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Sweat testing to evaluate autonomic function

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Abstract

Sudomotor dysfunction is one of the earliest detectable neurophysiologic abnormalities in distal small fiber neuropathy. Traditional neurophysiologic measurements of sudomotor function include thermoregulatory sweat testing (TST), quantitative sudomotor axon reflex testing (QSART), silicone impressions, the sympathetic skin response (SSR), and the recent addition of quantitative direct and indirect axon reflex testing (QDIRT). These testing techniques, when used in combination, can detect and localized pre- and postganglionic lesions, can provide early diagnosis of sudomotor dysfunction and can monitor disease progression or disease recovery. In this article, we review the common tests available for assessment of sudomotor function, detail the testing methodology, review the limitations and provide examples of test results.

Keywords

Sudomotor; Sweat testing; Autonomic Testing

Introduction

Changes in peripheral autonomic nervous system function may be the earliest manifestation of distal small fiber neuropathy [30]. Dysfunction of the sudomotor system may result in an increase or decrease in sweat production, resulting in disturbances in thermoregulation. Human thermoregulation is a complex and tightly controlled homeostatic system. Central thermoreceptors, in the preoptic anterior hypothalamus, and peripheral thermoreceptors, in the skin, viscera and spinal cord, provide information from the body core and body shell to the central thermoregulatory center located in the hypothalamus [22,35]. The hypothalamus integrates the thermal information with the non-thermal references (mainly changes in fluid volume and electrolyte concentrations) resulting in thermoregulatory activity [2,22]. An increase in body temperature can be achieved by shivering or non-shivering thermogenesis or through reduced convective heat loss via sympathetically controlled cutaneous vasoconstriction. Heat dissipation can be augmented by increased cutaneous blood flow resulting in convective heat loss or through an increase in sweating causing evaporative heat loss.

Sweating as a way to regulate body temperature is unique to humans and primates and is mediated through eccrine sweat glands [12,34]. The parasympathetic influence on sudomotor function is negligible, while the sympathetic influence is derived from the hypothalamus through preganglionic cholinergic neurons that synapse in the paravertebral ganglia with postganglionic sympathetic cholinergic sudomotor axons [26,27,29]. Tests of

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sudomotor function aid in localization, diagnosis and monitoring disease progression in neurologic disorders associated with autonomic neuropathy [24].

A direct sweat response can be obtained by stimulation of M3 muscarinic receptors on sweat glands via iontophoresis of cholinergic agonists, such as acetylcholine, pilocarpine or methacholine [25]. However, this stimulation also provokes a sudomotor axon reflex through binding of the cholinergic agents to the nicotinic receptors on sudomotor nerve terminals [25]. The evoked impulse travels antidromically along the postganglionic sympathetic sudomotor neuron. At a branch point this impulse travels orthodromically until it reaches another population of eccrine sweat glands causing an indirect axon-reflex mediated sweat response (Figure 1) [33].

Traditional neurophysiologic measurements of sudomotor function include thermoregulatory sweat testing (TST), quantitative sudomotor axon reflex testing (QSART), silicone impressions and sympathetic skin response (SSR), and the recent addition of quantitative direct and indirect axon reflex testing (QDIRT) [8,11,25]. Each of these tests has benefits and drawbacks; we describe the individual testing techniques and limitations for each of these tests of sudomotor function.

Thermoregulatory Sweat Testing

Thermoregulatory sweat testing (TST) is used to evaluate the integrity of central and peripheral sympathetic sudomotor pathways from the CNS to the cutaneous sweat glands [9,28]. The core body temperature is raised by increasing the ambient room temperature which in turn raises blood and skin temperature. The degree and extent of sweat production is then visualized with an indicator dye.

