-8** Effect of heating on villus structure. Representative light micrographs of rat small intestinal tissue over a 60-minute course at 41.5° to 42°C (106.7° to 107.6°F). Note the generally normal-appearing villi at 15 minutes (slight subepithelial space at villous tips), compared with initial sloughing of epithelia from villous tips at 30 minutes, massive lifting of epithelial lining at top and sides of villi at 45 minutes, and completely denuded villi at 60 minutes. *Bars* represent 100 µm. *(From Lambert GP, Gisolfi CV, Berg DJ, et al: Selected contribution: Hyperthermia-induced intestinal permeability and the role of oxidative and nitrosative stress,* J Appl Physiol *92:1750, 2002, with permission.)*

because 50% mortality rates from acute renal failure have been documented for this condition.

Liver failure is one of the most common causes of morbidity and mortality in patients during the later stages of recovery. The time course of liver damage differs from that of the other organs and often does not peak until approximately 24 to 48 hours after heat exposure. For example, liver damage consisting of centrilobular degeneration and necrosis with parenchymal damage was only evident in EHS patients who survived more than 30 hours.[197] In addition, enhanced breakdown of fat or inability of the mitochondria to use fat results in heatstroke-associated fatty liver changes.[53] Disturbances in plasma glucose homeostasis are a sign of liver damage that may cause hyperglycemia or hypoglycemia as a result of dysfunction of phosphoenolpyruvate carboxykinase, which is a regulatory enzyme of the liver's gluconeogenic pathway.[30,177] Liver dysfunction may also contribute to increased circulating endotoxin levels because of the important bacterial clearance function of this organ.[40,223] Unfortunately, many heatstroke patients require liver transplantation. Use of antipyretic drugs, such as acetaminophen (Tylenol), has been associated with hepatic failure.[102,123,124,263,318]

Many patients are released from the hospital after several days or weeks of treatment and continue to experience organ dysfunction during the ensuing years of recovery. Following the 2003 heat wave in France, mortality increased from 58% at day 28 of hospitalization (mean hospital stay, 24 days) to 71% by the second year of recovery.[10] An epidemiologic study of military EHS patients showed a twofold increased risk of death from cardiovascular, kidney, and liver disease within 30 years of hospitalization.[320] Several of the clinical responses (hyperthermia, dehydration, kidney/liver damage) occurring during progression or shortly after heatstroke collapse are clinically recognized and treated. However, those occurring during the months and years after hospitalization are underreported. The mechanisms responsible for long-term decrements in organ function remain poorly understood.

## CYTOKINES

Cytokines are a class of intercellular protein messengers released from macrophages, T and B cells, endothelial cells, astrocytes, and other cell types that mediate inflammatory reactions to disease and injury.[55,148,200,282,312] Cytokine-inducing stimuli include bacterial and viral infection,[76,245] psychological stress,[196,232] heat stress,[29,37,45,126,177,186] whole-body hyperthermia,[220] and exercise.[47,213,222,300] The defining characteristics of cytokines include a lack of constitutive production, the ability to regulate each other's production, and overlapping actions that depend on the target cell type and cytokine milieu in which they function. Cytokines act over short distances and time spans (half-life, generally <60 minutes) and are usually present at low concentrations in the circulation. Cytokines bind reversibly to high-affinity cell surface receptors and stimulate intracellular signaling pathways (e.g., NF-κB) that alter the transcription of genes involved in immune responses.

Several lines of evidence link cytokines with symptoms of the heat-induced SIRS. These include induction of heatstroke symptoms by cytokine injection in experimental animal models, association of increased circulating cytokine levels with heatstroke morbidity/mortality, and effectiveness of cytokine neutralization in altering heatstroke mortality in animal models. Peripheral injection of IL-1β, IL-2, IL-6, IL-10, TNF-α, and platelet-activating factor into experimental animals replicates the pathophysiologic responses observed in heatstroke, including hyperthermia, hypothermia, fever, increased vascular permeability, DIC, and death.[163,174,233,237,276,309] Simultaneous injection of multiple cytokines (e.g., IL-1 and TNF) is most effective in mimicking heatstroke symptoms and has shed light on cytokine interactions in vivo that orchestrate SIRS. Increased circulating levels of IL-1α, IL-1β, IL-1 receptor antagonist (IL-1ra, a naturally occurring antagonist of IL-1), IL-6, soluble IL-6 receptor (sIL-6R), IL-8, IL-10, IL-12, IFN-γ, TNF-α, and soluble TNF receptor (sTNFR) concentrations are typically observed at the time of heatstroke collapse or shortly after cooling.[29,36,37,118,122,177] Sustained high IL-6 levels during cooling correlate with heatstroke severity, tissue injury, and death, whereas high circulating IL-8 levels are implicated in leukocyte activation and coagulation in EHS patients.[33] The reciprocal regulation of IL-12 and IL-10 production suggests complex interactions in heat-induced SIRS, but the function of these cytokines has not been clearly delineated. As previously mentioned, high IFN-inducible gene expression and IFN-γ levels are clinical measures of viral or intracellular bacterial infection and are evident in EHS patients with preexisting infections.[291]

Failure of clinical and animal studies to correlate cytokine production with specific heatstroke responses probably results from the short half-life of these proteins, local tissue concentrations exceeding those in the circulation, and/or the presence of soluble cytokine receptors that mask detection or alter cytokine action(s).[3,29,33,36,118,122,165,275] For example, sTNFR inhibits the actions of TNF and is often higher in heatstroke survivors than in nonsurvivors, suggesting TNF might mediate lethality.[118] On the other hand, sIL-6R might potentiate endogenous IL-6 effects by increasing concentration of available IL-6 signaling receptors on cell membranes (known as a trans-signaling effect) or reducing IL-6 signaling through competitive binding with IL-6 receptors that are already present on the cell membrane (Figure 12-9).

Although cytokines are known to interact with one another, their soluble receptors, and other endogenous stress hormones (e.g., glucocorticoids) during SIRS, it remains unknown how these interactions in vivo affect heatstroke outcome. Taken together, results from the few antagonism/neutralization studies conducted to date indicate that high levels of cytokines may be detrimental for heatstroke recovery; however, baseline (permissive) actions of some cytokines (e.g., IL-6, TNF, or proteins affected by their actions) appear to be essential for survival.[175] Clearly, more research is required in this area to determine the multitude of cytokine actions in heat-induced SIRS and determine protective versus detrimental effects of the proteins on multiorgan system function.

## HEAT SHOCK PROTEINS

Heat shock proteins (HSPs) are molecular chaperones that prevent misfolding and aggregation of cellular proteins during exposure to stressful stimuli.[86,121,142,189] HSPs are found in organisms ranging from bacteria to humans. Their chaperoning activities protect against environmental (heavy metals, heat stress), physiologic (cell differentiation, protein translation), and pathologic (infections, ischemia/reperfusion) stimuli that cause cellular damage.[142,167,189] HSPs were originally discovered in *Drosophila melanogaster,* when puffs associated with novel protein synthesis appeared on the giant chromosomes of the salivary glands in response to heat stress.[262,306] It was later discovered that heat denaturation of mature proteins inside the cell was the cellular signal that increased protein synthesis in response to heat stress in *Drosophila.*[130]

Heat shock proteins are grouped into families according to their molecular mass, cellular localization, and function (Table 12-4).

Also referred to as sHSP, HSP 27 is a constitutively expressed cytosolic and nuclear protein with cytoskeletal stabilization and antiapoptotic functions.[12,173,243] HSP 60 exists in the mitochondria and cytosol, is released from PBMCs on LPS stimulation, and functions as a "danger" signal for the innate immune system. HSPs interact with PAMPs (e.g., TLRs) to stimulate monocytes, macrophages, and dendritic cells to produce cytokines.[44,224] The HSP 70 family has been extensively studied for protective function(s) against thermal stress,[149,338] ischemia/reperfusion,[201,251] tissue injury,[42] glucose deprivation,[332] and sepsis.[172,316] HSPs 70 function in concert with other molecular chaperones, such as HSP 90 and HSP 110, to facilitate LPS and antitumor responses.[136]

Gene expression of HSPs is mediated primarily at the level of gene transcription by a family of heat shock transcription factors (HSFs) that interact with the heat shock regulatory element (HSE) in the promoter region of genes. HSF-1 is the major stress responsive element in mammalian cells that is activated by febrile-range temperatures.[317,336] HSF-1 interacts with HSEs on cytokine genes to alter transcription and confer protection against endotoxin and

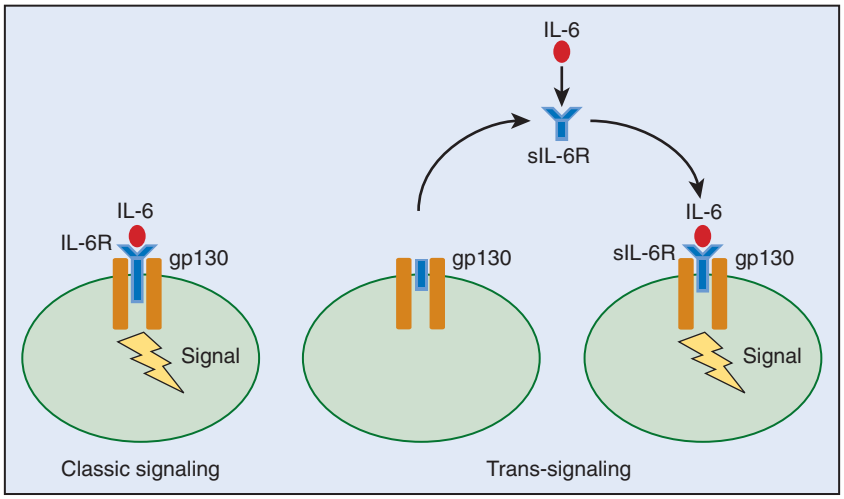



**FIGURE 12-9** Interleukin-6 receptor signaling pathways. Classic signaling involves binding of IL-6 to the membrane bound IL-6 receptor (IL-6R), which stimulates an interaction between the IL-6:IL-6R complex and the membrane-bound glycoprotein 130 (gp130) to initiate intracellular signaling. Trans-signaling occurs when the extracellular domain of the membrane-bound IL-6R is proteolytically cleaved, leading to generation of the soluble IL-6R (sIL-6R) that binds IL-6. The IL-6:sIL-6R complex can stimulate cells that only express gp130 (i.e., do not normally possess the transmembrane IL-6R) to transmit an intracellular signal. Cells that express gp130 only would not be able to respond to IL-6 in the absence of sIL-6R.



other infectious and inflammatory stimuli. In gene-transfected human PBMCs, inhibition of TNF-α, IL-1β, IL-10, and IL-12 in response to LPS was specific to HSPs 70 overexpression.[71] A lack of effect of HSP 70 on IL-6 gene transcription may be an indirect mechanism of protection, because IL-6 functions in a regulatory feedback loop to inhibit IL-1 and TNF production, which are $Th_1$ cytokines with potent proinflammatory activities.[71,82,83,324] In murine macrophages, HSP 70 inhibited IL-12 ($Th_1$) and stimulated IL-10 ($Th_2$) production in response to LPS.[324] The shift from $Th_1$ to $Th_2$ cytokine production may be a mechanism by which HSP 70 protects against bacterial infection.

**TABLE 12-4** Heat Shock Protein (HSP) Structure and Function

| Family | Function | Attributes |
|---|---|---|
| HSP 27 (sHSP) | Antiapoptotic | Constitutively expressed |
| | Cytoskeletal stabilization | Cytosolic and nuclear |
| HSP 60 | Protein refolding<br>Prevents aggregation of denatured proteins<br>Immune responses | Mitochondria and cytosol |
| HSP 70 family | | |
| HSP 72 | Thermotolerance | Highly inducible |
| HSP 73 (HSC 70) | Molecular chaperone | Constitutively expressed |
| HSP 75 | Molecular chaperone | Mitochondrial |
| HSP 78 (GRP 79, Bip) | Cytoprotection | Endoplasmic reticulum |
| HSP 90 family: HSP 90 | | |
| GRP 96 | Glucocorticoid receptor functioning<br>Glucose regulation | Cytosolic and nuclear<br>Endoplasmic reticulum |
| HSP 110/104 | Molecular chaperone<br>Tumor antigen presentation | Cytosolic |

Data from Hartl FU, Hayer-Hartl M: Molecular chaperones in the cytosol: From nascent chain to folded protein, *Science* 295:1852, 2002; and Kregel KC: Heat shock proteins: Modifying factors in physiological stress responses and acquired thermotolerance, *J Appl Physiol* 92:2177, 2002.
*Bip*, Binding protein; *GRP*, glucose-regulated protein; *HSC*, heat shock cognate.

*Heat strain* is a consequence of the time and intensity of heat exposure. These factors interact in vivo to influence the magnitude and kinetics of HSP expression. In human PBMCs, maximal expression of intracellular HSPs 70 was observed between 4 and 6 hours after a brief heat shock (43°C [109.4°F] for 20 minutes).[289] Increased expression of HSPs 10, 20, 40, 60, 70, 90, and 110 was observed in PBMCs from EHS patients or following exposure to hypoxia in vitro.[288,291] Anatomic differences in the magnitude and kinetics of in vivo expression have also been observed, with HSP 70 expression occurring within 1 hour in the brain, lungs, and skin and being delayed until 6 hours after heat exposure in the liver of rats.[26] In mice, liver expression of HSP 70 showed progressive increase beginning approximately 6 to 24 hours after collapse from passive heatstroke.[176] In rats, a high rate of passive heating (0.175°C [0.315°F]/min) induced greater HSP 70 expression in the liver, small intestine, and kidneys than did a lower rate of heating (0.05°C [0.09°F]/min), despite attaining the same maximum body temperature (42°C [107.6°F]).[90] Differences in tissue blood flow and metabolic activity likely account for regional differences in HSP expression during passive and exertional heat exposure.

*Thermotolerance* is the term used to describe the noninheritable, transient resistance to a lethal heat stress that is acquired after previous exposure to a nonlethal level of heat stress. Increased HSP 70 expression is a mechanism of thermotolerance that protects against heat-induced increases in epithelial permeability. A unique in vitro model system consisting of high-resistance Madin-Darby canine kidney (MDCK) epithelial cell monolayers was developed to examine the relationship between HSP 70 expression and changes in epithelial integrity with heat exposure. Following heat stress to 38.3°C (100.9°F), MDCK monolayers showed increase in permeability that was reversible with cooling.[216] If the monolayers were preexposed to a conditioning heat stress of 42°C (107.6°F) for 90 minutes, subsequent exposure to a higher temperature of 39.4°C (102.9°F) was required to increase monolayer permeability.[216] Association of a thermotolerant state with increased HSP 70 expression suggests that HSPs shift the temperature threshold upward to prevent heat-induced disruptions in epithelial permeability.[216] Follow-up studies showed that HSPs interact with proteins in the tight junctions of the epithelium to regulate permeability. Occludin is a

plasma membrane protein located at tight junctions that was increased, along with HSPs 27, 40, 70, and 90, in intestinal epithelial monolayer (Caco-2) cells exposed to 39° or 41°C (102.2° or 105.8°F). Treatment of Caco-2 cells with quercetin (an inhibitor of HSF-1) inhibited HSPs and occludin expression and reversed the thermotolerant state of these cells.[72] These studies demonstrate a complex interaction between HSPs and tight-junction proteins for modulation of epithelial barrier function during thermal stress.

It is interesting to speculate that differences in HSP expression profiles may be a sensitive marker of heat stress susceptibility among different populations. During the life of an organism, there is accumulation of protein damage caused by continual oxidant and free radical activity within cells. The life span of *Drosophila* was extended by heat shock treatment or the addition of HSP 70 gene copies, suggesting that increased protein-chaperoning activity may protect against aging.[155] In rats, aging was associated with a significant reduction in liver HSP expression after passive heat exposure, which was associated with greater liver damage compared with that observed in young rats.[168,339] Older animals do not appear to have a global inability to express HSP, because exertional heat stress can induce expression profiles similar to those of mature rats.[168] Rather, aging is associated with reduction in the threshold for HSP stimulation.[168] Similarly, Fargnoli and co-workers[83] showed that global reduction in protein synthesis was not responsible for decreased HSP induction in aged lung fibroblasts. Alzheimer's disease is thought to be a consequence of decreased HSP function that results in increased deposition of abnormally folded proteins.[215] It is anticipated that screening for altered HSP titers will help to identify individuals with reduced thermotolerance caused by aging, infection, or other conditions that may predispose to heatstroke.[159]

## HEATSTROKE TREATMENTS
(See Chapter 13)

Current heatstroke therapies fall into two categories: supportive therapies directed at the immediate clinical symptoms and therapies directed at the causative mechanisms of injury. The primary objectives of clinical heatstroke treatments are to reduce body temperature as rapidly as possible, reestablish normal CNS function, and stabilize peripheral multiorgan system function. Supportive therapies consist of rapid cooling and IV fluid administration for restoration of normal blood pressure and tissue perfusion. Advanced therapies are directed at coagulation and inflammatory disturbances that cause organ failure. Despite therapeutic efforts, heatstroke morbidity and mortality rates remain quite high, and multiorgan system dysfunction continues to claim the lives of heatstroke patients during ensuing years of recovery.[10,320] This section discusses conventional clinical treatments of heatstroke, as well as innovative treatment strategies targeted at SIRS to mitigate injury and death.

### COOLING

Rapid cooling is considered the single most important treatment for protection against permanent CNS damage and death from heatstroke. To facilitate cooling, the individual should be placed into a supine position and as many clothes as possible removed to expose a large surface area of the body to facilitate heat transfer. If comatose, the individual should be placed onto his or her side (recovery position) to facilitate an open airway. Ice-water immersion is an effective cooling technique that requires placement of a heatstroke patient in a tub of ice water while the extremities are massaged to promote increased skin blood flow for heat dissipation. This technique relies on conductive heat transfer and is currently recommended by the American College of Sports Medicine and the National Athletic Trainer's Association for treatment of EHS.[11,25] Ice-water immersion of military heatstroke patients was effective in reducing body temperature to approximately38.5°C (101.3°F) within 10 to 60 minutes.[19,61,229] Using an ice bath or ice packs on the skin surface has met with some resistance because it is thought that cooling of the skin will elicit peripheral vasoconstriction and shivering.[157,248,337] Young, fit test volunteers were heat-stressed to 40°C (104°F) and experienced shivering and cold sensations during immersion in cold water.[337] However, the threshold for activation of shivering is probably increased in heatstroke patients, such that the risk of cold-water or ice-water immersion eliciting such a response and compromising the benefits of cooling is unlikely. Ice-water immersion of young, healthy individuals is a safe and effective method of cooling, whereas this technique is not well tolerated in elderly patients with classic heatstroke.[120] Additional limitations to consider with ice-water immersion include inability to administer external defibrillation in an immersed individual and the need for multiple assistants for placement into and removal from the bath.

Evaporative cooling is based on the premise that conversion of 1.7 mL of water to a gaseous phase will remove 1 kcal of heat. Efficiency of this cooling technique is improved by removing all clothing and spraying tepid water on the patient while evaporation and convection are facilitated with fanning. To reduce peripheral vasoconstriction, a body-cooling unit was designed to spray atomized water (15°C [59°F]) and blow hot air (45°C [113°F]) over the entire body surface to maintain skin temperature at 32° to 33°C (89.6° to 91.4°F).[327] However, efficiency of this method for rapid cooling of classic heatstroke patients was similar to conventional methods that involved covering patients in a wet sheet sprayed with tap water accompanied by fan blowing.[4] Fanning is used to accelerate convective and evaporative cooling by increasing conversion of water to the gaseous phase. Helicopter downdraft is another method of evaporative cooling that was reported to have better results than the body-cooling unit, but availability and feasibility of this technique are limited.[248] Evaporative cooling techniques are reasonable alternatives to ice-water immersion for classic heatstroke patients because they are easily applied, readily accessible, and well tolerated by frail elderly individuals.

Dantrolene and NSAIDs have been tested for their effects on prevention of heat illness and for body cooling, but neither class of drugs has shown efficacy for protection against heatstroke. Dantrolene protects against malignant hyperthermia by lowering intracellular calcium concentrations in skeletal muscle to decrease muscle tone. Dantrolene is effective for the treatment of malignant hyperthermia, which is a genetic mutation that predisposes to involuntary muscle contractions and rigidity after exposure to general anesthetics or muscle-depolarizing agents. Dantrolene has been considered a treatment for heatstroke, but animal and human heatstroke studies have failed to validate its use for this condition. A randomized, double-blind, placebo-controlled trial of Hajj heatstroke patients failed to show a cooling advantage of dantrolene over traditional cooling methods.[31,52] As discussed later, malignant hyperthermia is distinct from exertional or passive heatstroke, so it is not surprising that dantrolene does not protect equally against these diverse conditions.

The NSAIDs have been considered therapeutic drugs based on their potent antiinflammatory and antipyretic effects. The actions of classic NSAIDs, such as aspirin, ibuprofen, and acetaminophen, are attributed primarily to blockade of the cyclooxygenase (COX) pathway of eicosanoid metabolism (Figure 12-10).