Methodology

TST is performed in a temperature and humidity controlled room or chamber (Figure 2). The temperature is adjusted to 45–50 °C with a relative humidity of 35–40%. The subject lies supine on a table and is covered with an indicator that changes color in the presence of moisture. Sweat produces a change in local pH resulting in the indicator dye changing color and marking the location of sweat production (sweat has a pH of 4.5–5.5 at low sweat rates of 15–100nL/gland per hour). Two common indicators include alizarin red powder (alizarin red, corn starch, sodium carbonate, 1:2:1) and iodine corn starch. Skin and oral temperature probes are mounted to measure body surface and core temperature. Mean skin temperature is kept between 38.5 – 39.5 °C using overhead infrared heaters. Oral temperature must rise at least 1.0°C above baseline temperature or to 38 °C (whichever is higher). Maximal sweating is achieved within 30–65 minutes. Heating time should not exceed 70 minutes to avoid a decline in total sweat production and hyperthermia [8]. The mean rise during a standard TST is 1.2 °C and the average heating time is 45 minutes. Sweating causes the indicator to change its color (from yellow to dark red for alizarin red and from brown to purple with iodine). Digital photographs are taken and a sweat density map is generated on standard anatomical drawings. Data are expressed as TST% which is the measured area of anhidrosis divided by the area of the anatomic figure, multiplied by 100 (Figure 3).

Results

Normal sweating patterns are generally symmetric but vary in quantity (Figure 3A). Asymmetric sweat patterns and anhidrotic areas (focal, segmental, regional, length-dependent) are noted. The TST% can provide a general index of severity of the autonomic failure (Figure 3B–E).

Limitations

TST can localize specific areas of sudomotor dysfunction but can not differentiate preganglionic from postganglionic lesions [24]. In combination with a test measuring postganglionic sudomotor function (QSART, QDIRT, silicone impression) the site of a lesion can be separated: preganglionic lesions show an abnormal TST, while the QSART, QDIRT or silicone imprints are normal. A postganglionic lesion will be abnormal in all tests [9,28]. Although the test has tremendous clinical utility, the TST is not routinely performed except in highly specialized testing centers because it is time-consuming, requires special equipment, a large clinical space and special preparation and treatment of the patient [8]. Unfortunately, poor reimbursement is likely the largest obstacle to more widespread clinical use of this test.

Quantitative sudomotor axon reflex test

Quantitative sudomotor axon reflex test (QSART) is used to evaluate postganglionic sympathetic cholinergic sudomotor function by measuring the axon-reflex mediated sweat response over time and has achieved widespread clinical use. Sweat glands are stimulated via iontophoresis of a cholinergic agent and the sweat production is measured as an increase of humidity through a hygrometer [25].

Methodology

Stimulation and recording are done through a multi-compartmental sweat capsule. Standard testing sites are forearm, proximal leg, distal leg and dorsum of the foot. The capsule is placed on the skin and the outer ring is filled with 10% acetylcholine (or the drug of choice). The inner ring has nitrogen gas flowing across the skin with the outflow humidity measured by a hygrometer (Figure 4). Once a stable baseline has been reached, iontophoresis of the acetylcholine is started at a 2mA current for 5 minutes. Humidity is continuously recorded from baseline to 15 minutes post stimulation. The output of the sweat production is measured by the change in humidity. Results are analyzed by area under the curve, maximal sweat production and sweat onset latency (Figure 5). Equipment is calibrated by injecting known volumes of water onto a small square of filter paper contained within the sudorometer: 0.5, 1, 2, 5 and 10μl volumes of water are injected sequentially and the area of the difference in relative humidity (ΔRH) time curve is regressed against the test volumes.

Results

In normal individuals, the sweat output starts with a delay of 1–2 minutes. The sweat output increases for up to 5 minutes after stimulation until it reaches the inflection point and decreases slowly. While males and females have similar latency the sweat output differs. Mean sweat output for males is 2–3 μl/cm^2 (approximate range 0.7–5.4 μl/cm^2) and for females 0.25–1.2 μl/cm^2 (approximate range 0.2–3 μl/cm^2) with some variation depending on the site of stimulation [10]. Sweat response can be absent, decreased or increased. A longer latency of the sweat onset can be seen as well as a lack of recovery, the “hung up” response (Figure 5C) [22]. Increased sweat production is often a sign of axonal excitability, seen in conditions such as diabetic neuropathy, reflex sympathetic dystrophy and other small fiber neuropathies. In diabetic neuropathy, especially during early stages, a length-dependent pattern of sweat reduction can be seen [8].

Limitations

QSART measures the postganglionic sudomotor response and will be unable to detect preganglionic lesions. QSART is also time-consuming, requires special equipment and is not widely available. In most settings only the axon-mediated response is measured. There are modifications of the QSART reported, where the multi-compartmental cell is replaced with

another unloaded cell which measures direct and indirect sweat response simultaneously, but this adds to the complexity of the test [17].

Silicone Impressions

The silicone impression method is used to evaluate the postganglionic sympathetic cholinergic sudomotor function by measuring the direct and axon-reflex mediated sweat response at specific time points. Sweat glands are stimulated by iontophoresis of acetylcholine, pilocarpine or methacholine, followed by application of a thin layer of moldable material on the skin [37]. Sweat droplets formed by activated sweat glands displace the silicone material during polymerization resulting in permanent impressions that can be quantified by various methods. Dental impression material is typically used, which has a working time of approximately 2 minutes and fully polymerizes within 5 minutes (depending on the temperature). Polyvinyl siloxane is the standard material for dental impression formulation. It is a two part system with a base and an accelerator which mixed in equal parts causes cross-linking of the vinyl and silane terminal groups after activation via a platinum salt catalyst [40].

Methodology

Acetylcholine (or other cholinergic agonist) is iontophoresed into the skin at a constant current of 2mA for 5 minutes. At the end of stimulation the drug delivery probe is removed, the skin is blotted dry and the compound is applied in a thin layer either immediately or at selected time points up to 20 minutes after iontophoresis (the two compounds of the dental impression kit are mixed thoroughly in even parts one minute before the target time point of application). In order to apply pressure more evenly, silicone material can be rolled out on a transparency sheet, placed over the testing region and applied by pulling down on the edges of the transparency. After polymerization (usually within 5 minutes), the silicone imprints are analyzed for number, distribution and droplet size either directly under a light microscope (by counting the more translucent sweat impressions) or through computer assisted analysis (the imprints can be stained with black toner and copied by scanning or digital photography) followed by computer aided quantitation of droplet number and size [11]. Data are reported as droplet number, size and distribution. Volume of sweat production can be estimated by assuming the droplets form a hemisphere [1].

Results

Normal individuals have 311±38 sweat droplets/cm^2 in the hand (lower limit 255) and 281±38 sweat droplets/cm^2 in the foot (lower limit 235) [15,16]. Abnormal impressions can be seen in postganglionic lesions, when the sweat duct is occluded, when the sweat glands themselves are damaged or when sweat glands are completely absent (Figure 6).

Limitations

Although the silicone impression method is probably the easiest method to conduct, it is prone to artifacts left by hairs, dirt, skin surface texture and air bubbles. Caution should also be taken when wearing rubber examination gloves. Traces of zinc diethyl dithiocarbamate, an accelerator used in the manufacture of certain hospital gloves, react with the platinum catalyst in the polyvinyl siloxane and delay or totally inhibit polymerization, which will dramatically alter testing results. Dental impression material has been modified over the past several decades. The original materials used were hydrophobic condensation-silicones. Modifications to the base polymer generated hydrophilic addition-silicones, which were further altered by adding compounds such as surfactants to increase water displacement, leading to a reduction in impression defects [31]. While these improvements have enhanced the quality of dental molds they reduced the ability of sweat droplets to create impressions.

Elasticon, a condensation-silicone, was the imprint material of choice for almost two decades. Elasticon generated better impressions of sweat droplets than polyvinyl siloxane based materials because of its hydrophobicity (but for that specific reason also lead to its discontinuation). A description of newer silicones that are currently available has been reported [40].

Quantitative direct and indirect axon reflex testing

Quantitative direct and indirect axon reflex testing is a novel technique to evaluate the postganglionic sympathetic cholinergic sudomotor function by measuring the direct and axon-reflex mediated sweat response in a dynamic fashion. Sweat glands are stimulated by acetylcholine iontophoresis and sweat is displayed via an activator dye followed by digital photographs over time [11].

Methodology

Acetylcholine (or other cholinergic agonist) is iontophoresed into the skin at a constant current of 2mA for 5 minutes. After iontophoresis the drug delivery probe is quickly removed, the area is blotted dry, a thin layer of alizarin red mixture is applied (alizarin red, corn starch, sodium carbonate, 1:2:1) and digital pictures are taken every 15 seconds for 7 minutes. Images of QDIRT are then uploaded on a computer as a sequence and processed (Image Pro Plus, Media Cybernetics, Bethesda, MD) with automated image stabilization and graphical thresholding. A full description of the image processing procedure has been published online as an accompaniment to the paper introducing QDIRT [11]. Sweat droplets are quantified by number, size and percent area over the area of interest, separating between direct and indirect sweat production. An entire test can be finished in approximately 15 minutes (Figure 7).