Prostaglandins are synthesized by the COX pathway in response to a variety of stimuli (e.g., bacterial infection, heat shock) and regulate a multitude of physiologic responses, including fever, inflammation, and cytokine production. During fever, prostaglandins are released in response to proinflammatory cytokines (e.g., IL-1, IL-6) and stimulate an increase in the temperature set point to induce fever.[294] Inhibition of prostaglandin production by NSAIDs is the primary mechanism for the antipyretic (i.e., fever-reducing) actions of these drugs. However, hyperthermia in response to heat exposure is not caused by an increase in the temperature set point, but rather by an unregulated increase in body temperature that occurs when heat gain exceeds heat loss in the absence of a change in the temperature set point. Furthermore, aspirin and acetaminophen may aggravate gut bleeding tendencies and accelerate liver damage,

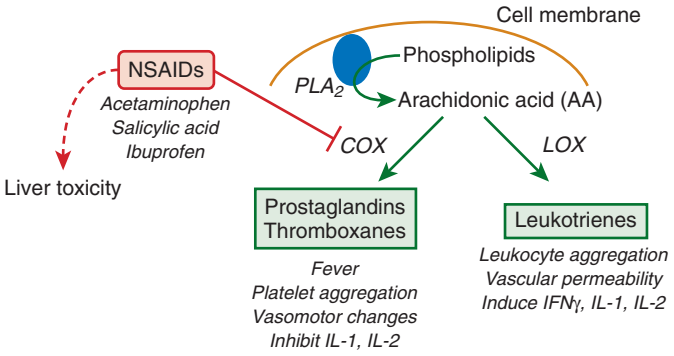



**FIGURE 12-10** Eicosanoid metabolism is initiated when cell membrane phospholipids are converted to arachidonic acid (*AA*) by enzymatic actions of phospholipase $A_2$ (*$PLA_2$*). Cyclooxygenase (*COX*) converts AA to prostaglandins and thromboxanes, whereas the lipooxygenase (*LOX*) pathway is responsible for production of leukotrienes. Nonsteroidal antiinflammatory drugs (*NSAIDs*) block the action of COX enzymes with potential toxic effects on the liver. *IFNγ,* Interferon-γ; *IL-1,* interleukin-1; *IL-2,* interleukin-2.

respectively. In a mouse model of heatstroke, an acute oral dose of indomethacin (a potent antipyretic NSAID) provided immediately before heat exposure resulted in a 40% increase in heatstroke mortality because of extensive gut hemorrhaging.[178] Increased mortality was also observed in heat-exposed rats injected peripherally with aspirin.[153] Aspirin has also been shown to attenuate protective, reflexive skin blood flow responses required for adequate heat dissipation.[131,206] Aspirin will therefore predispose to heatstroke collapse. Given that NSAIDs do not attenuate hyperthermia and that organ (e.g., gut, liver) toxicity of these drugs is exacerbated with heat, they are contraindicated for prophylaxis or treatment of heatstroke patients.

Alcohol sponge baths are inappropriate under any circumstances, because transcutaneous absorption of alcohol may lead to poisoning and coma.

## FLUID RESUSCITATION (See Chapter 89)

One of the first lines of defense against permanent tissue damage is treatment with resuscitation fluids. The objective of IV fluid administration is to restore intravascular volume and rehydrate the interstitium to stabilize cardiovascular functioning, improve tissue perfusion, and maintain immune function. The resuscitation fluid optimally needs to be safe, efficacious, and easy to transport for use in military or athletic settings and have the capability to restore tissue oxygen perfusion and minimize cellular and tissue injury. Blood provides oxygen-carrying capacity and volume, but supply is limited, with a risk for allergic or infectious reactions, difficulties with crossmatching, and potential for high hemoglobin levels to increase blood viscosity and reduce nutrient flow to the tissues.[259] Balanced salt solutions, such as saline and lactated Ringer's, have a long shelf life and are inexpensive and in unlimited supply, with a minimal risk for disease transmission. However, they are able freely to cross semipermeable capillary membranes, which increases the risk for tissue edema and makes frequent transfusions necessary to maintain adequate plasma volume.[119,152,307] Tissue edema increases the distance from blood vessels to tissue mitochondria and limits oxygen delivery to the tissues. There is a greater risk for edema in heatstroke patients because of increased capillary permeability and lack of muscle movement that limits lymph flow following collapse.

To minimize the adverse consequences of balanced salt solutions, these fluids may be replaced with colloid solutions. Natural colloids, such as albumin, possess antioxidant properties that reduce tissue injury during times of oxidant stress, but carry a risk for infection.[94,341] Dextran is an artificial colloid that was used after World War II until adverse hemostatic effects restricted its use to specific clinical conditions, such as deep vein thrombosis and pulmonary embolism.[21,66] Hydroxyethyl starch (HES) is a blood plasma substitute that exerts high colloidal pressure to stimulate movement of fluid from the interstitial space into the blood vessel lumen for plasma volume expansion.[238,334,341] Small-volume treatment with HES protected against heatstroke mortality in rats, but use of HES in other heatstroke animal models and humans has not been validated.[192] Because of severe dehydration and acute renal failure with heatstroke, fluid shifts from the interstitial fluid into the vessel lumen may mean HES will not be well tolerated in patients with severe heatstroke patients (see Chapter 13).

## ANTICOAGULANTS

Anticoagulants (e.g., heparin, aspirin) have been examined for heatstroke protection, with mixed results. Heparin therapy has been associated with positive heatstroke outcome in patients, although it is difficult to dissociate the direct effects of this therapy from other clinical treatments.[247,292] The mechanisms of heat-induced DIC may include prostaglandin synthesis, because aspirin has shown protection against platelet hyperaggregation in vitro and in animal models. In human volunteers, ingestion of aspirin 12 to 15 hours before blood sampling or heat exposure of cells was effective in inhibiting platelet hyperaggregation. However, aspirin was ineffective if provided after heat exposure, even though complete inhibition of the arachidonic acid pathway was achieved.[97] The ability of aspirin to protect guinea pigs from DIC induced by *Staphylococcus aureus* suggests that similar activities function in vivo to control platelet reactivity.[225] However, there is currently insufficient evidence to support the use of aspirin as a preventive measure in heatstroke patients. Given the hormonal and metabolic alterations that accompany heatstroke, including dehydration, increased catecholamine levels, and hypoxia, the mechanisms responsible for DIC extend beyond those mediated by prostaglandins alone. Furthermore, aspirin and other antiinflammatory drugs can cause liver damage if consumed in large quantities, as previously mentioned.

Recombinant activated protein C (APC) is an effective antiinflammatory drug for treatment of sepsis and may also hold promise as a treatment for heatstroke patients. APC efficacy appears to depend on a variety of patient conditions, including age (most effective in patients >50), extent of organ dysfunction (benefit not apparent if failure of only one organ), and the presence of shock at infusion, which improves its efficacy.[326] In rat heatstroke models, the efficacy of APC depends on the time of treatment. A single dose of recombinant human APC provided at the onset of heatstroke inhibited inflammation and coagulopathy, prevented organ failure, and improved survival; however, if treatment was delayed for 40 minutes after onset of heatstroke, there was no beneficial effect on survival time.[54] The efficacy of APC was less obvious in a baboon heatstroke model. Infusion for 12 hours after heatstroke onset attenuated plasma IL-6, thrombomodulin, and procoagulant components but had no effect on mortality.[35] APC is the first biologic agent approved in the United States for the treatment of severe sepsis based on two decades of research,[326] but there is insufficient evidence to justify use of this treatment in heatstroke patients.

## ANTICYTOKINE THERAPIES

As previously described, attenuations in splanchnic blood flow during heatstroke contribute to increased gut permeability and a rise in circulating endotoxin. This series of events is hypothesized to stimulate the increased plasma cytokine levels implicated in the adverse consequences of SIRS. Based on these findings, the question arises: Do anticytokine therapies represent an efficacious treatment strategy for heatstroke? No controlled studies have examined the efficacy of anticytokine therapies on patient outcome with heatstroke. However, clinical sepsis trials indicate that potential protective effects of anticytokine therapies need to be viewed with cautious optimism. Sepsis patients display high circulating IL-1 levels that correlate with morbidity and mortality, but IL-1ra treatment has been unsuccessful in reducing mortality.[236,257] A comparison of 12 randomized, double-blind multicenter trials of more than 6200 sepsis patients showed

no significant benefit of antiendotoxin antibodies, ibuprofen, plasminogen-activating factor receptor antagonist, anti-TNF monoclonal antibody, or IL-1ra on all-cause mortality.[68]

There are several explanations for negative results from anticytokine therapies, including the possibility that the mediator has no pathophysiologic role in the response, the agent failed to neutralize the protein (because of a lack of biologic activity, competition by other mediators, or inadequate anatomic distribution), compensatory increase of other mediators with similar activities, administration too early or too late in the course of disease, too-short therapy duration, or need for combination therapy.[203] Kinetic studies have shown that the half-life of IL-1ra is approximately 20 minutes, and Phase III clinical trials showed that circulating IL-1β levels at the time of clinical treatment were undetectable in 95% of the patient population.[87,249] Exposure to anticytokine therapies before sepsis onset is thought to be desirable (but practically is infeasible), although this may suppress shifts in $Th_1/Th_2$ immune responses that are important for resolution of infection. On the other hand, anticytokine therapies given too late in sepsis progression may shift the $Th_1/Th_2$ milieu in an unpredictable manner or may have no effect because of the overwhelming nature of the septic event.[110] The transient nature of cytokine production and/or clearance and lack of correlation between serum levels and disease severity further complicate treatment scenarios. Given the short half-life of TNF-α (~6 to 7 minutes)[22] and biphasic clearance patterns of IL-1β and IL-6 (rapid disappearance in first 3 minutes followed by attenuated clearance over next 1 to 4 hours),[161] the narrow protective window in which anticytokine therapies may be effective is a difficult obstacle to overcome.

Interleukin-10 is a potent antiinflammatory cytokine that suppresses production of several proinflammatory cytokines, including IL-1β, IL-6, and TNF-α, and is part of an important negative feedback loop during infection and disease.[111,314] Few, if any, studies have investigated efficacy of IL-10 treatment for heatstroke recovery, although the cytokine has been frequently used in treatment of multiple autoimmune diseases, including rheumatoid arthritis, Crohn's disease, multiple sclerosis, and sepsis.[41,231] As with other cytokines, timing of IL-10 administration must be carefully considered. IL-10 decreases IFN-γ production by natural killer and $Th_1$ cells, which may suppress clearance of infectious organisms (via IFN-γ).[258,319] Consistent with anticytokine therapies, beneficial effects of exogenous IL-10 administration depend on multiple factors, including time of administration, route, and site where the cytokine is targeted.[231,267] These considerations, along with the immunosuppressive and unpredictable nature of IL-10–based therapies, have resulted in diminished enthusiasm for anticytokine therapies for sepsis.

## HEATSTROKE PREVENTION

Heatstroke is currently a more preventable than treatable disease. The most effective preventive measures include acclimatization to the heat, reductions in duration and extent of physical activity, rescheduling of activities to cooler times of the day, increased consumption of nonalcoholic fluids, and removing vulnerable populations, such as those with preexisting viral or bacterial infections, from the heat stress environment. Fan cooling has not shown protection against heatstroke and is associated with increased thermal discomfort at temperatures higher than 38°C (100.4°F).[158]

### HEAT ACCLIMATIZATION

Climatic heat stress and exercise interact synergistically to increase body temperature (core and skin) and cardiovascular strain, and to decrease performance in the heat. Heat acclimatization is one of the within-lifetime changes in an organism (vs. evolutionary changes) that protect against the negative effects of heat strain. *Heat acclimatization* occurs after exposure to the natural environment, whereas *heat acclimation* develops after exposure to artificial conditions. However, these terms are used interchangeably because they induce similar physiologic adaptations.[328] Heat acclimation occurs after repeated bouts of heat exposure that are of sufficient intensity, frequency, duration, and number to elevate core and skin temperature and induce profuse sweating. Heat acclimation may be achieved after exercise or rest in the heat, although the former method is more effective. It is important to note that heat acclimatization is specific to the climate and activity level; therefore, if individuals will be working in a hot, humid climate, heat acclimatization should be conducted under similar conditions (Box 12-3).

**BOX 12-3 Heat Acclimation Strategies**

**Must Mimic Climate of Athletic Event or Occupational Setting and Include Adequate Heat Stress**
- Heat must be sufficient to cause heavy sweating.
- Use exercise/rest cycles to intensify or diminish the effect of the heat stress on bodily functions.
- Include at least 6 to 14 days of adequate heat stress.
- Exercise daily for at least 90 minutes.

**Start with Acclimation and Exercise Training**
- Be flexible in scheduling training.
- Build confidence.
- Performance benefits may take longer to achieve than physiologic benefits.

**Methods of Heat Acclimation**
- Use a climate-controlled room (sauna or heat chamber) or hot weather.
- Incorporate training by including additional acclimation sessions.

**Days Leading to Athletic Performance or Event**
- Start slowly, and decrease training duration and intensity; limit heat exposure.
- Acclimatize in heat of the day.
- Train in coolest part of the day.
- Use appropriate work/rest cycles.
- Be vigilant of salt and fluid needs, especially during the first week of acclimation.

Although heat acclimation does not require daily exposure to heat and exercise, the rapidity with which biologic adaptations are achieved is slower with less frequent exposures. This was shown experimentally in human volunteers in whom heat acclimation was achieved after 10 days of daily heat exposure, but required 27 days when the frequency of exposure was reduced to every third day of experimentation (conditions: 47°C [116.6°F], 17% relative humidity).[84] Continual 24-hour exposures are also not required, because daily 100-minute periods of exposure were adequate to produce heat acclimation in participants exposed to dry heat.[188] However, because of the transient nature of the biologic adaptations, continued heat exposures are required to maintain the acclimated state. Aerobically trained athletes retain heat acclimation benefits longer than unfit individuals because they are exposed to high body temperatures during training exercises.[239]

Improvements in thermal comfort and exercise performance are achieved in heat-acclimated individuals through a variety of physiologic mechanisms, including a lower threshold and higher rate of skin blood flow, reduction in metabolic rate, earlier onset and rate of sweating, and improvements in cardiovascular function and fluid balance.[272] Figure 12-11 illustrates the effect of 10 days of heat acclimation on heart rate, core temperature, and mean skin temperature responses of individuals walking on a treadmill in a desert type of environment.[80] On the 10th day of acclimation, heart rate was lower by approximately 40 beats/min, and rectal and skin temperatures were reduced approximately 1°C (1.8°F) and 1.5°C (2.7°F), respectively.

Once heat acclimation is achieved, skin vasodilation and sweating are initiated at a lower core temperature threshold, and higher sweat rates can be sustained without the sweat glands becoming "fatigued."[60,91] Whereas an unacclimated individual will secrete sweat with a sodium concentration of approximately 60 mEq/L (or higher), the concentration of secreted sodium from the sweat glands of an acclimated individual is significantly

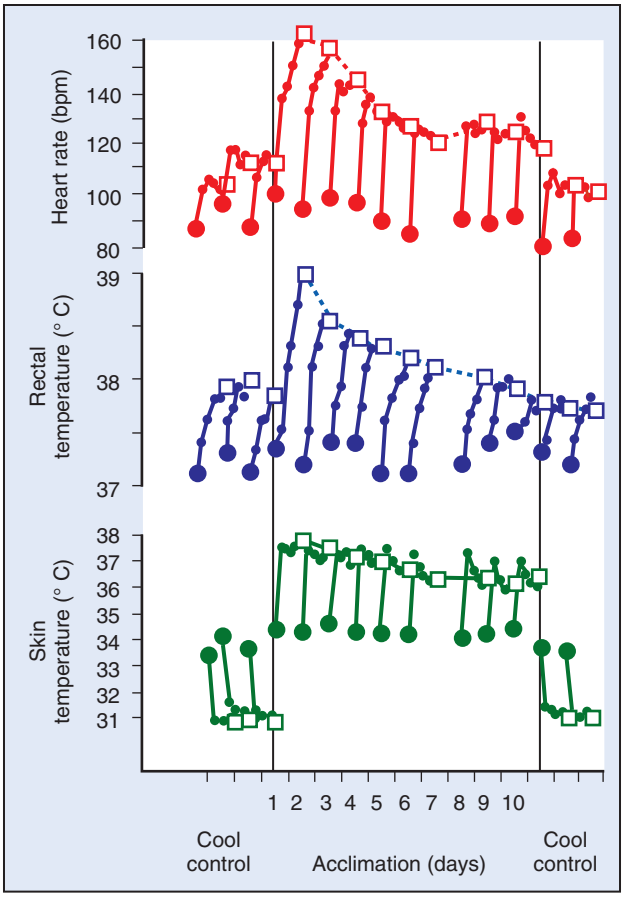



**FIGURE 12-11** Effect of 10 days' acclimation on heart rate and rectal and skin temperatures during a standard exercise (five 10-minute periods of treadmill, separated by 2-minute rests) in dry heat. *Large circles,* Values before start of the first exercise period each day; *small circles,* successive values; *squares,* the final values each day. Controls of exercise in cool environment before and after acclimation. *(Modified from Eichna LW, Park CR, Nelson N, et al: Thermal regulation during acclimatization in a hot, dry (desert type) environment,* Am J Physiol *163:585, 1950.)*

lower, at about 5 mEq/L.[264] This effect of heat acclimation on salt conservation is thought to be caused by increased aldosterone secretion or responsiveness of the sweat glands to this steroid hormone, which is released by the adrenal cortex and increases resorption of ions and water in the distal tubules and collecting ducts of the kidneys.[92,160]

Overall improvements in fluid balance with heat acclimation include reduced sweat sodium losses, better matching of thirst to body water needs, and increased total body water and blood volume.[195] Provided that fluids are not restricted during physical activities, heat-acclimated individuals will be better able to maintain hydration during exercise and show a marked reduction in "voluntary" dehydration.[17,80,272] Although controversy surrounds the ability of heat acclimation to alter the maximum temperature that can be tolerated during exercise in the heat,[221] individuals who live or train in hot environments may experience reduced incidence of syncope[17,107,250] (Figure 12-12).

An essential cellular adaptation of heat acclimation is altered expression or reprogramming of genes that encode constitutive and stress-inducible proteins.[133] Heat acclimation is associated with downregulation of genes associated with energy metabolism, food intake, mitochondrial energy metabolism, and cellular maintenance processes and upregulation of genes that are linked with immune responsiveness.[133] The HSPs are the most extensively studied heat-inducible proteins and show faster transcriptional response and elevated cellular reserves (HSP 72 specifically) in heat-acclimated versus nonacclimated individuals.[133,134,198,205] That is, whereas nonacclimated individuals require de novo HSP 72 synthesis for cellular protection, individuals who reside in hot climates maintain elevated HSP 72 levels.[194] The cellular mechanisms of heat acclimation are not fully understood, but are thought to involve global and tissue-specific changes in genes involved in thermal responsiveness, DNA repair and synthesis, free radical scavenging, and apoptosis.[133]

## GENETIC POLYMORPHISMS

Heatstroke susceptibility is influenced by complex interactions between environmental and host genetic factors. Emerging molecular technologies have improved our understanding of the genetic mutations and polymorphisms that might predispose to heat illness or inhibit resolution of SIRS. It is anticipated that ability to prescreen individuals for genetic polymorphisms that may prevent resolution of SIRS will help in developing more effective therapies to alleviate morbidity/mortality in these individuals.

### SINGLE NUCLEOTIDE POLYMORPHISMS

Single nucleotide polymorphisms (SNPs) are variations in the nucleotide sequence of DNA that can affect physiologic responses to environmental stimuli. SNPs have been implicated in a variety of diseases, including sepsis, type 1 diabetes, arthritis, inflammatory bowel disease, and rheumatic fever.[89,143,253,297] The identification of SNPs in the promoter region of genes suggests that disease susceptibility may be affected by altered transcription of immune determinants of clinical outcome. SNPs have been identified in IL-1, IL-2, TNF, IFN-γ, IL-10, IL-1ra, TLR2, and TLR4. The risk for death from sepsis is significantly increased in patients with a genetic polymorphism in the TNF-α or TNF-β gene.[93] Even for cytokine polymorphisms located distal to a critical promoter region that do not directly affect gene transcription rates, coinheritance of multiple immune-responsive genes by a process known as linkage disequilibrium can alter immune function. Some TNF-α polymorphisms exist in linkage disequilibrium with human leukocyte antigen (HLA) haplotypes that encode cell surface antigens. Coinheritance of these genes may ultimately be responsible for poor sepsis outcome.[146,297]

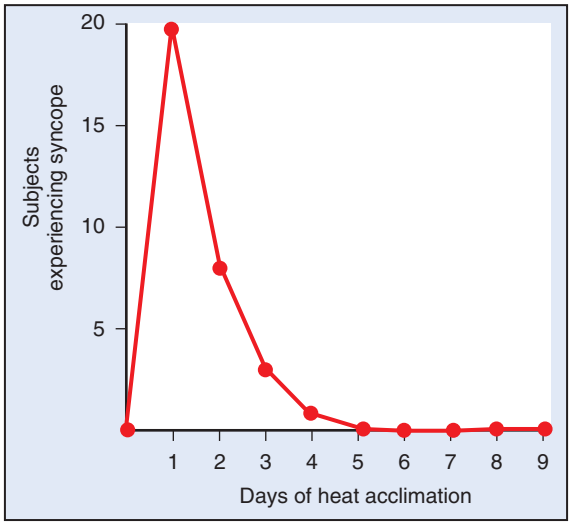



**FIGURE 12-12** Incidence of syncope among 45 participants who lived in and trained at cool ambient temperatures and could complete a physical training regimen without mishap. They were then relocated to a hot environment, where they carried out the same physical training regimen. *(Modified from Bean WB, Eichna LW: Performance in relation to environmental temperature: Reactions of normal young men to stimulated desert environment,* Fed Proc *2:144, 1943; and Hubbard RW, Armstrong LE: The heat illness: Biochemical, ultrastructural, and fluid-electrolyte considerations. In Pandolf KB, Sawka MN, Gonzalez RR, editors:* Human performance and environmental medicine at terrestrial extremes, *Indianapolis, 1988, Benchmark Press, pp 305-359.)*

## MALIGNANT HYPERTHERMIA

Malignant hyperthermia (MH) is a genetic disorder that causes muscle rigidity, hyperthermia, tachycardia, and metabolic acidosis during exposure to volatile anesthetics or depolarizing skeletal muscle relaxants. Exercise, heat stress, and emotional stress also trigger reactions in 5% to 10% of MH patients.[70,325] MH reactions result from massive release of calcium from the type 1 ryanodine receptor (RyR1) of the sarcoplasmic reticulum, which overwhelms cellular mechanisms of calcium homeostasis and activates actin-myosin filaments to cause muscle rigidity and hyperthermia.[230] RyR1 is the most common mutation in skeletal muscle, but additional isoforms have been identified in B and T cells, thalamus, hippocampus, and heart.[169,208,302] Activation of RyR1 by a variety of pharmacologic compounds, including caffeine, halothane, and the muscle relaxant 4-chloro-m-cresol, has led to development of an in vitro contracture test of skeletal muscle biopsies to identify MH individuals.[268,342] Dantrolene is used to treat MH reactions by lowering intracellular calcium stores, decreasing muscle metabolic activity, and preventing hyperthermia. Using dantrolene, in combination with improved monitoring standards and early detection with the in vitro contracture test, has helped reduce mortality from greater than 70% to less than 5% in MH patients.[191]

Malignant hyperthermia has been identified in several animal species, including dogs,[228] boars,[277] cats,[18] and horses,[6] but the most common experimental animal is a porcine MH model that possesses a single mutation in the skeletal muscle *RyR1* gene. These animals develop the MH syndrome in response to inhalational anesthetics, exercise, heat, and other stressors.[313] Mild exercise exacerbates MH symptoms in response to anesthetics in MH pigs, suggesting that inflammatory mediators released by skeletal muscle may contribute to the MH syndrome.[313] MH patients show an approximately fivefold higher expression of IL-1β when stimulated with caffeine and 4-chloro-m-cresol compared with control cells.[103] Recent development of a transgenic mouse model that overexpresses the RyR1 receptor has proved useful to study the MH/EHS link and could shed light on the role played in this syndrome by inflammatory cytokine production from skeletal muscle or other organs.[79] Association of RyR1 mutations with EHS incidence suggests that screening young, healthy individuals (e.g., athletes, military personnel) for the MH mutation could be a powerful tool to determine heatstroke susceptibility.