Results

QDIRT is a new technique and requires further study in disorders of the autonomic nervous system. QDIRT is simple, inexpensive and can be used by clinicians without more sophisticated autonomic laboratories.

Limitations

This technique has been tested in selected patients with small fiber neuropathy, but has not been used to study other disorders of the autonomic nervous system [11].

Sympathetic skin response

Sympathetic skin response (SSR, also referred to as galvanic skin response) is a measure of electrodermal activity and provides a surrogate measure of sympathetic cholinergic sudomotor function. Perturbation of the autonomic nervous system, through rapid inspiration or electrical stimulation, induces a change in skin potential [6,7,14,18,19,36]. Changes in skin potential are also seen in response to emotion or attention and have been widely studied in psychiatry and law enforcement as the “lie detector” [4,32]. The source of the skin potential is presumed to be the sweat glands and the epidermis, although it is present in subjects with congenital absence of sweat glands [5,10]. SSR measures a polysynaptic reflex with a spinal, a bulbar and a suprabulbar component [39]. Although this is not a test of “sweat” function, it is often included in this category as a measure of sudomotor activity.

Methodology

Recording electrodes are placed on the dorsal and ventral surface of the hand, medial forearm, proximal leg, distal leg or proximal foot. Recordings are taken by any standard EMG, with low frequency filters set to 0.5Hz or below to prevent attenuation of the potential. The response can be triggered by an inspiratory gasp, forceful expiration, startle response, or electrical stimulation [20]. SSR's are reported as present or absent and for amplitude and latency (Figure 8). Absent potentials can occur due to inadequate stimulation and habituation.

Results

The SSR in the hands traditionally has larger amplitudes and shorter latencies than the feet (hands: 1.5 seconds latency, 0.5–1.3mV amplitude, feet: 1.9–2.1 seconds latency, 0.15 – 0.8mV amplitude) [10]. Abnormalities of SSR's are seen in many disease states, including general autonomic failure, peripheral neuropathy and even CNS degeneration, such as Alzheimer's disease [3,13,21].

Limitations

Although this method is extremely easy to perform, there is high variability within and between subjects. SSR declines with age, and may not be seen in many subjects over 50 [10]. It should also be noted that this method is only a surrogate measure of sudomotor function; patients with congenital absence of sweat glands (ectodermal anhidrotic dysplasia) will still have a response [38].

Summary

Quantitative assessment of sudomotor function is an important component to autonomic testing. Sudomotor abnormalities can confirm a diagnosis of autonomic dysfunction, monitor disease progression and identify the success of treatment. The choice of which test to perform is made on the availability of testing equipment, lesion localization and the type of suspected disease. The TST provides an assessment of pre- and postganglionic function over the whole body. TST can be combined with any test of postganglionic function (QSART, silicone impression, QDIRT) to separate pre- and postganglionic lesions. QSART identifies the axon reflex sudomotor response by change in relative humidity and onset latency while silicone impressions identify sweat droplets in both direct and indirect regions, but only at a single time point [25,37]. QDIRT combines many aspects of QSART and silicone impressions, but requires further validation for clinical use [11]. All tests of sudomotor function are prone to artifacts and confounding variables. Ambient temperature, hydration status, medication use, age and gender can alter sudomotor responses [24]. Previous exposure of the skin to alcohol, repeated testing over the same region and application of moisturizing creams can also alter the results [23]. In order to obtain a high level of reproducibility and reliability all of these factors should be controlled as tightly as possible. Despite these limitations and restrictions, neurophysiologic assessment of the sudomotor system complements other measures of autonomic function, and remains one of the most sensitive and specific means to detect distal small fiber neuropathy [30].

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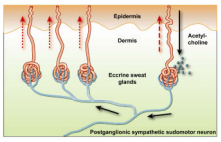

Figure 1. The sudomotor axon reflex

Cholinergic agonists (such as acetylcholine) applied through iontophoresis (shown with the black arrow) bind to muscarinic receptors causing local sweat production (dashed arrow). The cholinergic agonist simultaneously binds to nicotinic receptors on nerve terminals of sudomotor fibers and an impulse travels antidromically. At branch points this impulse travels orthodromically to a neighboring population of eccrine sweat glands causing an indirect axon mediated sweat response (dotted arrows).

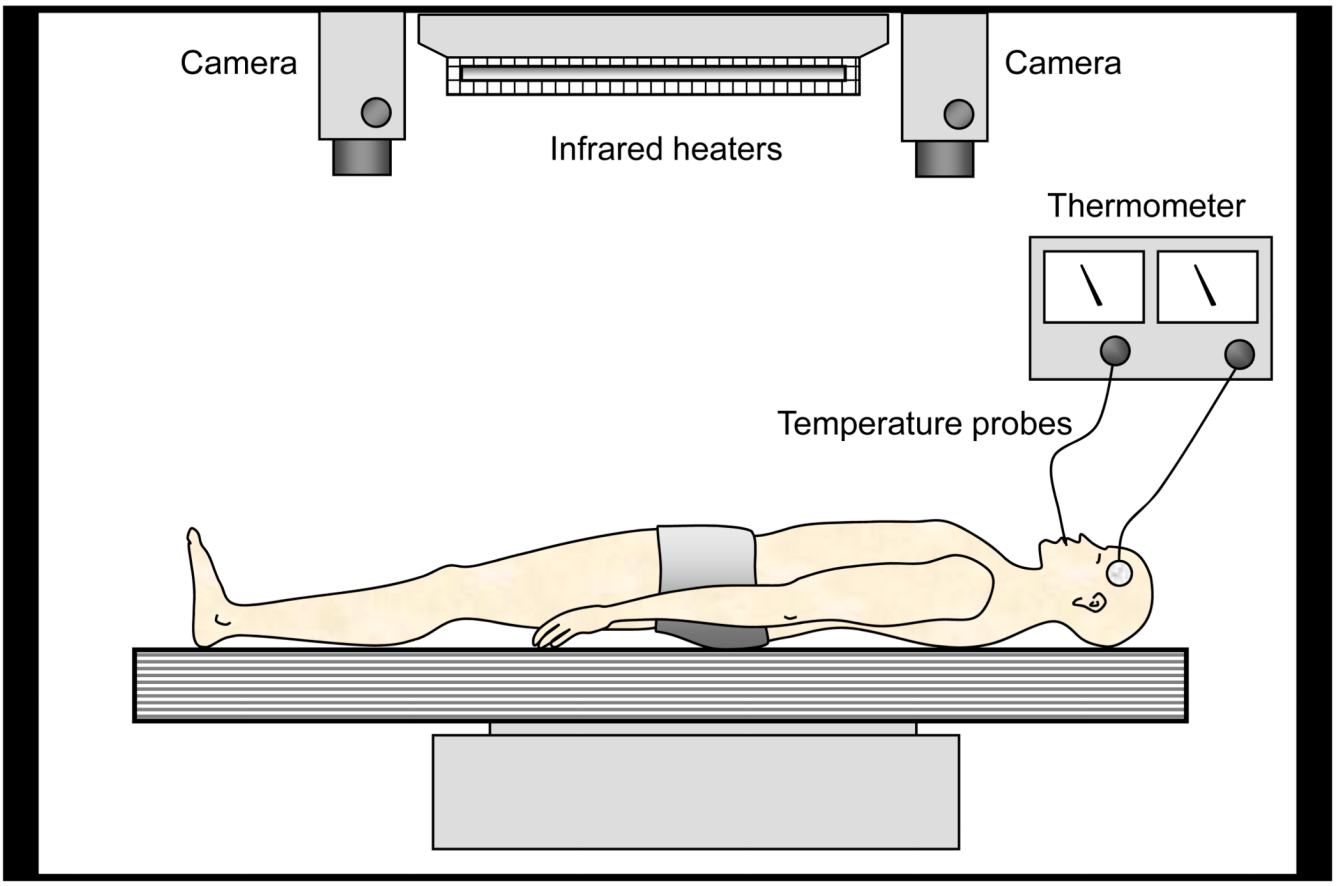

Figure 2. Thermoregulatory sweat testing (TST)

A TST chamber is temperature and humidity controlled. Ceiling mounted infrared heaters control the patient's temperature. The patient is placed in the supine position. Oral and cutaneous temperature probes are attached. During the application of the indicator dye, the patient's eyes, nose and mouth should be protected. To achieve even distribution of the indicator powder, an atomizer should be used. The test is started by increasing the room temperature. Oral temperature must rise at least 1.0°C above baseline temperature or to 38 °C (whichever is higher). At the end of the test pictures are taken and used to generate a topographical map of the sweat pattern.