## REFERENCES

***Complete references used in this text are available online at expertconsult.inkling.com.***



# CHAPTER 13
# Clinical Management of Heat-Related Illnesses

KAREN K. O'BRIEN, LISA R. LEON, ROBERT W. KENEFICK, AND FRANCIS G. O'CONNOR

This chapter discusses definitions, clinical manifestations, medical management from the field through hospital discharge, return-to-activity considerations, and prevention of heat-related illnesses. The spectrum of injuries ranges from milder conditions such as heat cramps to fatal manifestations such as arrhythmias. Heat-related illnesses generate complications such as rhabdomyolysis and multiorgan dysfunction syndrome and may result in death from overwhelming cell necrosis caused by a lethal heat shock exposure. Exertional heatstroke (EHS) is usually characterized by development of mental status changes or collapse during physical activity in a warm environment. Severity of heat illness depends on degree and duration of elevation in core temperature ($T_{co}$). Heatstroke is an extreme medical emergency that can be fatal if not treated promptly with rapid cooling. To prevent and minimize complications and save lives, proper prevention, management, and clinical care are essential.

## EXERTIONAL HEAT ILLNESS

Dehydration and heat exposure can impair exercise performance and contribute to various illnesses. Exertional heat illnesses include both minor and serious disorders. Minor heat and dehydration-related illnesses include heat cramps, erythromelalgia, and heat syncope. *Heat cramps* are characterized by intense muscle spasms, typically in the legs, arms, and abdomen. Heat cramps result from fluid and electrolyte deficits and occur most often in persons who have not been fully acclimated to a combination of intense muscular activity and environmental heat. Individuals susceptible to heat cramps are often believed to be profuse sweaters who sustain large sodium losses.[16,114] *Heat syncope* (fainting) is characterized by dizziness and weakness during or after prolonged standing or after rapidly standing up from a lying or sitting position during heat exposure. Heat syncope results from blood pooling in the cutaneous and skeletal vasculature and occurs most often in dehydrated and inactive persons who are not acclimated.[101] *Erythromelalgia* is characterized by pain and swelling of the feet and hands, triggered by exposure to elevated temperatures.[70]

Serious illnesses include exertional heat injury (EHI) and EHS. These illnesses have many overlapping diagnostic features; it has been suggested that they exist along a continuum on the severity scale.[20] *Heat exhaustion* is characterized by inability to sustain cardiac output in the presence of moderate (>38.5°C [101°F]) to high (>40°C [104°F]) body temperature and is frequently accompanied by hot skin and dehydration. EHI is a moderate to severe illness characterized by injury to an organ (e.g., liver, kidneys, gut, muscle) and usually (but not always) involves a high $T_{co}$ of more than 40°C (104°F). EHS is a severe illness characterized by central nervous system (CNS) dysfunction (e.g., confusion, disorientation, impaired judgment) and is usually accompanied by a $T_{co}$ above 40.5°C (105°F). EHI and EHS can be complicated by cardiac arrhythmia, liver damage, rhabdomyolysis, coagulopathy, fluid and electrolyte imbalances, and kidney failure. Rhabdomyolysis is most often observed with novel and strenuous overexertion. Clinical evidence suggests that dehydration increases the likelihood or severity of acute renal failure associated

## REFERENCES


1. Reference deleted in proofs.
2. Adams KF Jr, Uddin N, Patterson JH. Clinical predictors of in-hospital mortality in acutely decompensated heart failure: Piecing together the outcome puzzle. Congest Heart Fail 2008;14(3):127–34.
3. Aderka D, Engelmann H, Maor Y, et al. Stabilization of the bioactivity of tumor necrosis factor by its soluble receptors. J Exp Med 1992; 175(2):323–9.
4. Al-Harthi SS, Yaqub BA, Al-Nozha MM. Management of heat stroke patients by rapid cooling at Mecca pilgrimage. Saudi Med J 1986;7:369.
5. Albukrek D, Bakon M, Moran DS, et al. Heat-stroke-induced cerebellar atrophy: Clinical course, CT and MRI findings. Neuroradiology 1997;39(3):195–7.
6. Aleman M, Riehl J, Aldridge BM, et al. Association of a mutation in the ryanodine receptor 1 gene with equine malignant hyperthermia. Muscle Nerve 2004;30(3):356–65.
7. American Burn Association. National Burn Repository: 2012 report. Chicago: American Burn Association; 2012.
8. American College of Chest Physicians. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. In: Proceedings of ACCP/Society of Crtical Care Medicine Consensus Conference. 1992. p. 864–74.
9. Reference deleted in proofs.
10. Argaud L, Ferry T, Le QH, et al. Short- and long-term outcomes of heatstroke following the 2003 heat wave in Lyon, France. Arch Intern Med 2007;167(20):2177–83.
11. Armstrong LE, Casa DJ, Millard-Stafford M, et al. American College of Sports Medicine Position Stand: Exertional heat illness during training and competition. Med Sci Sports Exerc 2007;39(3):556–72.
12. Arrigo AP, Suhan JP, Welch WJ. Dynamic changes in the structure and intracellular locale of the mammalian low-molecular-weight heat shock protein. Mol Cell Biol 1988;8(12):5059–71.
13. Asakura H, Suga Y, Yoshida T, et al. Pathophysiology of disseminated intravascular coagulation (DIC) progresses at a different rate in tissue factor-induced and lipopolysaccharide-induced DIC models in rats. Blood Coagul Fibrinolysis 2003;14(3):221–8.
14. Austin MG, Berry JW. Observations on one hundred cases of heat stroke. J Am Med Assoc 1956;161(16):1525–9.
15. Bagley WH, Yang H, Shah KH. Rhabdomyolysis. Intern Emerg Med 2007;2(3):210–18.
16. Barbui T, Falanga A. Disseminated intravascular coagulation in acute leukemia. Semin Thromb Hemost 2001;27(6):593–604.
17. Bean WB, Eichna LW. Performance in relation to environmental temperature: Reactions of normal young men to simulated desert environment. Fed Proc 1943;22:144–58.
18. Bellah JR, Robertson SA, Buergelt CD, McGavin AD. Suspected malignant hyperthermia after halothane anesthesia in a cat. Vet Surg 1989;18(6):483–8.
19. Beller GA, Boyd AE III. Heat stroke: A report of 13 consecutive cases without mortality despite severe hyperpyrexia and neurologic dysfunction. Mil Med 1975;140(7):464–7.
20. Ben-Simchon C, Tsur H, Keren G, et al. Heat tolerance in patients with extensive healed burns. Plast Reconstr Surg 1981;67(4):499–504.
21. Bergqvist D. Dextran and haemostasis: A review. Acta Chir Scand 1982;148(8):633–40.
22. Beutler BA, Milsark IW, Cerami A. Cachectin/tumor necrosis factor: Production, distribution, and metabolic fate in vivo. J Immunol 1985; 135(6):3972–7.
23. Bianchi ME. DAMPs, PAMPs and alarmins: All we need to know about danger. J Leukoc Biol 2007;81(1):1–5.
24. Biedenkapp JC, Leon LR. Increased cytokine and chemokine gene expression in the CNS of mice during heat stroke recovery. Am J Physiol Regul Integr Comp Physiol 2013;305(9):R978–86.
25. Binkley HM, Beckett J, Casa DJ, et al. National Athletic Trainers' Association Position Statement: Exertional Heat Illnesses. J Athl Train 2002;37(3):329–43.
26. Blake MJ, Gershon D, Gargnoli J, Holbrook NJ. Discordant expression of heat shock protein mRNAs in tissues of heat-stressed rats. J Biol Chem 1990;265(25):15275–9.
27. Blatteis CM. The onset of fever: new insights into its mechanism. Prog Brain Res 2007;162:3–14.
28. Blligh J. Temperature regulation in mammals and other vertebrates. Amsterdam: North-Holland Publishing Co.; 1973.
29. Bouchama A, al-Sedairy S, Siddiqui S, et al. Elevated pyrogenic cytokines in heatstroke. Chest 1993;104(5):1498–502.
30. Bouchama A, Bridey F, Hammami MM, et al. Activation of coagulation and fibrinolysis in heatstroke. Thromb Haemost 1996;76(6): 909–15.
31. Bouchama A, Cafege A, Devol EB, et al. Ineffectiveness of dantrolene sodium in the treatment of heatstroke. Crit Care Med 1991; 19(2):176–80.
32. Bouchama A, Dehbi M, Mohamed G, et al. Prognostic factors in heat wave related deaths: A meta-analysis. Arch Intern Med 2007;167(20): 2170–6.
33. Bouchama A, Hammami MM, Al Shail E, De Vol E. Differential effects of in vitro and in vivo hyperthermia on the production of interleukin-10. Intensive Care Med 2000;26(11):1646–51.
34. Bouchama A, Knochel JP. Heat stroke. N Engl J Med 2002;346(25): 1978–88.
35. Bouchama A, Kunzelmann C, Dehbi M, et al. Recombinant activated protein C attenuates endothelial injury and inhibits procoagulant microparticles release in baboon heatstroke. Arterioscler Thromb Vasc Biol 2008;28(7):1318–25.
36. Bouchama A, Parhar RS, el-Yazigi A, et al. Endotoxemia and release of tumor necrosis factor and interleukin 1 alpha in acute heatstroke. J Appl Physiol 1991;70(6):2640–4.
37. Bouchama A, Roberts G, Al Mohanna F, et al. Inflammatory, hemostatic, and clinical changes in a baboon experimental model for heatstroke. J Appl Physiol 2005;98(2):697–705.
38. Boulant JA. Hypothalamic neurons regulating body temperature. In: Fregly MJ, Blatteis CM, editors. Handbook of physiology. Section 4. Environmental physiology. New York: Oxford University; 1996. p. 105–25.
39. Bowers WD Jr, Hubbard RW, Leav I, et al. Alterations of rat liver subsequent to heat overload. Arch Pathol Lab Med 1978;102(3): 154–7.
40. Bradfield JW. Control of spillover: The importance of Kupffer-cell function in clinical medicine. Lancet 1974;2(7885):883–6.
41. Brandtzaeg P, Osnes L, Ovstebo R, et al. Net inflammatory capacity of human septic shock plasma evaluated by a monocyte-based target cell assay: Identification of interleukin-10 as a major functional deactivator of human monocytes. J Exp Med 1996;184(1): 51–60.
42. Brown IR, Rush S, Ivy GO. Induction of a heat shock gene at the site of tissue injury in the rat brain. Neuron 1989;2(6):1559–64.
43. Buchanan TA, Cane P, Eng CC, et al. Hypothermia is critical for survival during prolonged insulin-induced hypoglycemia in rats. Metabolism 1991;40(3):330–4.
44. Bukau B, Horwich AL. The Hsp70 and Hsp60 chaperone machines. Cell 1998;92(3):351–66.
45. Butkow N, Mitchell D, Laburn H, Kenedi E. Heat stroke and endotoxaemia in rabbits. In: Hales JRS, editor. Thermal biology. New York: Raven Press; 1984. p. 511–14.
46. Bynum G, Brown J, Dubose D, et al. Increased survival in experimental dog heatstroke after reduction of gut flora. Aviat Space Environ Med 1979;50(8):816–19.
47. Camus G, Poortmans J, Nys M, et al. Mild endotoxaemia and the inflammatory response induced by a marathon race. Clin Sci (Lond) 1997;92(4):415–22.
48. Carter R III, Cheuvront SN, Sawka MN. A case report of idiosyncratic hyperthermia and review of U.S. Army heat stroke hospitalizations. J Sport Rehabil 2007;16:238–43.
49. Carter R III, Cheuvront SN, Williams JO, et al. Epidemiology of hospitalizations and deaths from heat illness in soldiers. Med Sci Sports Exerc 2005;37(8):1338–44.
50. Centers for Disease Control and Prevention. Heat-related deaths—United States, 1999–2003. MMWR 2006;55(29):796–8.
51. Chang DM. The role of cytokines in heat stroke. Immunol Invest 1993;22(8):553–61.
52. Channa AB, Seraj MA, Saddique AA, et al. Is dantrolene effective in heat stroke patients? Crit Care Med 1990;18(3):290–2.
53. Chao TC, Sinniah R, Pakiam JE. Acute heat stroke deaths. Pathology 1981;13(1):145–56.
54. Chen CM, Hou CC, Cheng KC, et al. Activated protein C therapy in a rat heat stroke model. Crit Care Med 2006;34(7):1960–6.
55. Chensue SW, Shmyr-Forsch C, Otterness IG, Kunkel SL. The beta form is the dominant interleukin 1 released by murine peritoneal macrophages. Biochem Biophys Res Commun 1989;160:404–8.
56. Reference deleted in proofs.
57. Clark JF. Some effects of the urban structure on heat mortality. Environ Res 1972;5:93–104.
58. Clarkson PM, Kearns AK, Rouzier P, et al. Serum creatine kinase levels and renal function measures in exertional muscle damage. Med Sci Sports Exerc 2006;38(4):623–7.
59. Climate change 2001: The scientific basis. Contribution of Working Group I to the Third Assessment Report, Intergovernmental Panel on Climate Change. Cambridge, UK: Cambridge University Press; 2001.
60. Collins KJ, Crockford GW, Weiner JS. Sweat-gland training by drugs and thermal stress. Arch Environ Health 1965;11(4):407–22.
61. Costrini A. Emergency treatment of exertional heatstroke and comparison of whole body cooling techniques. Med Sci Sports Exerc 1990;22(1):15–18.

62. Crandall CG, Davis SL. Cutaneous vascular and sudomotor responses in human skin grafts. J Appl Physiol (1985) 2010;109(5): 1524–30.
63. Curriero FC, Heiner KS, Samet JM, et al. Temperature and mortality in 11 cities of the eastern United States. Am J Epidemiol 2002; 155(1):80–7.
64. Davis SL, Shibasaki M, Low DA, et al. Impaired cutaneous vasodilation and sweating in grafted skin during whole-body heating. J Burn Care Res 2007;28(3):427–34.
65. Davis SL, Shibasaki M, Low DA, et al. Sustained impairments in cutaneous vasodilation and sweating in grafted skin following long-term recovery. J Burn Care Res 2009;30(4):675–85.
66. De Jonge E, Levi M. Effects of different plasma substitutes on blood coagulation: A comparative review. Crit Care Med 2001;29(6): 1261–7.
67. Dehbi M, Uzzaman T, Baturcam E, et al. Toll-like receptor 4 and high-mobility group box 1 are critical mediators of tissue injury and survival in a mouse model for heatstroke. PLoS ONE 2012;7(9):e44100.
68. Deitch EA. Animal models of sepsis and shock: A review and lessons learned. Shock 1998;9(1):1–11.
69. Dematte JE, O'Mara K, Buescher J, et al. Near-fatal heat stroke during the 1995 heat wave in Chicago. Ann Intern Med 1998;129(3): 173–81.
70. Denborough M. Malignant hyperthermia. Lancet 1998;352(9134): 1131–6.
71. Ding XZ, Fernandez-Prada CM, Bhattacharjee AK, Hoover DL. Overexpression of hsp-70 inhibits bacterial lipopolysaccharide-induced production of cytokines in human monocyte-derived macrophages. Cytokine 2001;16(6):210–19.
72. Dokladny K, Wharton W, Lobb R, et al. Induction of physiological thermotolerance in MDCK monolayers: Contribution of heat shock protein 70. Cell Stress Chaperones 2006;11(3):268–75.
73. Donaldson GC, Keatinge WR, Nayha S. Changes in summer temperature and heat-related mortality since 1971 in North Carolina, South Finland, and Southeast England. Environ Res 2003;91:1–7.
74. Donaldson GC, Kovats RS, Keatinge WR, et al. Heat- and cold-realted mortality and morbidity and climate change. London: Department of Health; 2001.
75. Dorozynski A. Chirac announces investigation into heat wave's death toll. BMJ 2003;327(7413):465.
76. Drexler AM. Tumor necrosis factor: its role in HIV/AIDS. STEP Perspect 1995;7(1):13–15.
77. DuBose DA, Basamania K, Maglione L, Rowlands J. Role of bacterial endotoxins of intestinal origin in rat heat stress mortality. J Appl Physiol 1983;54(1):31–6.
78. DuBose DA, McCreary J, Sowders L, Goode L. Relationship between rat heat stress mortality and alterations in reticuloendothelial carbon clearance function. Aviat Space Environ Med 1983;54:1090–5.
79. Durham WJ, Racena-Parks P, Long C, et al. RyR1 S-nitrosylation underlies environmental heat stroke and sudden death in Y522S RyR1 knockin mice. Cell 2008;133(1):53–65.
80. Eichna LW, Park CR, Nelson N, et al. Thermal regulation during acclimatization in a hot, dry (desert type) environment. Am J Physiol 1950;163(3):585–97.
81. Elizondo RS. Regulation of body temperature. Boston: Little, Brown; 1995.
82. Ensor JE, Wiener SM, McCrea KA, et al. Differential effects of hyperthermia on macrophage interleukin-6 and tumor necrosis factor-alpha expression. Am J Physiol 1994;266(4 Pt 1):C967–74.
83. Fargnoli J, Kunisada T, Fornace AJ, et al. Decreased expression of heat shock protein 70 mRNA and protein after heat treatment in cells of aged rats. Proc Natl Acad Sci U S A 1990;87(2):846–50.
84. Fein JT, Haymes EM, Buskirk ER. Effects of daily and intermittent exposures on heat acclimation of women. Int J Biometeorol 1975; 19(1):41–52.
85. Feterowski C, Emmanuilidis K, Miethke T, et al. Effects of functional Toll-like receptor-4 mutations on the immune response to human and experimental sepsis. Immunology 2003;109(3):426–31.
86. Fink AL. Chaperone-mediated protein folding. Physiol Rev 1999; 79(2):425–49.
87. Fischer E, Marano MA, Barber AE, et al. Comparison between effects of interleukin-1 alpha administration and sublethal endotoxemia in primates. Am J Physiol 1991;261(2 Pt 2):R442–52.
88. Fisher CJ Jr, Yan SB. Protein C levels as a prognostic indicator of outcome in sepsis and related diseases. Crit Care Med 2000;28 (9 Suppl.):S49–56.
89. Fishman D, Faulds G, Jeffery R, et al. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest 1998;102(7):1369–76.
90. Flanagan SW, Ryan AJ, Gisolfi CV, Moseley PL. Tissue-specific HSP70 response in animals undergoing heat stress. Am J Physiol 1995; 268:R28–32.
91. Fox RH, Goldsmith R, Kidd DJ, Lewis HE. Acclimatization to heat in man by controlled elevation of body temperature. J Physiol 1963; 166:530–47.
92. Francesconi RP, Sawka MN, Pandolf KB. Hypohydration and heat acclimation: Plasma renin and aldosterone during exercise. J Appl Physiol Respir Environ Exerc Physiol 1983;55(6):1790–4.
93. Freeman BD, Buchman TG. Gene in a haystack: Tumor necrosis factor polymorphisms and outcome in sepsis. Crit Care Med 2000; 28(8):3090–1.
94. Frei B, Stocker R, Ames BN. Antioxidant defenses and lipid peroxidation in human blood plasma. Proc Natl Acad Sci USA 1988;85(24): 9748–52.
95. Frumkin H. Urban sprawl and public health. Public Health Rep 2002; 117(3):201–17.
96. Gabow PA, Kaehny WD, Kelleher SP. The spectrum of rhabdomyolysis. Medicine (Baltimore) 1982;61(3):141–52.
97. Gader AM, al-Mashhadani SA, al-Harthy SS. Direct activation of platelets by heat is the possible trigger of the coagulopathy of heat stroke. Br J Haematol 1990;74(1):86–92.
98. Gagge AP, Gonzalez RR. Mechanisms of heat exchange: Biophysics and physiology. In: Blatteis CM, Fregly MJ, editors. Handbook of physiology. Environmental physiology. Bethesda, Md: American Physiological Society; 1996.
99. Gathiram P, Gaffin SL, Brock-Utne JG, Wells MT. Time course of endotoxemia and cardiovascular changes in heat-stressed primates. Aviat Space Environ Med 1987;58(11):1071–4.
100. Gathiram P, Wells MT, Brock-Utne JG, Gaffin SL. Antilipopolysaccharide improves survival in primates subjected to heat stroke. Circ Shock 1987;23(3):157–64.
101. Gemmell RT, Hales JR. Cutaneous arteriovenous anastomoses present in the tail but absent from the ear of the rat. J Anat 1977; 124(Pt 2):355–8.
102. Giercksky T, Boberg KM, Farstad IN, et al. Severe liver failure in exertional heat stroke. Scand J Gastroenterol 1999;34(8):824–7.
103. Girard T, Cavagna D, Padovan E, et al. B-lymphocytes from malignant hyperthermia-susceptible patients have an increased sensitivity to skeletal muscle ryanodine receptor activators. J Biol Chem 2001; 276(51):48077–82.
104. Gisolfi CV, Wenger CB. Temperature regulation during exercise: old concepts, new ideas. Exerc Sport Sci Rev 1984;12:339–72.
105. Glazer SF. Adverse reactions to sunlight. Compr Ther 1981;7(1): 44–9.
106. Goddard CJ, Warnes TW. Raised liver enzymes in asymptomatic patients: investigation and outcome. Dig Dis 1992;10(4):218–26.
107. Gonzalez-Alonso J, Teller C, Andersen SL, et al. Influence of body temperature on the development of fatigue during prolonged exercise in the heat. J Appl Physiol (1985) 1999;86(3):1032–9.
108. Graber CD, Reinhold RB, Breman JG, et al. Fatal heat stroke. Circulating endotoxin and gram-negative sepsis as complications. JAMA 1971;216(7):1195–6.
109. Graf R, Krishna S, Heller HC. Regulated nocturnal hypothermia induced in pigeons by food deprivation. In: 1989, pp. R733-8.
110. Grau GE, Maennel DN. TNF inhibition and sepsis: Sounding a cautionary note. Nat Med 1997;3(11):1193–5.
111. Greenberger MJ, Strieter RM, Kunkel SL, et al. Neutralization of IL-10 increases survival in a murine model of *Klebsiella* pneumonia. J Immunol 1995;155(2):722–9.
112. Haber MM, West AB, Haber AD, Reuben A. Relationship of aminotransferases to liver histological status in chronic hepatitis C. Am J Gastroenterol 1995;90(8):1250–7.
113. Hagberg L, Briles DE, Eden CS. Evidence for separate genetic defects in C3H/HeJ and C3HeB/FeJ mice, that affect susceptibility to gram-negative infections. J Immunol 1985;134(6):4118–22.
114. Hainsworth FR. Saliva spreading, activity, and body temperature regulation in the rat. Am J Physiol 1967;212(6):1288–92.
115. Hakre S, Gardner JW, Kark JA, Wenger CB. Predictors of hospitalization in male Marine Corps recruits with exertional heat illness. In: 2004, pp. 169-75.
116. Hales JR, Brown GD. Net energetic and thermoregulatory efficiency during panting in the sheep. Comp Biochem Physiol A Comp Physiol 1974;49(3A):413–22.
117. Hall DM, Buettner GR, Oberley LW, et al. Mechanisms of circulatory and intestinal barrier dysfunction during whole body hyperthermia. Am J Physiol Heart Circ Physiol 2001;280(2):H509–21.
118. Hammami MM, Bouchama A, Al-Sedairy S, et al. Concentrations of soluble tumor necrosis factor and interleukin-6 receptors in heatstroke and heatstress. Crit Care Med 1997;25(8):1314–19.
119. Handrigan MT, Bentley TB, Oliver JD, et al. Choice of fluid influences outcome in prolonged hypotensive resuscitation after hemorrhage in awake rats. Shock 2005;23(4):337–43.
120. Hart GR, Anderson RJ, Crumpler CP, et al. Epidemic classical heat stroke: Clinical characteristics and course of 28 patients. Medicine (Baltimore) 1982;61(3):189–97.