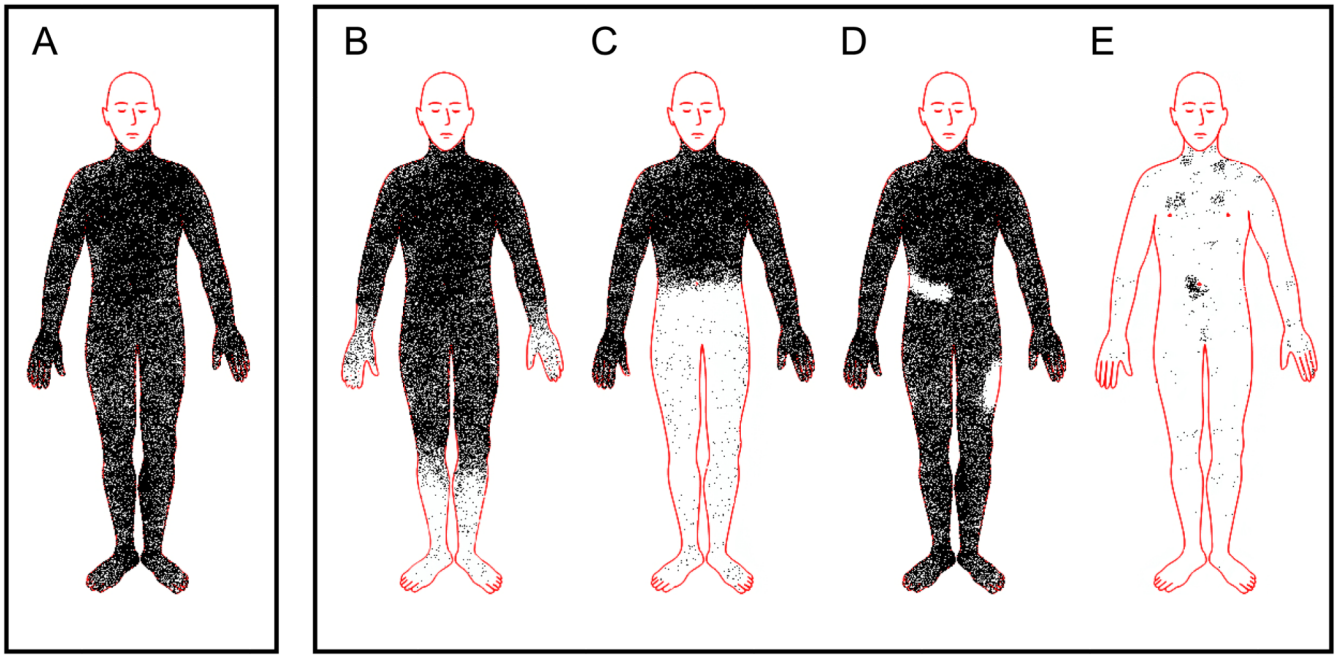

Figure 3. Thermoregulatory sweat test (TST) results

Normal sweat patterns show a sweat response present over the entire body that may be variable in intensity (A). In (B), a length dependent neuropathy from diabetes with stocking and glove distribution loss is seen. A patient with a complete myelopathy at T9 is shown in (C). Lesions to individual nerves can show focal or dermatomal sweat defects. A patient with a right T10 radiculopathy and a left lateral femoral cutaneous neuropathy can be identified in (D). A patient with complete anhidrosis secondary to pure autonomic failure is seen in (E).