121. Hartl FU, Hayer-Hartl M. Molecular chaperones in the cytosol: From nascent chain to folded protein. Science 2002;295(5561):1852–8.
122. Hashim IA, Al-Zeer A, Al-Shohaib S, et al. Cytokine changes in patients with heatstroke during pilgrimage to Makkah. Mediators Inflamm 1997;6(2):135–9.
123. Hassanein T, Perper JA, Tepperman L, et al. Liver failure occurring as a component of exertional heatstroke. Gastroenterology 1991;100(5 Pt 1):1442–7.
124. Hassanein T, Razack A, Gavaler JS, Van Thiel DH. Heatstroke: Its clinical and pathological presentation, with particular attention to the liver. Am J Gastroenterol 1992;87(10):1382–9.
125. Hatada T, Wada H, Nobori T, et al. Plasma concentrations and importance of High Mobility Group Box protein in the prognosis of organ failure in patients with disseminated intravascular coagulation. Thromb Haemost 2005;94(5):975–9.
126. Haveman J, Geerdink AG, Rodermond HM. Cytokine production after whole body and localized hyperthermia. Int J Hyperthermia 1996;12(6):791–800.
127. Heidecke CD, Hensler T, Weighardt H, et al. Selective defects of T lymphocyte function in patients with lethal intraabdominal infection. Am J Surg 1999;178(4):288–92.
128. Heinrich B, Heinrich MJE. Heterothermia in foraging workers and drones of the bumblebee *Bombus terricola*. Physiol Zool 1983;56: 563–7.
129. Henderson RA, Whitehurst ME, Morgan KR, Carroll RG. Reduced metabolic rate accompanies the hemorrhage-induced hypothermia in conscious rats. Resuscitation 2000;44(2):129–38.
130. Hightower LE. Cultured animal cells exposed to amino acid analogues or puromycin rapidly synthesize several polypeptides. J Cell Physiol 1980;102(3):407–27.
131. Holowatz LA, Kenney WL. Chronic low-dose aspirin therapy attenuates reflex cutaneous vasodilation in middle-aged humans. J Appl Physiol (1985) 2009;106(2):500–5.
132. Holti G. Measurements of the vascular responses in skin at various time intervals after damage with histamine and ultra-violet radiation. Clin Sci (Lond) 1955;14(1):143–55.
133. Horowitz M. Heat acclimation and cross-tolerance against novel stressors: Genomic-physiological linkage. Prog Brain Res 2007;162: 373–92.
134. Horowitz M, Maloyan A, Shlaier J. HSP 70 kDa dynamics in animals undergoing heat stress superimposed on heat acclimation. Ann N Y Acad Sci 1997;813:617–19.
135. Hreggvidsdottir HS, Ostberg T, Wahamaa H, et al. The alarmin HMGB1 acts in synergy with endogenous and exogenous danger signals to promote inflammation. J Leukoc Biol 2009;86(3):655–62.
136. Hutchison KA, Dittmar KD, Czar MJ, Pratt WB. Proof that hsp70 is required for assembly of the glucocorticoid receptor into a heterocomplex with hsp90. J Biol Chem 1994;269(7):5043–9.
137. Hutchison VH, Murphy K. Behavioral thermoregulation in the salamander *Necturus maculosus* after heat shock. Comp Biochem Physiol 1985;82A:391–4.
138. Ibuka N, Fukurama K. Unpredictable deprivation of water in probability of torpor in the Syrian hamster. Physiol Behav 1997;62: 551–6.
139. Inoue Y, Shibasaki M, Ueda H, Ishizashi H. Mechanisms underlying the age-related decrement in the human sweating response. Eur J Appl Physiol Occup Physiol 1999;79(2):121–6.
140. Ito T, Kawahara K, Nakamura T, et al. High-mobility group box 1 protein promotes development of microvascular thrombosis in rats. J Thromb Haemost 2007;5(1):109–16.
141. IUPS. Glossary of terms for thermal physiology. Jpn J Physiol 2001; 51:245–80.
142. Jaattela M. Heat shock proteins as cellular lifeguards. Ann Med 1999;31(4):261–71.
143. Jahromi MM, Millward BA, Demaine AG. A polymorphism in the promoter region of the gene for interleukin-6 is associated with susceptibility to type 1 diabetes mellitus. J Interferon Cytokine Res 2000;20(10):885–8.
144. Janeway CA Jr, Medzhitov R. Innate immune recognition. Annu Rev Immunol 2002;20:197–216.
145. Jones TS, Liang AP, Kilbourne EM, et al. Morbidity and mortality associated with the July 1980 heat wave in St Louis and Kansas City, Mo. JAMA 1982;247(24):3327–31.
146. Jongeneel CV, Briant L, Udalova IA, et al. Extensive genetic polymorphism in the human tumor necrosis factor region and relation to extended HLA haplotypes. Proc Natl Acad Sci USA 1991;88(21): 9717–21.
147. Kalnay E, Cai M. Impact of urbanization and land-use change on climate. Nature 2003;423(6939):528–31.
148. Kelker HC, Oppenheim JD, Stone-Wolff D, et al. Characterization of human tumor necrosis factor produced by peripheral blood monocytes and its separation from lymphotoxin. Int J Cancer 1985; 36(1):69–73.
149. Kelty JD, Noseworthy PA, Feder ME, et al. Thermal preconditioning and heat-shock protein 72 preserve synaptic transmission during thermal stress. J Neurosci 2002;22(1):RC193.
150. Kenefick RW, Cheuvront SN, Sawka MN. Thermoregulatory function during the marathon. Sports Med 2007;37(4–5):312–15.
151. Kenney MJ, Fels RJ. Sympathetic nerve regulation to heating is altered in senescent rats. Am J Physiol Regul Integr Comp Physiol 2002;283(2):R513–20.
152. Kentner R, Safar P, Prueckner S, et al. Titrated hypertonic/hyperoncotic solution for hypotensive fluid resuscitation during uncontrolled hemorrhagic shock in rats. Resuscitation 2005;65(1): 87–95.
153. Keplinger ML, Lanier GE, Deichmann WB. Effects of environmental temperature on the acute toxicity of a number of compounds in rats. Toxicology 1959;1(2):156–61.
154. Keren G, Epstein Y, Magazanik A. Temporary heat intolerance in a heatstroke patient. Aviat Space Environ Med 1981;52(2):116–17.
155. Khazaeli AA, Tatar M, Pletcher SD, Curtsinger JW. Heat-induced longevity extension in *Drosophila*. I. Heat treatment, mortality, and thermotolerance. J Gerontol A Biol Sci Med Sci 1997;52(1):B48–52.
156. Khogali M. Epidemiology of heat illnesses during the Makkah Pilgrimages in Saudi Arabia. Int J Epidemiol 1983;12(3):267–73.
157. Kielblock AJ, Van Rensburg JP, Franz RM. Body cooling as a method for reducing hyperthermia: An evaluation of techniques. S Afr Med J 1986;69(6):378–80.
158. Kilbourne EM, Choi K, Jones TS, Thacker SB. Risk factors for heatstroke. A case-control study. JAMA 1982;247(24):3332–6.
159. Kim H. Diagnostic significance of antibodies to heat shock proteins. Clin Chim Acta 2003;337(1–2):1–10.
160. Kirby CR, Convertino VA. Plasma aldosterone and sweat sodium concentrations after exercise and heat acclimation. J Appl Physiol (1985) 1986;61(3):967–70.
161. Klapproth J, Castell J, Geiger T, et al. Fate and biological action of human recombinant interleukin 1 beta in the rat in vivo. Eur J Immunol 1989;19(8):1485–90.
162. Klein MS, Conn CA, Kluger MJ. Behavioral thermoregulation in mice inoculated with influenza virus. Physiol Behav 1992;52(6):1133–9.
163. Kluger MJ. Fever: role of pyrogens and cryogens. Physiol Rev 1991;71(1):93–127.
164. Knochel JP. The pathophysiology and clinical characteristics of severe hypophosphatemia. Arch Intern Med 1977;137(2):203–20.
165. Knupfer H, Preiss R. sIL-6R: More than an agonist? Immunol Cell Biol 2008;86(1):87–91.
166. Kozak W, Soszynski D, Rudolph K, et al. Soluble tumor necrosis factor alpha receptor prevents decrease of body temperature in mice treated with indomethacin and lipopolysaccharide. Ann N Y Acad Sci 1997;813:264–71.
167. Kregel KC. Heat shock proteins: Modifying factors in physiological stress responses and acquired thermotolerance. J Appl Physiol 2002;92(5):2177–86.
168. Kregel KC, Moseley PL. Differential effects of exercise and heat stress on liver HSP70 accumulation with aging. J Appl Physiol (1985) 1996; 80(2):547–51.
169. Lai FA, Erickson HP, Rousseau E, et al. Purification and reconstitution of the calcium release channel from skeletal muscle. Nature 1988;331(6154):315–19.
170. Lambert GP, Gisolfi CV, Berg DJ, et al. Hyperthermia-induced intestinal and nitrosative stress. J Appl Physiol 2002;92:1750–61.
171. Landsberg HE. Man-made climatic changes: Man's activities have altered the climate of urbanized areas and may affect global climate in the future. Science 1970;170(3964):1265–74.
172. Lappas GD, Karl IE, Hotchkiss RS. Effect of ethanol and sodium arsenite on HSP-72 formation and on survival in a murine endotoxin model. Shock 1994;2(1):34–9, discussion 40.
173. Lavoie JN, Gingras-Breton G, Tanguay RM, Landry J. Induction of Chinese hamster HSP27 gene expression in mouse cells confers resistance to heat shock: HSP27 stabilization of the microfilament organization. J Biol Chem 1993;268(5):3420–9.
174. Leon LR. Hypothermia in systemic inflammation: Role of cytokines. Front Biosci 2004;9:1877–88.
175. Leon LR. The thermoregulatory consequences of heat stroke: Are cytokines involved? J Therm Biol 2006;31:67–81.
176. Leon LR. Heat stroke and cytokines. Prog Brain Res 2007;162: 481–524.
177. Leon LR, Blaha MD, DuBose DA. Time course of cytokine, corticosterone, and tissue injury responses in mice during heat strain recovery. J Appl Physiol 2006;100(4):1400–9.
178. Leon LR, Dineen SM, Plamper ML. Indomethacin increases organ damage and heat stroke mortality in mice. FASEB J 2014;28: 1104–13.
179. Leon LR, DuBose DA, Mason CW. Heat stress induces a biphasic thermoregulatory response in mice. Am J Physiol Regul Integr Comp Physiol 2005;288(1):R197–204.

180. Leon LR, Gordon CJ, Helwig BG, et al. Thermoregulatory, behavioral, and metabolic responses to heatstroke in a conscious mouse model. Am J Physiol Regul Integr Comp Physiol 2010;299(1): R241–8.
181. Leon LR, White AA, Kluger MJ. Role of IL-6 and TNF in thermoregulation and survival during sepsis in mice. Am J Physiol 1998;275(1 Pt 2):R269–77.
182. Levi M, de Jonge E, van der Poll T, ten Cate H. Disseminated intravascular coagulation. Thromb Haemost 1999;82(2):695–705.
183. Levine JA. Heat stroke in the aged. Am J Med 1969;47(2):251–8.
184. Liaw PC, Esmon CT, Kahnamoui K, et al. Patients with severe sepsis vary markedly in their ability to generate activated protein C. Blood 2004;104(13):3958–64.
185. Liebermeister C. Vorlesungen uber specielle pathologie und therapie. FCW Vogel; 1887.
186. Lin MT, Kao TY, Su CF, Hsu SS. Interleukin-1 beta production during the onset of heat stroke in rabbits. Neurosci Lett 1994;174(1): 17–20.
187. Lin XJ, Li YJ, Li ZL, et al. Pre-existing lipopolysaccharide may increase the risk of heatstroke in rats. Am J Med Sci 2009;337(4): 265–70.
188. Lind AR, Bass DE. Optimal exposure time for development of acclimatization to heat. Fed Proc 1963;22:704–8.
189. Lindquist S, Craig EA. The heat-shock proteins. Annu Rev Genet 1988;22:631–77.
190. Line RL, Rust GS. Acute exertional rhabdomyolysis. Am Fam Physician 1995;52(2):502–6.
191. Litman RS, Rosenberg H. Malignant hyperthermia: Update on susceptibility testing. JAMA 2005;293(23):2918–24.
192. Liu CC, Ke D, Chen ZC, Lin MT. Hydroxyethyl starch produces attenuation of circulatory shock and cerebral ischemia during heatstroke. Shock 2004;22(3):288–94.
193. Luterbacher J, Dietrich D, Xoplaki E, et al. European seasonal and annual temperature variability, trends, and extremes since 1500. Science 2004;303(5663):1499–503.
194. Lyashko VN, Vikulova VK, Chernicov VG, et al. Comparison of the heat shock response in ethnically and ecologically different human populations. Proc Natl Acad Sci U S A 1994;91(26):12492–5.
195. Mack GW, Nadell ER. Body fluid balance during heat stress in humans. In: Fregly MJ, Blatteis CM, editors. Environmental physiology. New York: Oxford University; 1996. p. 187–214.
196. Maes M, Christophe A, Bosmans E, et al. In humans, serum polyunsaturated fatty acid levels predict the response of proinflammatory cytokines to psychologic stress. Biol Psychiatry 2000;47(10):910–20.
197. Malamud N, Haymaker W, Custer RP. Heat stroke: Clinico-pathologic study of 125 fatal cases. Mil Surg 1946;99:397–449.
198. Maloyan A, Palmon A, Horowitz M. Heat acclimation increases the basal HSP72 level and alters its production dynamics during heat stress. Am J Physiol 1999;276(5 Pt 2):R1506–15.
199. Malvin GM, Wood SC. Behavioral hypothermia and survival of hypoxic protozoans *Paramecium caudatum*. Science 1992;255(5050): 1423–5.
200. Malyak M, Smith MF Jr, Abel AA, Arend WP. Peripheral blood neutrophil production of interleukin-1 receptor antagonist and interleukin-1 beta. J Clin Immunol 1994;14(1):20–30.
201. Marber MS, Mestril R, Chi SH, et al. Overexpression of the rat inducible 70-kD heat stress protein in a transgenic mouse increases the resistance of the heart to ischemic injury. J Clin Invest 1995;95(4): 1446–56.
202. Maron MB, Wagner JA, Horvath SM. Thermoregulatory responses during competitive marathon running. J Appl Physiol 1977;42(6): 909–14.
203. Marshall JC. The failure of clinical trials in sepsis: Challenges of clinical trial design. In: Redl H, Schlag G, editors. Cytokines in severe sepsis and septic shock. Basel/Boston/Berlin: Birkhauser; 1999. p. 349–62.
204. Martens WJ. Health impacts of climate change and ozone depletion: An ecoepidemiologic modeling approach. Environ Health Perspect 1998;106(Suppl. 1):241–51.
205. McClung JP, Hasday JD, He JR, et al. Exercise-heat acclimation in humans alters baseline levels and ex vivo heat inducibility of HSP72 and HSP90 in peripheral blood mononuclear cells. Am J Physiol Regul Integr Comp Physiol 2008;294(1):R185–91.
206. McCord GR, Cracowski JL, Minson CT. Prostanoids contribute to cutaneous active vasodilation in humans. Am J Physiol Regul Integr Comp Physiol 2006;291(3):R596–602.
207. McGill SN, Ahmed NA, Christou NV. Endothelial cells: role in infection and inflammation. World J Surg 1998;22(2):171–8.
208. McPherson PS, Campbell KP. The ryanodine receptor/$Ca^{2+}$ release channel. J Biol Chem 1993;268(19):13765–8.
209. Medvedev AE, Sabroe I, Hasday JD, Vogel SN. Tolerance to microbial TLR ligands: Molecular mechanisms and relevance to disease. J Endotoxin Res 2006;12(3):133–50.
210. Mendeloff AI, Smith DE. Extreme physical effort in summer heat followed by collapse, stupor, purpura, jaundice and azotemia. Am J Med 1955;18:659–70.
211. Mikkelsen TS, Toft P. Prognostic value, kinetics and effect of CVVHDF on serum of the myoglobin and creatine kinase in critically ill patients with rhabdomyolysis. Acta Anaesthesiol Scand 2005;49(6): 859–64.
212. Minson CT, Wladkowski SL, Cardell AF, et al. Age alters the cardiovascular response to direct passive heating. J Appl Physiol 1998;84(4): 1323–32.
213. Moldoveanu AI, Shephard RJ, Shek PN. The cytokine response to physical activity and training. Sports Med 2001;31:115–44.
214. Montain SJ, Sawka MN, Wenger CB. Hyponatremia associated with exercise: risk factors and pathogenesis. Exerc Sport Sci Rev 2001; 29(3):113–17.
215. Morrison-Bogorad M, Zimmerman AL, Pardue S. Heat-shock 70 messenger RNA levels in human brain: Correlation with agonal fever. J Neurochem 1995;64(1):235–46.
216. Moseley PL, Gapen C, Wallen ES, et al. Thermal stress induces epithelial permeability. Am J Physiol 1994;267(2 Pt 1):C425–34.
217. Mustafa KY, Omer O, Khogali M, et al. Blood coagulation and fibrinolysis in heat stroke. Br J Haematol 1985;61(3):517–23.
218. Nadel ER, Mitchell JW, Saltin B, Stolwijk JA. Peripheral modifications to the central drive for sweating. J Appl Physiol 1971;31(6):828–33.
219. Naughton MP, Henderson A, Mirabelli MC, et al. Heat-related mortality during a 1999 heat wave in Chicago. Am J Prev Med 2002;22(4): 221–7.
220. Neville AJ, Sauder DN. Whole body hyperthermia (41-42 degrees C) induces interleukin-1 in vivo. Lymphokine Res 1988;7(3):201–6.
221. Nielsen B, Hales JR, Strange S, et al. Human circulatory and thermoregulatory adaptations with heat acclimation and exercise in a hot, dry environment. J Physiol 1993;460:467–85.
222. Nieman DC, Henson DA, Smith LL, et al. Cytokine changes after a marathon race. J Appl Physiol 2001;91(1):109–14.
223. Nolan JP. Endotoxin, reticuloendothelial function, and liver injury. Hepatology 1981;1(5):458–65.
224. Nomoto K, Yoshikai Y. Heat-shock proteins and immunopathology: Regulatory role of heat-shock protein-specific T cells. Springer Semin Immunopathol 1991;13(1):63–80.
225. Nussbaum E, Tuazon CU, Kessler CM. Aspirin (ASA) prevents the disseminated intravascular coagulation (DIC) induced by *S. aureus* and its purified peptidoglycan (PEP). Blood 1988;72(Suppl. 5):305a.
226. Nybo L. Exercise and heat stress: Cerebral challenges and consequences. Prog Brain Res 2007;162:29–43.
227. O'Brien KK, Montain SJ, Corr WP, et al. Hyponatremia associated with overhydration in U.S. Army trainees. Mil Med 2001;166(5): 405–10.
228. O'Brien PJ, Cribb PH, White RJ, et al. Canine malignant hyperthermia: Diagnosis of susceptibility in a breeding colony. Can Vet J 1983;24(6):172–7.
229. O'Donnell TF Jr. Acute heat stroke: Epidemiologic, biochemical, renal, and coagulation studies. JAMA 1975;234(8):824–8.
230. O'Sullivan GH, McIntosh JM, Heffron JJ. Abnormal uptake and release of $Ca^{2+}$ ions from human malignant hyperthermia-susceptible sarcoplasmic reticulum. Biochem Pharmacol 2001;61(12):1479–85.
231. Oberholzer A, Oberholzer C, Moldawer LL. Interleukin-10: A complex role in the pathogenesis of sepsis syndromes and its potential as an anti-inflammatory drug. Crit Care Med 2002;30(1 Suppl.):S58–63.
232. Oka T, Oka K, Hori T. Mechanisms and mediators of psychological stress-induced rise in core temperature. Psychosom Med 2001;63(3): 476–86.
233. Okusawa S, Gelfand JA, Ikejima T, et al. Interleukin 1 induces a shock-like state in rabbits: Synergism with tumor necrosis factor and the effect of cyclooxygenase inhibition. J Clin Invest 1988;81(4): 1162–72.
234. Oliver SR, Phillips NA, Novosad VL, et al. Hyperthermia induces injury to the intestinal mucosa in the mouse: Evidence for an oxidative stress mechanism. Am J Physiol Regul Integr Comp Physiol 2012; 302(7):R845–53.
235. Ookura R, Shiro Y, Takai T, et al. Diffusion-weighted magnetic resonance imaging of a severe heat stroke patient complicated with severe cerebellar ataxia. Intern Med 2009;48(12):1105–8.
236. Opal SM, Fisher CJ Jr, Dhainaut JF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a Phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. Crit Care Med 1997;25(7):1115–24.
237. Oshima T, Laroux FS, Coe LL, et al. Interferon-( and interleukin-10 reciprocally regulate endothelial junction integrity and barrier function. Microvasc Res 2001;61:130–43.
238. Oz MC, Zikria BA, McLeod PF, Popilkis SJ. Hydroxyethyl starch macromolecule and superoxide dismutase effects on myocardial reperfusion injury. Am J Surg 1991;162(1):59–62.

239. Pandolf KB, Burse RL, Goldman RF. Role of physical fitness in heat acclimatisation, decay and reinduction. Ergonomics 1977;20(4): 399–408.
240. Pandolf KB, Gange RW, Latzka WA, et al. Human thermoregulatory responses during heat exposure after artificially induced sunburn. Am J Physiol 1992;262(4 Pt 2):R610–16.
241. Pandolf KB, Griffin TB, Munro EH, Goldman RF. Heat intolerance as a function of percent of body surface involved with miliaria rubra. Am J Physiol 1980;239(3):R233–40.
242. Pandolf KB, Griffin TB, Munro EH, Goldman RF. Persistence of impaired heat tolerance from artificially induced miliaria rubra. Am J Physiol 1980;239(3):R226–32.
243. Parcellier A, Gurbuxani S, Schmitt E, et al. Heat shock proteins, cellular chaperones that modulate mitochondrial cell death pathways. Biochem Biophys Res Commun 2003;304(3):505–12.
244. Patel DR, Gyamfi R, Torres A. Exertional rhabdomyolysis and acute kidney injury. Phys Sports Med 2009;37(1):71–9.
245. Patel RT, Deen KI, Youngs D, et al. Interleukin 6 is a prognostic indicator of outcome in severe intra-abdominal sepsis. Br J Surg 1994;81(9):1306–8.
246. Pease S, Bouadma L, Kermarrec N, et al. Early organ dysfunction course, cooling time and outcome in classic heatstroke. Intensive Care Med 2009;35(8):1454–8.
247. Perchick JS, Winkelstein A, Shadduck RK. Disseminated intravascular coagulation in heat stroke: Response to heparin therapy. JAMA 1975; 231(5):480–3.
248. Poulton TJ, Walker RA. Helicopter cooling of heatstroke victims. Aviat Space Environ Med 1987;58(4):358–61.
249. Pruitt JH, Welborn MB, Edwards PD, et al. Increased soluble interleukin-1 type II receptor concentrations in postoperative patients and in patients with sepsis syndrome. Blood 1996;87(8):3282–8.
250. Pugh LG, Corbett JL, Johnson RH. Rectal temperatures, weight losses, and sweat rates in marathon running. J Appl Physiol 1967;23(3): 347–52.
251. Rajdev S, Hara K, Kokubo Y, et al. Mice overexpressing rat heat shock protein 70 are protected against cerebral infarction. Ann Neurol 2000;47:782–91.
252. Raju SF, Robinson GH, Bower JD. The pathogenesis of acute renal failure in heat stroke. South Med J 1973;66(3):330–3.
253. Ramasawmy R, Fae KC, Spina G, et al. Association of polymorphisms within the promoter region of the tumor necrosis factor-alpha with clinical outcomes of rheumatic fever. Mol Immunol 2007;44(8): 1873–8.
254. Rasch W, Samson P, Cote J, Cabanac M. Heat loss from the human head during exercise. J Appl Physiol 1991;71(2):590–5.
255. Rausch RN, Crawshaw LI, Wallace HL. Effects of hypoxia, anoxia, and endogenous ethanol on thermoregulation in goldfish, *Carassius auratus*. Am J Physiol Regul Integr Comp Physiol 2000;278(3): R545–55.
256. Rav-Acha M, Hadad E, Epstein Y, et al. Fatal exertional heat stroke: A case series. Am J Med Sci 2004;328(2):84–7.
257. Remick DG. Cytokine therapeutics for the treatment of sepsis: Why has nothing worked? Curr Pharm Des 2003;9(1):75–82.
258. Rennick DM, Fort MM, Davidson NJ. Studies with IL-10−/− mice: An overview. J Leukoc Biol 1997;61(4):389–96.
259. Replogle RL, Merrill EW. Experimental polycythemia and hemodilution: Physiologic and rheologic effects. J Thorac Cardiovasc Surg 1970;60(4):582–8.
260. Reynolds WW, Casterlin ME, Covert JB. Behavioural fever in teleost fishes. Nature 1976;259(5538):41–2.
261. Richards SA. The biology and comparative physiology of thermal panting. Biol Rev Camb Philos Soc 1970;45(2):223–64.
262. Ritossa F. A new puffing pattern induced by temperature shock and DNP in *Drosophila melanogaster:* Relation to chromosome puffs. Experientia 1962;18:571–3.
263. Roberts WO. Death in the heat: Can football heat stroke be prevented? Curr Sports Med Rep 2004;3(1):1–3.
264. Robinson S, Robinson AH. Chemical composition of sweat. Physiol Rev 1954;34(2):202–20.
265. Romanovsky AA, Kulchitsky VA, Akulich NV, et al. First and second phases of biphasic fever: Two sequential stages of the sickness syndrome? Am J Physiol 1996;271(1 Pt 2):R244–53.
266. Romanovsky AA, Shido O, Sakurada S, et al. Endotoxin shock-associated hypothermia: How and why does it occur? Ann NY Acad Sci 1997;813:733–7.
267. Roncarolo MG, Battaglia M, Gregori S. The role of interleukin 10 in the control of autoimmunity. J Autoimmun 2003;20(4): 269–72.
268. Rosenberg H, Antognini JF, Muldoon S. Testing for malignant hyperthermia. Anesthesiology 2002;96(1):232–7.
269. Roskind JL, Petrofsky J, Lind AR, Paletta FX. Quantitation of thermoregulatory impairment in patients with healed burns. Ann Plast Surg 1978;1(2):172–6.
270. Rosner MH. Urinary biomarkers for the detection of renal injury. Adv Clin Chem 2009;49:73–97.
271. Saissy JM. Liver transplantation in a case of fulminant liver failure after exertion. Intensive Care Med 1996;22(8):831.
272. Sawka MN, Coyle EF. Influence of body water and blood volume on thermoregulation and exercise performance in the heat. Exerc Sport Sci Rev 1999;27:167–218.
273. Scaffidi P, Misteli T, Bianchi ME. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature 2002; 418(6894):191–5.
274. Schar C, Jendritzky G. Climate change: Hot news from summer 2003. Nature 2004;432(7017):559–60.
275. Schobitz B, Pezeshki G, Pohl T, et al. Soluble interleukin-6 (IL-6) receptor augments central effects of IL-6 in vivo. FASEB J 1995; 9(8):659–64.
276. Sculier JP, Bron D, Verboven N, Klastersky J. Multiple organ failure during interleukin-2 administration and LAK cells infusion. Intensive Care Med 1988;14(6):666–7.
277. Seeler DC, McDonell WN, Basrur PK. Halothane and halothane/succinylcholine induced malignant hyperthermia (porcine stress syndrome) in a population of Ontario boars. Can J Comp Med 1983; 47(3):284–90.
278. Senay LC Jr. Relationship of evaporative rates to serum $[Na^+]$, $[K^+]$, and osmolarity in acute heat stress. J Appl Physiol 1968;25(2): 149–52.
279. Seth P, Juliana P. Exertional heat stroke in a marathon runner with extensive healed deep burns: A case report. Int J Emerg Med 2011; 4:12.
280. Shapiro Y, Epstein Y, Ben-Simchon C, Tsur H. Thermoregulatory responses of patients with extensive healed burns. J Appl Physiol Respir Environ Exerc Physiol 1982;53(4):1019–22.
281. Shapiro Y, Seidman DS. Field and clinical observations of exertional heat stroke patients. Med Sci Sports Exerc 1990;22(1): 6–14.
282. Sharif SF, Hariri RJ, Chang VA, et al. Human astrocyte production of tumour necrosis factor-alpha, interleukin-1 beta, and interleukin-6 following exposure to lipopolysaccharide endotoxin. Neurol Res 1993;15(2):109–12.
283. Sherman KE. Alanine aminotransferase in clinical practice: A review. Arch Intern Med 1991;151(2):260–5.
284. Shibolet S, Coll R, Gilat T, Sohar E. Heatstroke: Its clinical picture and mechanism in 36 cases. Q J Med 1967;36(144):525–48.
285. Shibolet S, Lancaster MC, Danon Y. Heat stroke: A review. Aviat Space Environ Med 1976;47(3):280–301.
286. Smalley B, Janke RM, Cole D. Exertional heat illness in Air Force basic military trainees. Mil Med 2003;168(4):298–303.
287. Snell ES, Atkins E. The mechanisms of fever. New York: Academic Press; 1968.
288. Sonna LA, Cullivan ML, Sheldon HK, et al. Effect of hypoxia on gene expression by human hepatocytes (HepG2). Physiol Genomics 2003;12(3):195–207.
289. Sonna LA, Gaffin SL, Pratt RE, et al. Effect of acute heat shock on gene expression by human peripheral blood mononuclear cells. J Appl Physiol 2002;92(5):2208–20.
290. Sonna LA, Kuhlmeier MM, Khatri P, et al. A microarray analysis of the effects of moderate hypothermia and rewarming on gene expression by human hepatocytes (HepG2). Cell Stress Chaperones 2010;15(5):687–702.
291. Sonna LA, Wenger CB, Flinn S, et al. Exertional heat injury and gene expression changes: A DNA microarray analysis study. J Appl Physiol 2004;96(5):1943–53.
292. Srichaikul T, Prayoonwiwat W, Sanguanwong S, et al. Clinical manifestations and therapy of heat stroke: Consumptive coagulopathy successfully treated by exchange transfusion and heparin. Southeast Asian J Trop Med Public Health 1989;20(3):479–91.
293. Stauss HM, Morgan DA, Anderson KE, et al. Modulation of baroreflex sensitivity and spectral power of blood pressure by heat stress and aging. Am J Physiol 1997;272(2 Pt 2):H776–84.
294. Stitt JT. Prostaglandin E as the neural mediator of the febrile response. Yale J Biol Med 1986;59(2):137–49.
295. Stricker EM, Hainsworth FR. Evaporative cooling in the rat: Interaction with heat loss from the tail. Q J Exp Physiol Cogn Med Sci 1971;56(4):231–41.
296. Strother SV, Bull JM, Branham SA. Activation of coagulation during therapeutic whole body hyperthermia. Thromb Res 1986;43(3): 353–60.
297. Stuber F, Petersen M, Bokelmann F, Schade U. A genomic polymorphism within the tumor necrosis factor locus influences plasma tumor necrosis factor-alpha concentrations and outcome of patients with severe sepsis. Crit Care Med 1996;24(3):381–4.
298. Sudhakar PJ, Al-Hashimi H. Bilateral hippocampal hyperintensities: A new finding in MR imaging of heat stroke. Pediatr Radiol 2007; 37(12):1289–91.

299. Sunden-Cullberg J, Norrby-Teglund A, Rouhiainen A, et al. Persistent elevation of high mobility group box-1 protein (HMGB1) in patients with severe sepsis and septic shock. Crit Care Med 2005;33(3): 564–73.
300. Suzuki K, Nakaji S, Yamada M, et al. Impact of a competitive marathon race on systemic cytokine and neutrophil responses. Med Sci Sports Exerc 2003;35(2):348–55.
301. Szold O, Reider-Groswasser II, Abraham RB, et al. Gray-white matter discrimination: A possible marker for brain damage in heat stroke? Eur J Radiol 2002;43:1–5.
302. Takeshima H, Nishimura S, Matsumoto T, et al. Primary structure and expression from complementary DNA of skeletal muscle ryanodine receptor. Nature 1989;339(6224):439–45.
303. Tamaki Y, Nakayama T, Kanosue K. Effects of peripheral chemo- and baro-receptor denervation on responses of preoptic thermosensitive neurons to inspired $CO_2$. Pflugers Arch 1989;414(5):495–9.
304. Tamaki Y, Nakayama T, Matsumura K. Effects of carbon dioxide inhalation on preoptic thermosensitive neurons. Pflugers Arch 1986; 407(1):8–13.
305. Taylor FB Jr, Chang A, Esmon CT, et al. Protein C prevents the coagulopathic and lethal effects of *Escherichia coli* infusion in the baboon. J Clin Invest 1987;79(3):918–25.
306. Tissieres A, Mitchell HK, Tracy UM. Protein synthesis in salivary glands of *Drosophila melanogaster*: relation to chromosome puffs. J Mol Biol 1974;84(3):389–98.
307. Tollofsrud S, Bjerkelund CE, Kongsgaard U, et al. Cold and warm infusion of Ringer's acetate in healthy volunteers: The effects on haemodynamic parameters, transcapillary fluid balance, diuresis and atrial peptides. Acta Anaesthesiol Scand 1993;37(8):768–73.
308. Toner MM, Mcardle WD. Human thermoregulatory responses to acute cold stress with special reference to water immersion. In: Fregly MJ, Blatteis CM, editors. Handbook of physiology. Section 4. Environmental Physiology. New York: Oxford University; 1996.
309. Tracey KJ, Beutler B, Lowry SF, et al. Shock and tissue injury induced by recombinant human cachectin. Science 1986;234(4775):470–4.
310. Tsujimoto H, Ono S, Efron PA, et al. Role of Toll-like receptors in the development of sepsis. Shock 2008;29(3):315–21.
311. Tsujimoto H, Ono S, Majima T, et al. Neutrophil elastase, MIP-2, and TLR-4 expression during human and experimental sepsis. Shock 2005;23(1):39–44.
312. Van Dam AM, Brouns M, Louisse S, Berkenbosch F. Appearance of interleukin-1 in macrophages and in ramified microglia in the brain of endotoxin-treated rats: A pathway for the induction of non-specific symptoms of sickness? Brain Res 1992;588(2):291–6.
313. Van den HC, Lister D, Muylle E, et al. Malignant hyperthermia in Belgian Landrace pigs rested or exercised before exposure to halothane. Br J Anaesth 1976;48(9):821–9.
314. Van der Poll T, Jansen J, Levi M, et al. Regulation of interleukin 10 release by tumor necrosis factor in humans and chimpanzees. J Exp Med 1994;180(5):1985–8.
315. Vandentorren S, Suzan F, Medina S, et al. Mortality in 13 French cities during the August 2003 heat wave. Am J Public Health 2004; 94:1518–20.
316. Villar J, Ribeiro SP, Mullen JB, et al. Induction of the heat shock response reduces mortality rate and organ damage in a sepsis-induced acute lung injury model. Crit Care Med 1994;22(6):914–21.
317. Voellmy R. Transduction of the stress signal and mechanisms of transcriptional regulation of heat shock/stress protein gene expression in higher eukaryotes. Crit Rev Eukaryot Gene Expr 1994;4(4): 357–401.
318. Wagner M, Kaufmann P, Fickert P, et al. Successful conservative management of acute hepatic failure following exertional heatstroke. Eur J Gastroenterol Hepatol 2003;15(10):1135–9.
319. Wagner RD, Maroushek NM, Brown JF, Czuprynski CJ. Treatment with anti-interleukin-10 monoclonal antibody enhances early resistance to but impairs complete clearance of *Listeria monocytogenes* infection in mice. Infect Immun 1994;62(6):2345–53.
320. Wallace RF, Kriebel D, Punnett L, et al. Prior heat illness hospitalization and risk of early death. Environ Res 2007;104(2):290–5.
321. Wallimann T, Hemmer W. Creatine kinase in non-muscle tissues and cells. Mol Cell Biochem 1994;133-134:193–220.
322. Wang AY, Li PK, Lui SF, Lai KN. Renal failure and heatstroke. Ren Fail 1995;17(2):171–9.
323. Wang H, Bloom O, Zhang M, et al. HMGB-1 as a late mediator of endotoxin lethality in mice. Science 1999;285(5425):248–51.
324. Wang X, Zou Y, Wang Y, et al. Differential regulation of interleukin-12 and interleukin-10 by heat shock response in murine peritoneal macrophages. Biochem Biophys Res Commun 2001;287(5):1041–4.
325. Wappler F. Malignant hyperthermia. Eur J Anaesthesiol 2001;18(10): 632–52.
326. Warren HS, Suffredini AF, Eichacker PQ, Munford RS. Risks and benefits of activated protein C treatment for severe sepsis. N Engl J Med 2002;347(13):1027–30.
327. Weiner JS, Khogali M. A physiological body-cooling unit for treatment of heat stroke. Lancet 1980;1(8167):507–9.
328. Wenger CB. Human heat acclimatization. In: Pandolf KB, Sawka MN, Gonzales RR, editors. Human performance physiology and environmental medicine at terrestial extremes. Indianapolis: Benchmark; 1988. p. 153–97.
329. Wenger CB. The regulation of body temperature. In: Tanner GA, editor. Medical physiology. Boston: Little, Brown; 1995. p. 590.
330. White JG. Effects of heat on platelet structure and function. Blood 1968;32(2):324–35.
331. Wilkinson DA, Burholt DR, Shrivastava PN. Hypothermia following whole-body heating of mice: effect of heating time and temperature. Int J Hyperthermia 1988;4(2):171–82.
332. Williams RS, Thomas JA, Fina M, et al. Human heat shock protein 70 (hsp70) protects murine cells from injury during metabolic stress. J Clin Invest 1993;92(1):503–8.
333. Winkenwerder M, Sawka MN. Disorders due to heat and cold. In: Goldman L, Ausiello D, Arend W, et al., editors. Cecil textbook of medicine. 23rd ed. Philadelphia: Saunders, Elsevier Science; 2007. p. 763–7.
334. Wisselink W, Patetsios P, Panetta TF, et al. Medium molecular weight pentastarch reduces reperfusion injury by decreasing capillary leak in an animal model of spinal cord ischemia. J Vasc Surg 1998; 27(1):109–16.
335. Wright CL, Boulant JA. Carbon dioxide and pH effects on temperature sensitive and insensitive hypothalamic neurons. J Appl Physiol (1985) 2007;102(4):1357–66.
336. Wu C. Heat shock transcription factors: Structure and regulation. Annu Rev Cell Dev Biol 1995;11:441–69.
337. Wyndham CH, Strydom NB, Cooke HM, et al. Methods of cooling subjects with hyperpyrexia. J Appl Physiol 1959;14:771–6.
338. Yang YL, Lu KT, Tsay HJ, et al. Heat shock protein expression protects against death following exposure to heatstroke in rats. Neurosci Lett 1998;252(1):9–12.
339. Zhang HJ, Xu L, Drake VJ, et al. Heat-induced liver injury in old rats is associated with exaggerated oxidative stress and altered transcription factor activation. In: 2003.
340. Zhang XY, Li J. Susceptibility-weighted imaging in heat stroke. PLoS ONE 2014;9(8):e105247.
341. Zikria BA, Subbarao C, Oz MC, et al. Hydroxyethyl starch macromolecules reduce myocardial reperfusion injury. Arch Surg 1990; 125(7):930–4.
342. Zorzato F, Fujii J, Otsu K, et al. Molecular cloning of cDNA encoding human and rabbit forms of the $Ca^{2+}$ release channel (ryanodine receptor) of skeletal muscle sarcoplasmic reticulum. J Biol Chem 1990;265(4):2244–56.

with rhabdomyolysis.[22,99] Among U.S. soldiers hospitalized for serious heat illness, 25% had rhabdomyolysis and 13% had acute renal failure.[25]

Exertional heatstroke is usually associated with prolonged exertion in a warm climate; in many cases, however, EHS occurs within the first 2 hours of exercise and not necessarily at high ambient temperatures.[20,40] This is because exertion and environmental heat stress during the 72 hours that precede such an event strongly influence the individual's susceptibility to heat illness.[43] Using $T_{co}$ of 40.5°C (104.9°F) as a critical temperature initially to diagnose EHS is arbitrary. Mental status changes in an individual performing exertion in the heat should be the defining characteristic of heatstroke unless the individual has sustained head trauma. At the stage of collapse, profuse sweating is still likely to be present unless heatstroke develops in an already anhidrotic individual. Dry skin may be evident either in situations where the climate is very dry and sweat evaporates easily or when heatstroke coincides with a severe degree of dehydration.[39]

Heatstroke is often categorized as either *classic* or *exertional,* with the classic form primarily observed in elderly individuals or otherwise sick or compromised populations and EHS in apparently healthy and physically fit persons.