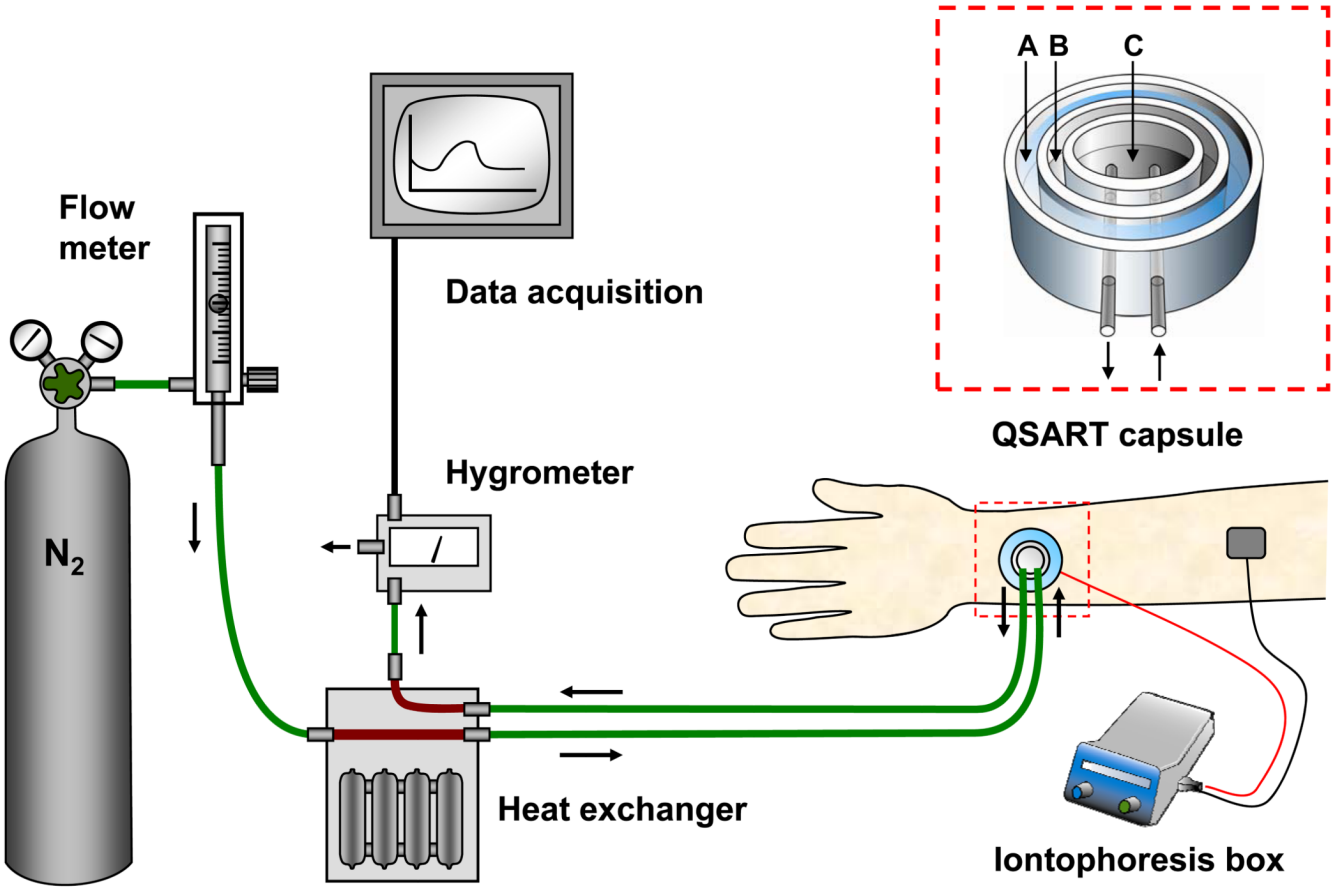

Figure 4. Quantitative sudomotor axon reflex test (QSART)

An overview of the QSART testing procedure: A multi-compartmental sweat capsule has an outer ring (A, 1.5mm wide) for iontophoretic stimulation and an inner compartment (C, 1cm diameter) for measuring humidity. The stimulation and recording sites are separated by a small compartment (B, 1.5mm wide) to prevent direct stimulation of the sweat glands and leakage of the iontophoresis fluid. Dry nitrogen gas is released at a steady rate of flow (typically 100 cc/min) controlled through a flow meter. The gas flows through a temperature controlled heat exchanger and into the sweat capsule (C). Upon exiting the capsule the gas flows back through the heat exchanger and to a hygrometer, where changes in humidity are recorded on a computer.