## CLINICAL MANIFESTATIONS

Clinical manifestations of heatstroke vary, depending on whether the person experiences classic heatstroke, which is a common disorder of older adults during heat waves and occurs in the form of epidemics, or EHS,[1] which occurs when excess heat generated by muscular exercise exceeds the body's ability to dissipate it (Table 13-1). Some overlap in presentation may occur; treatment with a medication (e.g., antihypertensive or antipsychotic) that places an older adult at risk for classic heatstroke also places an exercising individual at risk for EHS. The clinical picture of heatstroke usually follows a distinct pattern of events with three phases: (1) acute, (2) hematologic or enzymatic, and (3) late.[41]

### Acute Phase

The acute phase of heatstroke is characterized by CNS manifestations. Because brain function is very sensitive to hyperthermia, this phase is present in all heatstroke patients. Early signs of CNS dysfunction are typically cerebellar and include ataxia, poor coordination, and dysarthria.[124] Advanced signs of CNS depression include irritability, aggressiveness, stupor, delirium, and coma.[2,24,110] Mental status changes usually resolve after return to normal $T_{co}$. After a return to normothermia, persistence of coma is a poor prognostic sign.[62,110] Other symptoms include fecal incontinence, flaccidity, and hemiplegia. Cerebellar symptoms may persist beyond the acute phase.[77,110,124]

Other common disturbances during the acute phase occur in the gastrointestinal (GI) and respiratory systems. GI dysfunction, including diarrhea and vomiting, often occurs. However, the vomiting may reflect translocation of toxic gram-negative bacterial lipopolysaccharide from the lumen of the intestines because of poor splanchnic perfusion as a result of hypotension caused by increased skin blood flow and from CNS impairment.[21,44,110] Hyperventilation and elevation of $T_{co}$ primarily lead to respiratory alkalosis, which in EHS may be masked by metabolic acidosis as a result of increased glycolysis and hyperlacticacidemia.[29,82] Hypoxemia may be present in patients with respiratory complications.[31,82,113] Also, oxygen consumption is elevated during hyperthermia, with a 10% to 13% increase for every degree Celsius above euthermia.[35]

Exertional heatstroke shares many common findings with systemic inflammatory response syndrome (SIRS).[20,105] Endotoxemia, hyperthermia, and other risk factors (e.g., preexisting infection) and stressors associated with EHS can trigger this exaggerated inflammatory response. Patients should be assessed for SIRS after admission with the use of the following criteria[19]: body temperature less than 36°C (98.6°F) or more than 38°C (100.4°F); heart rate greater than 90 beats/min, tachypnea, or an arterial partial pressure of carbon dioxide ($PaCO_2$) less than 4.3 kPa (32 mm Hg); and white blood cell count less than 4000 cells/$mm^3$ ($4 \times 10^9$ cells/L) or of more than 12,000 cells/$mm^3$ ($12 \times 10^9$ cells/L), or the presence of more than 10% immature neutrophils. When two or more of these criteria are met, SIRS can be diagnosed. The presence of systemic inflammatory response markers during the acute phase predicts the severity of subsequent phases.

### Hematologic and Enzymatic Phase

Hematologic and enzymatic disorders peak 24 to 48 hours after collapse. In the hematologic and enzymatic phase of EHS, hematologic, enzymatic, and other blood parameters are altered. In humans and experimental animals, hyperthermia results in leukocyte activation[49] and changes in lymphocyte subpopulations, both in absolute numbers and percentages.[2] Leukocytes may range from 20 to 30 $\times$ $10^3$/$mm^3$ or higher.[13,54] In severe cases, leukocyte activation is associated with systemic activation of coagulation cascades.[59] In one study, all fatal cases of EHS involved disturbances in the blood coagulation system.[13,109] Prothrombin time, partial thromboplastin time, and the level of fibrin

**TABLE 13-1** Comparison of Classic and Exertional Heatstroke

| Characteristics | Classic | Exertional |
|---|---|---|
| Age group | Young children and older adults | Men ages 15 to 45 |
| Health status | Chronically ill | Healthy |
| Concurrent activity | Sedentary | Strenuous exercise |
| Drug use | Diuretics, antidepressants, antihypertensives, anticholinergics, and antipsychotics | Usually none |
| Sweating | May be absent | Usually present |
| Lactic acidosis | Usually absent; poor prognosis if present | Common |
| Hyperkalemia | Usually absent | Often present |
| Hypocalcemia | Uncommon | Frequent |
| Hypoglycemia | Uncommon | Common |
| Creatine phosphokinase | Mildly elevated | Greatly elevated |
| Rhabdomyolysis | Unusual | Frequently severe |
| Hyperuricemia | Mild | Severe |
| Acute renal failure | <5% of patients | 25%-30% of patients |
| Disseminated intravascular coagulation | Mild | Marked; poor prognosis |
| Mechanism | Poor dissipation of environmental heat | Excessive endogenous heat production and overwhelming heat loss mechanisms |

Modified from Knochel JP, Reed G: Disorders of heat regulation. In Kleeman CR, Maxwell MH, Narin RG, editors: *Clinical disorders of fluid and electrolyte metabolism*, New York, 1987, McGraw-Hill.

split products increased, with a fall in thrombocytes.[41] Clotting dysfunction peaked 18 to 36 hours after the acute phase of heatstroke; 2 to 3 days after heatstroke, prothrombin levels fell to 17% to 45% of normal. Depending on the severity of heatstroke, thrombocyte values ranged between $110 \times 10^3/mm^3$ and 0.[108,109] This systemic inflammatory response state resembles gram-negative bacterial sepsis, and it appears that lipopolysaccharide (a cell wall component of gram-negative bacteria) participates in the pathophysiology of EHS.[46]

### Enzymes

One of the prominent and almost pathognomonic characteristics of EHS is appearance of exceptionally high levels of certain cellular enzymes, which implies cell damage or death. Most patients with EHS show elevation of serum creatine phosphokinase (CPK) activity and myoglobinuria, which suggests damage to skeletal muscle.[40] CPK values in the range of $10^3$ to $10^4$ international units (IU) were typically found, with peak values occurring 24 to 48 hours after collapse.[33,104] At $T_{co}$ of 41.8° to 42.2°C (107.24° to 107.96°F), aspartate aminotransferase/transaminase (AST) and alanine aminotransferase/transaminase (ALT) levels rose by factors of 25 and 8, respectively, and bilirubin levels approximately doubled to 1.56 mg/dL.[90]

These rises in enzyme levels are related to tissue damage, which in turn depends on $T_{co}$ and its rates of rise and duration.[81] CPK was the most sensitive indicator of increases in $T_{co}$, followed by lactate dehydrogenase (LDH), which is an index of generalized tissue damage. CPK levels in EHI and EHS typically peak at 24 to 48 hours. Rising values after this point should alert the clinician to possibility of an occult compartment syndrome. An EHI patient may complain of lower-extremity pain that manifests as a compartment syndrome. During the 1994 Hajj, 26 heatstroke victims admitted to a heatstroke treatment unit had elevated levels of CPK, AST, ALT, and LDH; these levels remained high after 24 hours. Those who died had higher enzyme levels than the survivors. LDH concentration was useful for distinguishing between those who died and those who had a rapid recovery. The enzymes were better prognostic indicators than $T_{co}$, anion gap, and serum potassium level.

### Late Phase

The late phase of heatstroke manifests 3 to 5 days after collapse and is characterized by disturbances in renal and hepatic functions. These abnormalities are consistent with multiorgan dysfunction syndrome as a result of SIRS.

Acute renal failure is a common complication of severe cases and occurs in 25% to 30% of EHS patients.[65,73,108] Oliguria and anuria are characteristic features. During this phase, urine has been described as being like machine oil, with a high specific gravity.[89,92,100,108] Usually present in the urine are red and white cells, hyaline and granular casts, and mild to moderate proteinuria.[100] The etiology involves multiple causes,[89] but a major factor is reduced renal blood flow caused by heat-induced hypotension, hypohydration, and peripheral vasodilation. In addition, direct thermal injury may lead to widespread renal tissue damage.[100] Myoglobinuria and elevated blood viscosity that result from disseminated intravascular coagulation (DIC) may further contribute to acute oliguric renal failure.[92,100,112,119]

Usually, EHS is manifested by increased serum levels of liver enzymes, although acute liver failure has also been reported.[42,123] High bilirubin levels, which may last for several days, reflect hepatic dysfunction and hemolysis. In most cases of EHS, liver injury is usually asymptomatic and exhibits reversible elevation in plasma transaminase levels.[51] Acute liver failure is documented in 5% of patients with EHS.[66] Hypophosphatemia (<0.5 mmol/L) at admission may predict occurrence of acute liver failure.[42] Despite limited experience and that EHS patients with extensive liver damage may recover spontaneously, orthotopic liver transplantation had been suggested as a potential treatment.[15,50,97] Among 16 reported cases of EHS-induced liver failure,[48] three patients underwent liver transplantation. In the conservatively managed group, eight patients recovered spontaneously, and five died. Concomitantly, all three patients who received transplantation died. Hadad and co-workers[48] concluded that, because of the poor and limited results of liver transplantation after heatstroke, interpretation of prognostic criteria is crucial before listing a patient for such surgery.

## ON-SITE EMERGENCY MEDICAL TREATMENT

Early diagnosis of heat illness can be critical to therapeutic success. Early warning signs include flushed face, hyperventilation, headache, dizziness, nausea, tingling arms, piloerection, chilliness, incoordination, and confusion.[82] If the patient is alert and has no mental status changes, he or she can rest in the shade or indoors, and oral rehydration can be instituted with cold water or an electrolyte replacement beverage. The concentration of carbohydrates in such a beverage should not exceed 6%; otherwise, gastric emptying and fluid absorption by the intestines may be delayed. Responders should target an intake of 1 to 2 L (1.05 to 2.11 qt) over 1 hour. If the patient does not improve or in fact worsens, he or she should be evaluated by a medical provider. All persons with suspected heat injuries should be observed to ensure that decompensation does not occur. The patient should continue to rest and drink over the next 24 hours. As a general rule, for every pound of weight lost by sweating, 0.5 qt (2 cups or ~500 mL) of fluid should be consumed. It may require 36 hours to completely restore lost electrolytes and fluid volume to all body compartments via oral intake. After the acute episode, a medical provider should determine any possible host risk factors for heat illness and review with the patient the signs of heat illness and preventive measures to consider.

Any athlete who is performing exercise in warm weather and who develops mental status changes in the absence of trauma should be treated as an EHS patient until proved otherwise.[39] EHS is a medical emergency. Rapid reduction of elevated $T_{co}$ is the cornerstone of EHS management; duration of hyperthermia may be the primary determinant of outcome.[64,108] Cooling should not be delayed so that a temperature measurement can be obtained. Cooling measures should be only minimally delayed for vital resuscitation measures. Nevertheless, it is important to follow the ABCs (airway, breathing, and circulation) of stabilization while cooling efforts are initiated; see Box 13-1 for basic first-aid information. Before 1950, mortality with EHS was 40% to 75%.[7,38] Long-term survival is directly related to rapid institution of resuscitative measures.[52]

In the field, the sick individual should be placed in the shade and any restrictive clothing removed. There are multiple ways to cool patients in the field, with cold-water immersion (CWI) being the most effective modality.[27,94] In a remote setting, this can be accomplished by using a small children's pool filled with iced water. The patient should be submerged up to the shoulders and kept under immediate hands-on supervision at all times. Another expedient method in the field is to keep bed sheets soaked in a cooler full of iced water; the person can then be wrapped in the cold sheets. Particular care should be given to covering the head and submerging the sheets every few minutes to recool them.[85] Ice packs can be applied to the groin, axillae, sides of the neck, and head to augment iced-sheet cooling. Cooling should continue until emergency medical services (EMS) providers arrive. Nonmedical first responders should not attempt to evacuate heatstroke patients themselves, because this may distract from cooling efforts. If CWI or iced sheets are not available, the patient

**BOX 13-1 Basic First Aid for Heat Illnesses**

1. Place the patient in the shade.
2. Assess airway, breathing, and circulation.
3. Initiate cardiopulmonary resuscitation if the patient is pulseless or apneic.
4. Remove any restrictive clothing.
5. Initiate rapid cooling measures.
6. Activate emergency medical services (EMS).
7. Measure the patient's rectal temperature to confirm the diagnosis.
8. Evacuate the patient to the nearest medical facility via EMS.

should be kept wet by applying large quantities (20 to 30 L [5.3 to 7.9 gal]) of tap water or water from any source, and the person's body should be constantly fanned. Cooling blankets are generally ineffective as a single modality for inducing rapid lowering of body temperature required for treating heatstroke.

## EMERGENCY MEDICAL SERVICES TREATMENT

During evacuation, CWI is often not a viable method for treatment. Iced sheets and ice packs can be easily used en route during transport. Many EMS vehicles now carry refrigerated intravenous (IV) fluid to initiate induction of therapeutic hypothermia in cardiovascular emergencies. When used, chilled IV fluid (4°C [39°F]) should be peripherally administered.[68] Vascular access should be established without delay by inserting a 12- or 14-gauge IV catheter. Administration of normal saline or lactated Ringer's solution should be started. Recommendations vary regarding administration rate of fluids. Some clinicians advise a rate of 1200 mL (1.26 qt) over 4 hours,[87] whereas others encourage a 2-L (2.11-qt) bolus over the first hour and an additional liter of fluid per hour for the next 3 hours.[106] Patients should be placed on a cardiac monitor. Administration of supplemental oxygen may help to meet the patient's increased metabolic demands and may also be used to treat the hypoxia often associated with aspiration, pulmonary hemorrhage, pulmonary infarction, pneumonitis, or pulmonary edema.[37,73] Blood glucose determination should be performed, and adults with blood sugar level less than 60 mg/dL should be treated with one ampule of 50% IV dextrose solution. Children should be treated with 2 to 4 cc/kg of 25% IV dextrose solution.

Antipyretics are not effective and may potentially be harmful to heatstroke patients. Aspirin and acetaminophen lower $T_{co}$ by normalizing the elevated hypothalamic set point that regulates the fever response caused by pyrogens; in heatstroke, the set point is normal, with $T_{co}$ elevation reflecting a failure of normal cooling mechanisms. Furthermore, acetaminophen may induce additional hepatic damage, and administration of aspirin may aggravate bleeding tendencies. Aspirin has also been shown to attenuate protective, reflexive skin blood flow responses that are required for adequate heat dissipation,[57,75] which will predispose to heatstroke collapse. In a mouse model of heatstroke, an acute oral dose of indomethacin (a potent antipyretic nonsteroidal antiinflammatory drug [NSAID]) provided immediately before heat exposure resulted in about a 40% increase in heatstroke mortality because of extensive gut hemorrhage.[69] Similar results were observed in rats injected peripherally with aspirin.[61] Because NSAIDs do not attenuate $T_{co}$ during environmental heat exposure, and their toxicity on the gut and liver is exacerbated with heat, using these drugs prophylactically or for treatment of heatstroke patients is not warranted. Alcohol sponge baths are inappropriate under any circumstances, because transcutaneous absorption of alcohol may lead to poisoning and coma.

In a comatose patient, airway control should be established by inserting a cuffed endotracheal tube. Positive-pressure ventilation (PPV) is indicated if hypoxia persists despite supplemental oxygen administration.

The patient's altered mental status may adversely affect the ability of emergency department (ED) personnel to obtain a detailed history of precipitating events. Lack of such information may delay diagnosis. EMS transport personnel should attempt to obtain this history before evacuating the patient and should communicate the information to medical staff. Of particular importance is the duration, and when available, maximum degree of hyperthermia.

## HOSPITAL EMERGENCY MEDICAL TREATMENT

Patients with suspected heatstroke should be placed in a large treatment room to accommodate the needed number of staff. Patients are often combative and disoriented before reestablishing their baseline mental status. Aggressive cooling measures should continue until mental status returns to normal and $T_{co}$ is 39°C (102°F).[27] After discontinuation of cooling, $T_{co}$ should be monitored every 5 minutes to ensure that it does not increase.

The $T_{co}$ reported in the field for heatstroke patients may be significantly higher (e.g., 41.1°C [106.9°F]), than those documented in the hospital ED (e.g., 37.8°C [100°F]) because $T_{co}$ may fall during transport to the hospital.[107] Documenting only a mild elevation in $T_{co}$ on arrival does not exclude the diagnosis of heatstroke. CNS disturbances (coma, convulsions, confusion, or agitation) that accompany hyperthermia may also result from CNS infection, sepsis, or other disease process. Other diagnoses should be considered when the patient does not regain normal mental status after the $T_{co}$ is normalized in less than 30 minutes. When $T_{co}$ remains elevated longer, there is a decreased likelihood that mental status will normalize with euthermia.[20]

Core temperature can be measured at several anatomic sites, but oral, tympanic, esophageal, and rectal temperatures show regional variations as a result of differences in tissue metabolic activity, local blood supply, and temperature gradients between neighboring tissues. During exercise, active skeletal muscle temperature differs dramatically from that of other areas of the body not directly involved in the activity. Oral temperature is considered to be similar to blood temperature as a result of the rich blood supply of the tongue, but it is also influenced by hyperventilation and drinking fluids. Rectal temperature is a highly reliable indicator of body temperature, but it has a slower response rate and gives slightly higher readings than do other sites in the body.

The comparison of oral and rectal temperature values in heat-stressed underground miners showed a difference of approximately 1°C (2°F), with oral temperatures underestimating rectal values.[116] Tympanic temperature responds more rapidly to cooling or heating than does rectal temperature, but it is influenced by changes in the skin temperature of the head and neck.[47,74] The ear should be insulated from the environment to prevent cool ambient temperatures (<30°C [86°F]) from affecting this measurement. Esophageal temperature is the most accurate and responsive to changes in blood temperature, but its instrumentation is impractical in severely injured or unresponsive patients.

If airway control was not previously established and the patient is still unconscious, a cuffed endotracheal tube should be inserted to protect against aspiration of oral secretions. Supplemental oxygen should be provided, as well as PPV when hypoxia ($Pa_{O_2}$ <55 mm Hg) or hypotension is present. Overvigorous fluid resuscitation may precipitate pulmonary edema, so careful monitoring is indicated. Ideally, 1 to 2 L (1.05 to 2.11 qt) of fluid should be administered during the first hour after collapse, and additional fluids should be administered until satisfactory urine output (0.5 cc/kg/hr in adult and 1.0 cc/kg/hr in child) is established.[41] Most heatstroke patients arrive with a high cardiac index, low peripheral vascular resistance, and mild right-sided heart failure with elevated central venous pressure (CVP). Only moderate fluid replacement is indicated if effective cooling results in vasoconstriction and increased blood pressure. Providers should consider noninvasive intravascular volume monitoring or the minimally invasive monitoring of systolic volume variation and pulse pressure variation. If these methods are not adequate, a Swan-Ganz pulmonary artery catheter may be necessary to assess appropriate fluid supplementation. Some patients have a low cardiac index, hypotension, and elevated central venous pressure. These persons have been successfully treated with an isoproterenol drip (1 mg/min).[87] Patients with low cardiac index, low CVP, hypotension, and low pulmonary capillary wedge pressure should receive fluid. Unless the patient has rhabdomyolysis, aggressive fluid hydration is seldom required after initial treatment.

Cardiac monitoring should be maintained during at least the first 24 hours of hospitalization. Arrhythmia is most likely to occur during hyperthermia, but it may also occur as a result of electrolyte abnormalities. Using norepinephrine and other α-adrenergic drugs should be avoided because they cause vasoconstriction, thereby reducing heat exchange through the skin. Anticholinergic drugs that inhibit sweating (e.g., atropine) should also be avoided.

Cooling techniques are ineffective when the patient has seizures that increase body heat storage; therefore, convulsions should be controlled. IV benzodiazepines are preferred for their

efficacy and renal clearance. Initial dosing is either 4 to 8 mg of IV lorazepam or 10 mg of IV diazepam. If seizures persist for more than 10 minutes after the first dose, an additional 4 mg of lorazepam or 10 mg of diazepam should be administered.

As a result of drastic cooling, skin temperature may decrease enough to cause shivering. Administration of 12.5 mg of meperidine via slow IV push[111] or 5 mg of IV diazepam is effective to suppress shivering and prevent additional rise in $T_{co}$ from metabolic heat production. If CWI is used, the increase in metabolic rate as a result of shivering will be more than offset by the high rate of heat transfer. Therefore, presence of shivering should not be a cause for concern when this method of cooling is used.[27,91]

Severe muscle cramping may be caused by electrolyte imbalances. Magnesium levels should be obtained. If magnesium levels are low, consideration may be given to the use of 50% IV magnesium sulfate (4 g in 250 mL of 5% dextrose injection at a rate that does not exceed 3 mL/min).[17,18]

A Foley catheter should be placed to monitor urine output. Renal damage from myoglobinuria and hyperuricemia can be prevented by promoting renal blood flow by administering IV mannitol (0.25 mg/kg) or furosemide (1 mg/kg).[106] If CPK levels exceed 100,000 IU, alkalinize the urine of patients with exertional rhabdomyolysis; there is no advantage to alkalinization when levels are lower. Hemodialysis should be reconsidered if anuria, oliguria (<0.5 mL/kg/hr of urine for >6 hours), uremia, or hyperkalemia develops. Cooling and hydration usually correct acid-base abnormalities; however, serum electrolytes should be monitored and appropriate modifications of IV fluids made. Glucose should be monitored repeatedly, because either hypoglycemia or hyperglycemia may occur after EHS.[103] Oral and gastric secretions are evacuated via a nasogastric tube connected to continuous low suction. Although antacids, proton pump inhibitors, and histamine-2 ($H_2$) blockers have been used to prevent GI bleeding, no studies to date demonstrate their efficacy for heatstroke patients.

### Induced Hypothermia

Induced hypothermia is increasingly being used for many neurologic and cardiovascular emergencies, including acute stroke, neonatal hypoxic-ischemic encephalopathy, and after cardiac arrest.[12,53,84,102] This therapeutic modality has not been evaluated for effectiveness in individuals with EHS, but may have a role in cooling severe refractory cases. There may be a role for a period of induced hypothermia after severe EHS.

### Dantrolene

No drug has been found to have a significant effect for reducing $T_{co}$. Antipyretics are ineffective because the thermoregulatory set point is not affected in heatstroke. Furthermore, antipyretics might be harmful because they cannot be readily metabolized in the heat-affected liver, and interactions between NSAIDs and heat can cause extensive gut injury. However, dantrolene has been used quite successfully for treatment of several hypercatabolic syndromes, such as malignant hyperthermia, neuroleptic malignant syndrome, and other conditions characterized by muscular rigidity or spasticity.[115,122] Dantrolene stabilizes the calcium ion ($Ca^{2+}$) release channel in muscle cells, thereby reducing the amount of $Ca^{2+}$ released from cellular calcium stores. This lowers intracellular $Ca^{2+}$ concentrations, muscle metabolic activity, muscle tone, and thus heat production.[30,83] In some studies, dantrolene was claimed to be effective for treatment of heatstroke, whereas in others it improved neither rate of cooling nor survival.[28,34,72,117] In six patients with rhabdomyolysis, intramuscular $Ca^{2+}$ concentrations were 11 times higher than in controls, and dantrolene successfully lowered the elevated $Ca^{2+}$ level.[71] Collectively, the limited data available are at best inconsistent. Despite growing evidence for a possible benefit of dantrolene treatment in patients with heatstroke, justification for its routine use in such cases is not proved, although future clinical trials may change this assessment.

Moran and colleagues[79] studied dantrolene in a hyperthermic rat model, and found it to be effective as a prophylactic agent in sedentary animals only. Dantrolene induced more rapid cooling by depressing $Ca^{2+}$ entry into the sarcoplasm; this led to relaxation of peripheral blood vessels with attenuated production of metabolic heat. Dantrolene may also be effective in treating heatstroke by increasing the cooling rate. In other animal models, however, dantrolene was not superior to conventional cooling methods.[125] As such, dantrolene is not recommended.

### Antibiotic Therapy

As previously discussed, in the clinical manifestations of EHI, EHS shares many common findings with the SIRS.[20,106] This relationship has created an interest in recognition and treatment of occult or comorbid infection. Numerous systematic reviews and case reports have identified infection as a risk factor for EHS. In addition, others postulate that bacterial translocation from the gut microbiome may take part in the pathophysiology of heatstroke. Therefore, individual patients with EHS need to be carefully examined for overt and occult infection so that appropriate therapies can be initiated. Most importantly, future research is warranted to address the issue of whether antibiotic treatment should be evaluated in all heatstroke patients.

## SEQUELAE

The combination of the rapid reduction of $T_{co}$, control of seizures, proper rehydration, and prompt evacuation to an emergency medical facility results in a 90% to 95% survival rate in heatstroke patients, with morbidity directly related to duration of hyperthermia.[20,106] A poor prognosis is associated with $T_{co}$ of more than 41°C (105.8°F), prolonged duration of hyperthermia, hyperkalemia, acute renal failure, and elevated serum levels of liver enzymes. Therefore, misdiagnosis, early inefficient treatment, and delay in evacuation are the major causes of clinical deterioration. Full recovery without evidence of neurologic impairment has been achieved even after coma of 24 hours' duration and subsequent seizures.[109] Persistence of coma after return to normothermia is a poor prognostic sign.[110] Red blood cell apoptosis (i.e., cell blebbing, asymmetry, and shrinkage) on early peripheral blood smears is a sign of a very poor prognosis and may indicate extensive cellular necrosis. Neurologic deficits may persist, but usually only last for a limited period of 12 to 24 months, and only rarely for longer.

Central nervous system dysfunction becomes increasingly severe with prolonged duration of hyperthermia and associated circulatory failure. Nevertheless, coma that persists for up to 24 hours, even with subsequent seizures, is usually followed by complete recovery without evidence of mental or neurologic impairment.[2,96] However, chronic disability may prevail for several weeks or months in the forms of cerebellar deficits, hemiparesis, aphasia, and mental deficiency.[2,65,96] Only in exceptional cases, when coma persisted for more than 24 hours, did mental and neurologic impairment become chronic and prevail for years. However, in one study of classic heatstroke, 78% of patients had minimal to severe neurologic impairment, such as ataxia or dysarthria.[33] Long-term EHS patients may have increased mortality from heart, liver, and kidney disease.[121]

## RETURN TO ACTIVITY

Return-to-play/activity (RTP) decision making for the individual with a history of EHI can be complex. Although the final decision is most often left in the hands of the providing physician, the assessments, in particular with athletes, frequently require incorporation of both information and execution from the athletic trainer, physical therapist, coach, and family members, as well as the athlete. An American College of Sports Medicine (ACSM) guideline on RTP identified the following key considerations to assist in safely returning athletes to activity[3]:

- Status of anatomic and functional healing
- Status of recovery from acute illness and associated sequelae
- Status of chronic injury or illness
- Whether the athlete poses an undue risk to the safety of other participants
- Restoration of sport-specific skills
- Psychosocial readiness

- Ability to perform safely with equipment modification, bracing, and orthoses
- Compliance with applicable federal, state, local, school, and governing-body regulations

The cornerstone assessment in the RTP decision requires fundamental understanding of the anatomic as well as functional healing of the particular disorder that affects the athlete. Exertional heat illness RTP is especially challenging because there is incomplete understanding of the pathophysiologic processes involved in development of and recovery from EHI.[26,76]

Despite the frequency of EHI, current civilian and military RTP guidelines for a particular athlete are largely based on anecdotal observation, prudence, and caution.[76,86] At this time, no evidence-based guidelines or recommendations exist for returning individuals, athletes, or soldiers to play or duty. Most guidelines are commonsense recommendations that require an asymptomatic state and normal laboratory parameters, coupled with a cautious reintroduction of activity and gradual heat acclimatization. Current suggestions range from 7 days to 15 months before EHS patients return to full activity.[8] This lack of consistency and clinical agreement can negatively impact athletes and soldiers and makes it difficult for medical providers to determine the best solution for each individual; the inconsistencies also can directly impact military readiness. Additionally, whereas current guidance states that EHS patients may return to practice and competition when they have reestablished heat tolerance, no evidence-based tools are available to assess when the body's thermoregulatory system has returned to normal.[76]

This lack of clear evidence-based guidance has allowed some medical professionals to clear individuals and athletes for RTP after EHS without considering exercise heat tolerance deficits, neuropsychological impairments, or the altered fitness status and acclimatization status from not being actively engaged in training during recovery.[11,77,96] As with any other injury, RTP should involve a carefully planned and incrementally increased physical challenge that is closely supervised by an athletic trainer and physician, as previously identified in the ACSM conference statement. Current research indicates that most individuals eventually recover fully from EHS; indeed, this occurs in the vast majority of cases when the athlete is treated promptly with aggressive cooling strategies (i.e., ice-water immersion).[11,26,95]

### Current Civilian Recommendations

In our opinion, the consensus RTP guidelines set forth by the ACSM are clear and succinct and provide a rational process for guiding athletes who have sustained an EHI. Current recommendations from the ACSM for returning an athlete to training and competition follow[8]:

1. Refrain from exercise for at least 7 days following release from medical care.
2. Follow up about 1 week after the incident for a physical examination and laboratory testing or diagnostic imaging of the affected organs, based on the clinical course of the heatstroke.
3. When cleared for RTP, begin exercise in a cool environment and gradually increase the duration, intensity, and heat exposure over 2 weeks to demonstrate heat tolerance and to initiate acclimatization.
4. If RTP is not accomplished over 4 weeks, a laboratory exercise–heat tolerance test should be considered.
5. Clear the athlete for full competition if heat tolerant between 2 and 4 weeks of full training.

## PREVENTION

Prevention of heat illness relies on an awareness of host risk factors, a change in behavior and physical activity to match these risk factors and environmental conditions, and a requirement for appropriate hydration during physical exercise in the heat. More aggressive educational activity that explains heat illness and its prevention to the public should be strongly promoted. Primary care physicians should incorporate this information into the anticipatory guidance of routine health assessment. Despite a wealth of medical literature about heat injury, some athletic coaches continue to use physical or psychological methods to force athletes to compete or train under intolerably hot conditions. This practice should be viewed as irresponsible, dangerous, and possibly criminally negligent.

The importance of recognizing milder forms of heat illness cannot be overstated. Any time heat injuries occur, coaches and trainers should reassess all athletes and determine what other measures can be implemented to prevent occurrence of additional or more serious injuries.

### Awareness of Host Risk Factors

Shapiro and Moran[104] studied 82 cases of EHS in Israeli soldiers and concluded that at least one factor that predisposes an individual to heatstroke (e.g., diarrhea, lack of acclimatization, poor fitness) was associated with each case. Correcting individual risk factors should lead to strategies that can prevent heatstroke. Any underlying condition that causes dehydration or increased heat production or that causes decreased dissipation of heat interferes with normal thermoregulatory mechanisms and predisposes an individual to heat injury. Older individuals are less tolerant to EHI than younger persons and are more susceptible to classic heatstroke because of decreased secretory ability of their sweat glands and decreased ability of their cardiovascular systems to increase blood flow to the skin. When healthy young adults exercise strenuously in the heat, EHS may occur despite the absence of host risk factors.

Elite and professional athletes, the general public, and the military have widely used ergogenic aids (e.g., the herb ephedra [*ma huang*]) that contain ephedrine to improve performance and for weight loss. Because ephedra increases metabolic rate, it has caused numerous cases of heat illness and deaths worldwide and has been banned by reputable sports authorities. Because there are no clear ergogenic benefits to ephedra alone, use of ephedra-containing substances should be discouraged.[88]

The ratio of basal metabolic rate to surface area is higher in children than in adults. As a result, a child's skin temperature is higher for any given $T_{co}$. Although the secretory rates of their sweat glands are lower, children have greater numbers of active sweat glands per area of skin than adults and overall greater sweat rates per unit area.[58] Any reduction in the rate of sweating puts children especially at risk. The primary mechanism for heatstroke in young children is hot-vehicle entrapment. Between 1998 and 2010, 462 children died from heatstroke as a result of vehicular hyperthermia.

The primary means of heat dissipation is production and evaporation of sweat. Any condition that reduces this process places the individual at risk for thermal injury. Poor physical conditioning, fatigue, sleep deprivation, cardiovascular disease, and lack of acclimation all limit the cardiovascular response to heat stress.[43,60] Obesity places an individual at risk as a result of reduced cardiac output, the increased energy cost of moving extra mass, increased thermal insulation, and altered distribution of heat-activated sweat glands.[80] Older adults and younger individuals show decreased efficiency of thermoregulatory functions and increased risk for heat injury.

Several congenital or acquired skin abnormalities affect sweat production and evaporation. Ectodermal dysplasia is the most common form of congenital anhidrosis. Widespread psoriasis, poison ivy, sunburn, scleroderma, miliaria rubra ("prickly heat," caused by the plugging of sweat ducts with keratin), deep burns, and prior skin grafting may also limit sweat production.

Dehydration affects both central thermoregulation and sweating. A mere 2% decrease in body mass through fluid loss produces increased heart rate, increased $T_{co}$, and decreased plasma volume. In an otherwise healthy adult, GI infection with vomiting and diarrhea may cause sufficient dehydration to place the individual at risk for EHS.

Chronic conditions that may contribute to heat illness include diabetes mellitus, diabetes insipidus, spinal cord injury, eating disorders (especially bulimia), and mental retardation. Alcoholism and illicit drug use are among the 10 major risk factors for heatstroke in the general population.[63] An important effect of alcohol consumption is inhibition of antidiuretic hormone secretion, which leads to relative dehydration. Autonomic

**BOX 13-2 Drugs That Interfere with Thermoregulation**

**Drugs That Increase Heat Production**
- Thyroid hormone
- Amphetamines
- Tricyclic antidepressants
- Lysergic acid diethylamide

**Drugs That Decrease Thirst**
- Haloperidol

**Drugs That Decrease Sweating**
- Antihistamines
- Anticholinergics
- Phenothiazines
- Benztropine mesylate

Data from references 15, 34, 53, 72, 113, and 115.

dysfunction, which is present with many chronic diseases, impairs thermoregulation.[55]

Despite evidence that hypohydration limits physical performance, voluntary dehydration continues to be routine in certain athletic arenas.[6,9,23,118] Wrestlers, jockeys, boxers, and bodybuilders typically lose 3% to 5% of their body mass 1 to 2 days before competition. In addition to restricting fluid and food, they use other pathogenic weight control measures, such as self-induced vomiting, laxatives, diuretics, and exposure to heat (e.g., saunas, hot tubs, "sauna suits"). Athletes undergoing rapid dehydration are at risk not only for heat injury but also for other serious medical conditions, such as pulmonary embolism.[32]

Box 13-2 highlights common medications that interfere with thermoregulation. Special attention should be paid to the role of antihistamines in reducing sweating. This class of medications is often obtained over the counter, so the general population should be warned about the dangers of exercising in the heat when they are taking antihistamines.

Although it has been widely believed that sustaining an episode of heatstroke predisposes the individual to future heat injury, this has been refuted in a recent study of heatstroke patients.[10] Ten heatstroke patients were tested for their ability to acclimate to heat; by definition, the ability to acclimate to heat indicates heat tolerance. Nine of the patients demonstrated heat tolerance within 3 months after the heatstroke episode; the remaining patient acclimated to heat 1 year after injury. In no patient was heat intolerance permanent. Although individuals may show transient heat intolerance after thermal injury, evidence for permanent susceptibility to thermal injury is lacking.

# ADAPTATION TO ENVIRONMENTAL CONDITIONS

Appropriate adaptation to hot environmental conditions encompasses many forms of behavior, including modifying clothing, degree of physical activity, searching for shade, anticipatory enhancement of physical conditioning, acclimation to heat stress, and paying attention to level of hydration.

## CLOTHING

Different regions of the body are not equivalent with regard to sweat production.[56] The face and the scalp account for 50% of total sweat production, whereas the lower extremities contribute only 25%. When exercising under conditions of high heat load, maximal sweat evaporation is facilitated by maximal skin exposure. Clothing should be lightweight and absorbent. Although significant improvement has been made in fabrication of athletic uniforms, uniforms and protective gear required by certain branches of the military and public safety officers continue to add to the risk of heat injury. Developing protective clothing that permits for more effective heat dissipation is indicated. Uniforms should be modified to decrease the amount of extra protective equipment and head gear needed as much as is safely possible during the first week of training and during times of high heat stress conditions.

## ACTIVITY

Behavioral actions can effectively minimize occurrence of classic heatstroke. Lack of residential air conditioning places indigent persons at risk during heat waves. By sitting in a cool or tepid bath periodically throughout the day, the individual can decrease heat stress and thereby prevent heat injury. The more than 10,000 deaths during the 2003 heat wave in Europe could have been reduced by simple announcements by public health officials of this preventive measure. This type of "heat dumping" activity can also include taking cool showers instead of warm showers. In addition, forearms and hands can be immersed into water that has been cooled to 10° to 20°C (50° to 68°F) for 10 minutes. This action will achieve reduction in $T_{co}$ of 0.7°C (1.3°F) and provide the athlete with sustained capability to train in the heat.[45]

In addition to forearm and hand immersion in cool or cold water, the concept of cooling the palm by various devices, some of which add vacuum pressure to the palm in addition to cooling, has recently become popular. A comprehensive review of cooling rates of various cooling modalities shows that this methodology is no more effective in lowering body core temperature than limb immersion in tap water (15°C [59°F]).[26] Recent research on these devices reports that the addition of negative pressure with cooling did not enhance any cooling effect.[67] In addition, these devices have been shown to be ineffective in slowing development of hyperthermia when used between exercise bouts[5] and in improvement of high-intensity, intermittent exercise.[120] Cold or ice water has been reported to have a cooling power five to eight times greater than hand/palm cooling devices.[26] Given the low cooling power of these devices, their use in a field or athletic setting, especially for treatment of heat injury or illness, should be questioned. This is also true when viewed in terms of cost when compared with limb immersion modalities. Regarding use in a wilderness setting, these devices have additional drawbacks, including the need for electrical power with batteries and the added weight of transport.

Athletes should be placed in the shade whenever possible during periods of rest and instruction. If shade is not available in areas where warm-weather training is routinely conducted, consideration should be given to constructing overhead shelters. If toilets/latrines are not easily accessed at training areas, consideration should be given to placing portable toilets nearby to prevent voluntary fluid restriction. We recommend spacing runners widely apart during group runs to allow for optimal heat dissipation.

Modification of physical activity should not be based solely on any individual parameter of ambient temperature ($T_{amb}$), relative humidity, or solar radiation, because all these contribute to heat load. The wet bulb globe temperature (WBGT) is an index of heat stress that incorporates all three factors. This value may be calculated (Table 13-2) or obtained directly from portable digital heat stress monitors that measure all three parameters simultaneously to compute WBGT. When heat stress monitors are used, care should be taken to ensure that they are calibrated

**TABLE 13-2 Determination of Wet Bulb Globe Temperature Heat Index**

| Temperature (T [°F]) | Factor | Example |
|---|---|---|
| Wet bulb T | ×0.7 | 78 × 0.7 = 54.6 |
| Dry bulb T | ×0.1 | 80 × 0.1 = 8.0 |
| Black globe T | ×0.2 | 100 × 0.2 = 20.0 |
| Heat index | | 82.6 |

Wet bulb reflects humidity, dry bulb reflects ambient air temperature, and black globe reflects radiant heat load; the heat index is the sum of the three.
*Alternative equation:* Wet bulb globe temperature = (0.567 $T_{db}$) + (0.393 $P_a$) + 3.94, where $T_{db}$ is dry bulb temperature and $P_a$ is water vapor pressure.

**TABLE 13-3** Modification of Sports Activity Based on Wet Bulb Globe Temperature

| Index | Limitation |
|---|---|
| <10° C (50° F) | There is a low risk for hyperthermia but a possible risk for hypothermia. |
| <18.3° C (65° F) | There is a low risk for heat illness. |
| 18.3°-22.8° C (65°-73° F) | There is a moderate risk toward the end of the workout. |
| 22.8°-27.8° C (73°-82° F) | Those at high risk for heat injury should not continue to train; all athletes should practice in shorts and T-shirts during the first week of training. |
| 27.8°-28.9° C (82°-84° F) | Care should be taken by all athletes to maintain adequate hydration. |
| 28.9°-31.1° C (85°-88° F) | Unacclimated persons should stop training; all outdoor drills in heavy uniforms should be canceled. |
| 31.1°-32.2° C (88°-90° F) | Acclimated athletes should exercise caution and continue workouts only at reduced intensity; they should wear light clothing only. |
| ≥32.2° C (90° F) | Stop all training. |

yearly and are not left out in the heat for long periods without use. Care should also be taken to ensure that the device measures radiant heat, humidity, air movement, and shaded temperature to calculate WBGT. Devices that measure the heat stress index, relative humidity, and wind speed should not be used to estimate WGBT. Current recommendations from the ACSM for preventing EHI during workouts and competition are based on the WBGT.[4] Most heat injuries occur during cooler WBGT periods as a result of cumulative heat exposure from preceding days. Some clinicians propose that heat-warning systems base their alerts on cumulative heat stress rather than solely on the current WBGT.[121] Other clinicians suggest using syndromic surveillance to help alert the public about periods of high heat stress.[14]

Table 13-3 presents a suggested modification of sports activity that is also based on the WBGT. Although ACSM guidelines for the summer indicate that vigorous physical activity should be scheduled in the morning or evening, individuals should be cautioned that the highest humidity of the day is usually early morning. In 1999, Montain and co-workers[78] updated fluid replacement guidelines for warm-weather training (see Chapter 89, Table 89-5). It is important to note that compliance with these recommendations does not remove all risk of heat injury. The development of another index of heat stress that provides a better basis for the prevention of EHS is indicated.

Rav-Acha and colleagues[93] assembled a case series of six fatal cases of EHS in the Israeli Defense Forces and examined the circumstances that led to the deaths. A significant association between accumulation of predisposing factors and EHS totality was found. In almost all the fatal cases, seven predisposing factors were noticed: (1) low physical fitness, (2) sleep deprivation, (3) high heat load, (4) high solar radiation, (5) physical exercise unmatched to physical fitness, (6) absence of proper medical triage, and (7) training during the hottest hours. These fatality factors primarily concerned organizational training regulations and not individual factors, which emphasizes the importance of proper guidelines and safety measures in a warm climate for preventing EHS fatalities. It follows that a combination of predisposing factors that were already found to impair heat tolerance[43] is a strong predictor of a poor prognosis. Dehydration was found in only two of the six fatal cases reported.

## CONDITIONING

The contribution of cardiovascular conditioning to thermoregulation is discussed in Chapter 6. Ideally, an individual should train under temperate or thermoneutral conditions before exercising in the heat. For the previously sedentary individual, an exercise regimen that incorporates 20 to 30 minutes of aerobic activity 3 to 4 days a week will improve cardiovascular function after 8 weeks.

It is important to remember that even physically active individuals may lack physical conditioning relative to a particularly stressful competition or activity. Heat illness in runners usually occurs when novices exceed their training effort during races or when well-trained athletes increase their pace above normal during long-distance events.

## ACCLIMATIZATION

During initial exposure to a hot environment, workouts should be moderate in intensity and duration. A gradual increase in the time and intensity of physical exertion over 8 to 10 days should allow for optimal acclimatization.[36] Early-season high school heatstroke deaths are most likely to occur during the first 4 days of practice.[95] Children and teenagers require 10 to 14 days to achieve an appropriate acclimatization response. Acclimatization can be induced by simulating hot environmental conditions indoors. Aerobic activity should be conducted during exposure to the hot environment so that the individual can achieve optimal acclimatization.[98] If symptoms of heat illness develop during the acclimation period, all physical activity should be stopped and appropriate interventions begun. Acclimatization is not facilitated by restricting fluid intake; in fact, conscious attention to fluid intake is required to prevent dehydration. As with physical conditioning, there are limits to the degree of protection that acclimatization provides from heat stress. Given a sufficiently hot and humid environment, no one is immune to heat injury.

## RESEARCH

Areas for future research include improved clarification of when athletes can safely return to play; role of autonomic nervous system dysfunction in EHS; benefit of induced hypothermia for EHS treatment; and roles of clonidine, activated protein C, and antibiotics during initial treatment.


## ACKNOWLEDGMENTS

*The authors extend much appreciation to the previous authors of this chapter, Daniel S. Moran and Stephen L. Gaffin.*


# REFERENCES

***Complete references used in this text are available online at expertconsult.inkling.com.***

## REFERENCES


1. Abderrezak B, Al-Hussein K, Adra C, et al. Distribution of peripheral blood leucocytes in acute heat stroke. J Appl Physiol 1992;73: 405–9.
2. Al-Khawashki MI, Mustafa MKY, Khogali M, El-Sayed H. Clinical presentation of 172 heat stroke cases seen at Mina and Arafat. In: Khogali M, Hales JRS, editors. Heat stroke and temperature regulation. New York: Academic Press; 1983. p. 99–108.
3. American College of Sports Medicine. The team physician and return-to-play issues: A consensus statement. Med Sci Sports Exerc 2002;34:1212–14.
4. American College of Sports Medicine. Position stand on exertional heat illness during training and competition. Med Sci Sports Exerc 2007;39:556–72.
5. Amorim FT, Yamada PM, Robergs RA, Schneider SM. Palm cooling does not reduce heat strain during exercise in a hot, dry environment. Appl Physiol Nutr Metab 2010;35:480–9.
6. Amoroso P, Yore MM, Smith GS, Lopez M Analysis of military occupational specialties and hospitilization. Part 1. The 25 largest army enlisted occupations, T98-7, 1997.
7. Appenzeller O, Atkinson R. Sports medicine: fitness training injuries. Baltimore: 1981.
8. Armstrong LE, Casa DJ, Millard-Stafford M, et al. Exertional heat illness during training and competition. Med Sci Sports Exerc 2007;39:556–72.
9. Armstrong LE, Costill DL, Fink WJ. Influence of diuretic-induced dehydration on competitive running performance. Med Sci Sports Exerc 1985;17:456–61.
10. Armstrong LE, De Luca JP, Hubbard RW. Time course of recovery and heat acclimation ability of prior exertional heatstroke patients. Med Sci Sports Exerc 1990;22:36–48.
11. Armstrong LE, Maresh CM. Can humans avoid and recover from exertional heat stroke? In: Pandolf KB, Takeda N, Singal PK, editors. Adaptation biology and medicine: Molecular bases. New Delhi: Narosa; 1999. p. 344–51.
12. Arrich J, Holzer M, Herkner H, Mullner M. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. Cochrane Database Syst Rev 2009;(9):CD004128.
13. Assia E, Epstein Y, Shapiro Y. Fatal heatstroke after a short march at night: A case report. Aviat Space Environ Med 1985;56:441–2.
14. Bassil K. The relationship between temperature and 911 medical dispatch data for heat-related illness in Toronto, 2002-2005: An application of syndromic surveillance (dissertation). University of Toronto; 2009.
15. Berger J, Hart J, Millis M, Baker AL. Fulminant hepatic failure from heat stroke requiring liver transplantation. J Clin Gastroenterol 2000; 30:429–31.
16. Bergeron MF. Heat cramps: Fluid and electrolyte challenges during tennis in the heat. J Sci Med Sport 2003;6:19–27.
17. Berkelhammer C, Bear RA. A clinical approach to common electrolyte problems: Hypomagnesemia. Can Med Assoc J 1985;132:360–8.
18. Bilbey DL, Prabhakaran VM. Muscle cramps and magnesium deficiency: Case reports. Can Fam Physician 1996;42:1348–51.
19. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 2009;136:e28.
20. Bouchama A, Knochel JP. Heat stroke. N Engl J Med 2002;346: 1978–88.
21. Brock-Utne JG, Gaffin SL, Wells MT, et al. Endotoxaemia in exhausted runners after a long-distance race. S Afr Med J 1988;73:533–6.
22. Brown TP. Exertional rhabdomyolysis: early recognition is key. Phys Sportsmed 2004;32:15–20.
23. Caldwell JE. Diuretic therapy and exercise performance. Sports Med 1987;4:290–304.
24. Carter BJ, Cammermeyer M. A phenomenology of heat injury: The predominance of confusion. Mil Med 1988;153:118–26.
25. Carter R III, Cheuvront SN, Williams JO, et al. Epidemiology of hospitalizations and deaths from heat illness in soldiers. Med Sci Sports Exerc 2005;37:1338–44.
26. Casa DJ, Armstrong LE, Ganio MS, Yeargin SW. Exertional heat stroke in competitive athletes. Curr Sports Med Rep 2005;4:309–17.
27. Casa DJ, McDermott BP, Lee EC, et al. Cold water immersion: The gold standard for exertional heatstroke treatment. Exerc Sport Sci Rev 2007;35:141–9.
28. Channa AB, Seraj MA, Saddique AA, et al. Is dantrolene effective in heat stroke patients? Crit Care Med 1990;18:290–2.
29. Chao NHH. Clinical presentation of heat disorders. In: Yeo PPB, Lin NK, editors. Heat disorders. Singapore: Headquarters Medical Services; 1985. p. 6–15.
30. Chinet A, Giovannini P. Evidence by calorimetry for an activation of sodium-hydrogen exchange of young rat skeletal muscle in hypertonic media. J Physiol 1989;415:409–22.
31. Clowes GH Jr, O'Donnell TF Jr. Heat stroke. N Engl J Med 1974; 291:564–7.
32. Croyle PH, Place RA, Hilgenberg AD. Massive pulmonary embolism in a high school wrestler. JAMA 1979;241:827–8.
33. Dematte JE, O'Mara K, Buescher J, et al. Near-fatal heat stroke during the 1995 heat wave in Chicago. Ann Intern Med 1998;129:173–81.
34. Denborough MA. Heatstroke and malignant hyperpyrexia. Med J Aust 1982;1:204–5.
35. Du Bois EF. The basal metabolism in fever. JAMA 1921;77:352–5.
36. Eichna LW, Park CR, Nelson N, et al. Thermal regulation during acclimatization in a hot, dry (desert type) environment. Am J Physiol 1950;163:585–97.
37. El-Kassimi FA, Al-Mashhadani S, Abdullah AK, Akhtar J. Adult respiratory distress syndrome and disseminated intravascular coagulation complicating heat stroke. Chest 1986;90:571–4.
38. Ellis FP. Mortality from heat illness and heat-aggravated illness in the United States. Environ Res 1972;5:1–58.
39. Epstein Y, Moran DS. Extremes of temperature and hydration. In: Keystone JS, Kozarsky PE, Freedman DO, editors. Travel medicine. London: Mosby; 2003. p. 383–92.
40. Epstein Y, Moran DS, Shapiro Y, et al. Exertional heat stroke: A case series. Med Sci Sports Exerc 1999;31:224–8.
41. Epstein Y, Sohar E, Shapiro Y. Exertional heatstroke: A preventable condition. Isr J Med Sci 1995;31:454–62.
42. Garcin JM, Bronstein JA, Cremades S, et al. Acute liver failure is frequent during heat stroke. World J Gastroenterol 2008;14:158–9.
43. Gardner JW, Kark JA, Karnei K, et al. Risk factors predicting exertional heat illness in male Marine Corps recuits. Med Sci Sports Exerc 1996;28:939–44.
44. Gathiram P, Wells MT, Raidoo D, et al. Changes in lipopolysaccharide concentrations in hepatic portal and systemic arterial plasma during intestinal ischemia in monkeys. Circ Shock 1989;27:103–9.
45. Giesbrecht GG, Jamieson C, Cahill F. Cooling hyperthermic firefighters by immersing forearms and hands in 10 degrees C and 20 degrees C water. Aviat Space Environ Med 2007;78:561–7.
46. Graber CD, Reinhold RB, Breman JG, et al. Fatal heat stroke: Circulating endotoxin and gram-negative sepsis as complications. JAMA 1971;216:1195–6.
47. Greenleaf JE, Castle BL. External auditory canal temperature as an estimate of core temperature. J Appl Physiol 1972;32:194–8.
48. Hadad E, Ben-Ari Z, Heled Y, et al. Liver transplantation in exertional heat stroke: A medical dilemma. Intensive Care Med 2004;30: 1474–8.
49. Hammarstrom S, Hua XY, Dahle'n SE, et al. Microcirculatory effects of leukotrienes C4, D4, and E4 in the guinea pig. Prog Clin Biol Res 1985;199:35–46.
50. Hassanein T, Perper JA, Tepperman L, et al. Liver failure occurring as a component of exertional heatstroke. Gastroenterology 1991; 100:1442–7.
51. Hassanein T, Razack A, Gavaler JS, Van Thiel DH. Heatstroke: its clinical and pathological presentation, with particular attention to the liver. Am J Gastroenterol 1992;87:1382–9.
52. Heled Y, Rav-Acha M, Shani Y, et al. The "golden hour" for heatstroke treatment. Mil Med 2004;169:184–6.
53. Hemmen TM, Lyden PD. Induced hypothermia for acute stroke. S J C C A 2007;38:794–9.
54. Henderson A, Simon JW, Melia WM, et al. Heat illness: A report of 45 cases from Hong Kong. J R Army Med Corps 1986;132:76–84.
55. Hensel HT. Neural processes in thermoregulation. Physiol Rev 1973;53:948–1017.
56. Herrmann F, Prose PH, Sulzberger MB. Studies on sweating. V. Studies of quantity and distribution of thermogenic sweat delivery to the skin. J Invest Dermatol 1952;18:71–86.
57. Holowatz LA, Kenney WL. Chronic low-dose aspirin therapy attenuates reflex cutaneous vasodilation in middle-aged humans. J Appl Physiol 1985 2009;106:500–5.
58. Hori S. Adaptation to heat. Jpn J Physiol 1995;45:921–46.
59. Huisse MG, Pease S, Hurtado-Nedelec M, et al. Leukocyte activation: The link between inflammation and coagulation during heatstroke—A study of patients during the 2003 heat wave in Paris. Crit Care Med 2008;36:2288–95.
60. Kark JA, Burr PQ, Wenger CB, et al. Exertional heat illness in Marine Corps recruit training. Aviat Space Environ Med 1996;67:354–60.
61. Keplinger ML, Lanier GE, Deichmann WB. Effects of environmental temperature on the acute toxicity of a number of compounds in rats. Toxicology 1959;1:156–61.
62. Khogali M. Heat stroke: An overview. In: Khogali M, Hales JRS, editors. Heat stroke and temperature regulation. New York: Academic Press; 1983. p. 1–12.

63. Kilbourne EM, Choi K, Jones TS, Thacker SB. Risk factors for heatstroke: A case-control study. JAMA 1982;247:3332–6.
64. Knochel JP. Environmental heat illness: An eclectic review. Arch Intern Med 1974;33:841–64.
65. Knochel JP. Heat stroke and related heat stress disorders. Dis Mon 1989;35:301–77.
66. Knochel JP, Reed G. Disorders of heat regulation. In: Narins RG, editor. Maxwell & Kleeman's clinical disorders of fluid and electrolyte metabolism. 5th ed. New York: McGraw-Hill; 1987. p. 1197–232.
67. Kuennen MR, Gillum TL, Amorim FT, et al. Palm cooling to reduce heat strain in subjects during simulated armoured vehicle transport. Eur J Appl Physiol 2010;108:1217–23.
68. Leight AS, Sinclair WH, Patterson MJ. Influence of postexercise cooling techniques in heart rate variability in men. Exp Physiology 2009;94:695–703.
69. Leon LR, Dineen SM, Plamper ML. Indomethacin increases organ damage and heat stroke mortality in mice. FASEB J 2014;1104–13.
70. Lipsker D. Images in clinical medicine: A white hand and a red hand erythromelalgia. N Engl J Med 2010;363:1463.
71. Lopez JR, Rojas B, Gonzalez MA, Terzic A. Myoplasmic $Ca^{2+}$ concentration during exertional rhabdomyolysis. Lancet 1995;345:424–5.
72. Lydiatt JS, Hill GE. Treatment of heat stroke with dantrolene. JAMA 1981;246:41–2.
73. Malamud N, Haymaker W, Custer RP. Heatstroke: A clinicopathological study of 125 fatal cases. Mil Surgeon 1946;99:397–449.
74. McCaffrey TV, McCook RD, Wurster RD. Effect of head skin temperature on tympanic and oral temperature in man. J Appl Physiol 1975;39:114–18.
75. McCord GR, Cracowski JL, Minson CT. Prostanoids contribute to cutaneous active vasodilation in humans. Am J Physiol Regul Integr Comp Physiol 2006;291:R596–602.
76. McDermott BP, Casa DJ, Yeargin SW, et al. Recovery and return to activity following exertional heat stroke: Considerations for the sports medicine staff. J Sport Rehabil 2007;16:163–81.
77. Mehta AC, Baker RN. Persistent neurological deficits in heat stroke. Neurology 1970;20:336–40.
78. Montain SJ, Latzka WA, Sawka MN. Fluid replacement recommendations for training in hot weather. Mil Med 1999;164:502–8.
79. Moran D, Epstein Y, Wiener M, Horowitz M. Dantrolene and recovery from heat stroke. Aviat Space Environ Med 1999;70:987–9.
80. Moran DS, Montain SJ, Pandolf KB. Evaluation of different levels of hydration using a new physiological strain index. Am J Physiol 1998;275:R854–60.
81. Moran DS, Pandolf KB. Wet bulb globe temperature (WBGT): To what extent is GT essential? Aviat Space Environ Med 1999;70:480–4.
82. Mustafa MK, Khogali M, Gumaa K. Respiratory pathophysiology in heat stroke. In: Khogali M, Hales JRS, editors. Heat stoke and temperature regulation. New York: Academic Press; 1983. p. 119–27.
83. Nemeth ZH, Hasko G, Szabo C, et al. Calcium channel blockers and dantrolene differentially regulate the production of interleukin-12 and interferon-gamma in endotoxemic mice. Brain Res Bull 1998;46:257–61.
84. Nolan JP, Morley PT, Hoek TL, Hickey RW. Therapeutic hypothermia after cardiac arrest. An advisory statement by the Advancement Life Support Task Force of the International Liaison Committee on Resuscitation. Resuscitation 2003;57:231–5.
85. O'Brien KK. Case studies of exertional heat injury/stroke in military populations. Med Sci Sports Exerc 2003;35.
86. O'Connor FG, Williams AD, Blivin S, et al. Guidelines for return to duty (play) after heat illness: A military perspective. J Sport Rehabil 2007;16:227–37.
87. O'Donnell TF. Medical problems of recruit training: A research approach. US Navy Med 1971;58:28–34.
88. Oh RC, Henning JS. Exertional heatstroke in an infantry soldier taking ephedra-containing dietary supplements. Mil Med 2003;168:429–30.
89. Pattison ME, Logan JL, Lee SM, Ogden DA. Exertional heat stroke and acute renal failure in a young woman. Am J Kidney Dis 1988;11:184–7.
90. Pettigrew RT, Galt JM, Ludgate CM, et al. Circulatory and biochemical effects of whole body hyperthermia. Br J Surg 1974;61:727–30.
91. Proulx CI, Ducharme MB, Kenny GP. Effect of water temperature on cooling efficiency during hyperthermia in humans. J Appl Physiol 2003;94:1317–23.
92. Rajan SF, Robinson GH, Borwer JD. The pathogenesis of acute renal failure in heatstroke. South Med J 1973;66:330–3.
93. Rav-Acha M, Hadad E, Epstein Y, et al. Fatal exertional heat stroke: A case series. Am J Med Sci 2004;328:84–7.
94. Roberts WO. A 12-yr profile of medical injury and illness for the Twin Cities Marathon. Med Sci Sports Exerc 2000;32:1549–55.
95. Roberts WO. Death in the heat: Can football heat stroke be prevented? Curr Sports Med Rep 2004;3:1–3.
96. Royburt M, Epstein Y, Solomon Z, Shemer J. Long-term psychological and physiological effects of heat stroke. Physiol Behav 1993;54:265–7.
97. Saissy JM. Liver transplantation in a case of fulminant liver failure after exertion. Intensive Care Med 1996;22:831.
98. Sawka MN, Young AJ. Physiological systems and their responses to conditions of heat and cold. In: Tipton CM, Sawka MN, Tate CA, Terjung RL, editors. ACSM's advanced exercise physiology. Baltimore: Lippincott, Williams & Wilkins; 2006. p. 535–63.
99. Sayers SP, Clarkson PM. Exercise-induced rhabdomyolysis. Curr Sports Med Rep 2002;1:59–60.
100. Schrier RW, Hano J, Keller HI, et al. Renal, metabolic, and circulatory responses to heat and exercise. Ann Intern Med 1970;73:213–23.
101. Seto CK, Way D, O'Connor N. Environmental illness in athletes. Clin Sports Med 2005;24:695–718.
102. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 2005;353:1574–84.
103. Shapiro Y, Cristal N. Hyperthermia and heat stroke: Effects on acid-base balance, blood electrolytes and hepato-renal function. In: Hales JRS, Richards D, editors. Heat stress: Physical exertion and environment. New York: Elsevier; 1987. p. 289–96.
104. Shapiro Y, Moran DS. Heat stroke: A consequence of maladaptation to heat-exercise exposure. In: Pandolf KB, Takeda N, Singal PK, editors. Adaptation biology and medicine: Molecular bases., New Delhi: Narosa; 1999. p. 159–70.
105. Shapiro Y, Rosenthal T, Sohar E. Experimental heatstroke. A model in dogs. Arch Intern Med 1973;131:688–92.
106. Shapiro Y, Seidman DS. Field and clinical observations of exertional heat stroke patients. Med Sci Sports Exerc 1990;22:6–14.
107. Shibolet S. The clinical picture of heat stroke. Proceedings of the Tel HaShomer Hospital. 1962. p. 80–3.
108. Shibolet S, Coll R, Gilat T, Sohar E. Heatstroke: Its clinical picture and mechanism in 36 cases. Q J Med 1967;36:525–48.
109. Shibolet S, Fisher S, Gilat T, et al. Fibrinolysis and hemorrhages in fatal heatstroke. N Engl J Med 1962;266:169–73.
110. Shibolet S, Lancaster MC, Danon Y. Heat stroke: A review. Aviat Space Environ Med 1976;47:280–301.
111. Silverstein JH, Appelbaum JL, Barlow JC. Practical guidelines for postanasthetic care. Anesthesiology 2002;742.
112. Sohal RS, Sun SC, Colcolough HL, Burch GE. Heat stroke: An electron microscopic study of endothelial cell damage and disseminated intravascular coagulation. Arch Intern Med 1968;122:43–7.
113. Sprung CL, Portocarrero CJ, Fernaine AV, Weinberg PF. The metabolic and respiratory alterations of heat stroke. Arch Intern Med 1980;140:665–9.
114. Stofan JR, Zachwieja JJ, Horswill CA, et al. Sweat and sodium losses in NCAA football players: A precursor to heat cramps? Int J Sport Nutr Exerc Metab 2005;15:641–52.
115. Strazis KP, Fox AW. Malignant hyperthermia: A review of published cases. Anesth Analg 1993;77:297–304.
116. Strydom NB, Morrison J, Booyens J, Peter J. Comparison of oral and rectal temperatures during work in heat. J Appl Physiol 1956;8:406–8.
117. Tayeb OS, Marzouki ZM. Effect of dantrolene pretreatment on heat stroke in sheep. Pharmacol Res 1990;22:565–72.
118. Torranin C, Smith DP, Byrd RJ. The effect of acute thermal dehydration and rapid rehydration on isometric and istonic endurance. J Sports Med Phys Fitness 1979;19:1–9.
119. Vertel RM, Knochel JP. Acute renal failure due to heat injury: An analysis of ten cases associated with a high incidence of myoglobinuria. Am J Med 1967;43:435–51.
120. Walker TB, Zupan MF, McGregor JN, et al. Is performance of intermittent intense exercise enhanced by use of a commercial palm cooling device? J Strength Cond Res 2009;23:2666–72.
121. Wallace RF, Kriebel D, Punnett L, et al. Prior heat illness hospitalization and risk of early death. Environ Res 2007;104:290–5.
122. Ward A, Chaffman MO, Sorkin EM. Dantrolene: A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in malignant hyperthermia, the neuroleptic malignant syndrome and an update of its use in muscle spasticity. Drugs 1986;32:130–68.
123. Weigand K, Riediger C, Stremmel W, et al. Are heat stroke and physical exhaustion underestimated causes of acute hepatic failure? World J Gastroenterol 2007;13:306–9.
124. Yaqub BA. Neurologic manifestations of heatstroke at the Mecca pilgrimage. Neurology 1987;37:1004–6.
125. Zuckerman GB, Singer LP, Rubin DH, Conway EE. Effects of dantrolene on cooling times and cardiovascular parameters in am immature porcine model of heatstroke. Crit Care Med 1997;25:135–9.