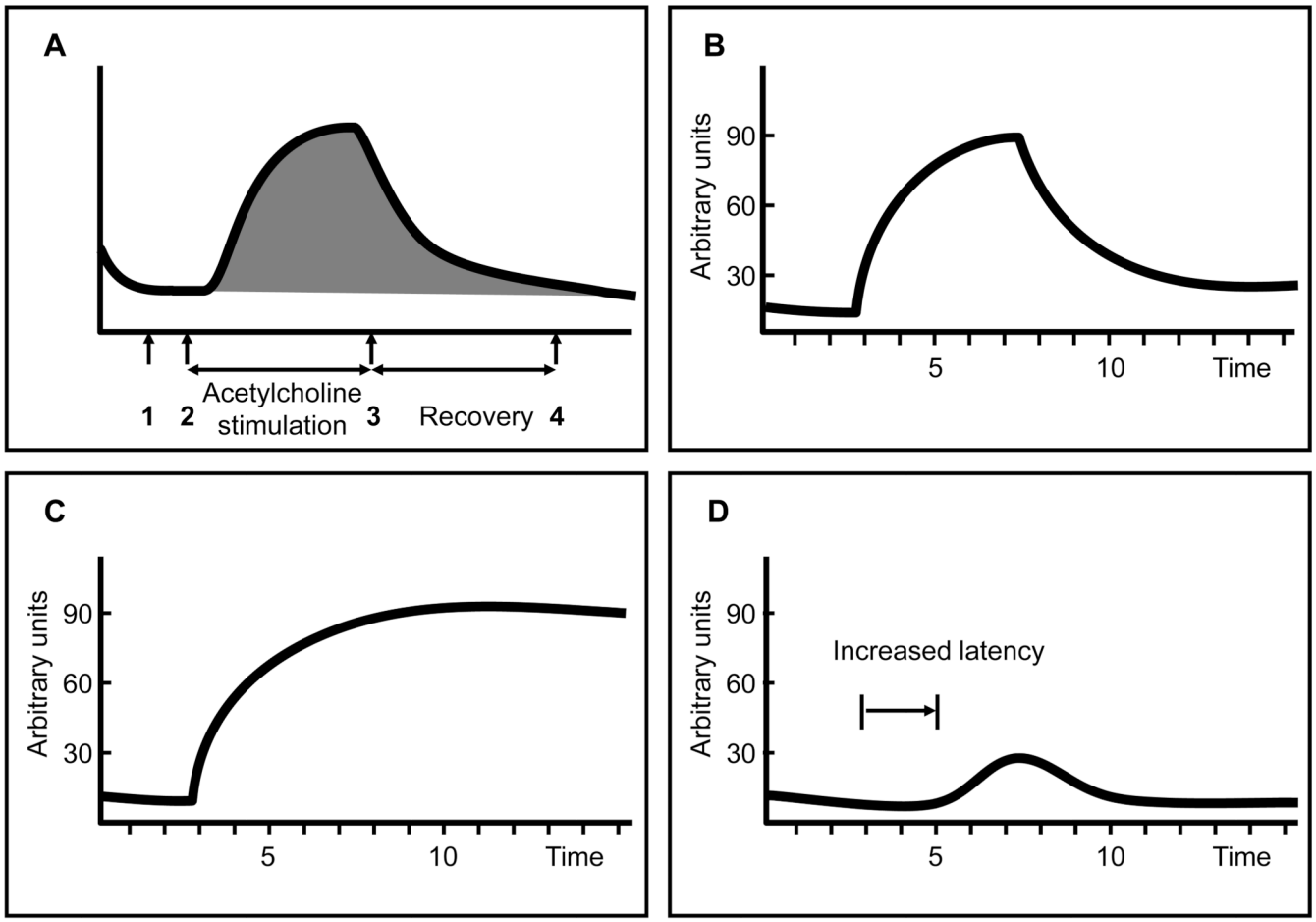

Figure 5. QSART results

Panel (A), after a baseline is reached (1) recording is started for at least 2 minutes. Iontophoresis is started (2) at 2mA for 5 minutes (3). Recording is continued to monitor recovery for at least another 10 minutes (4) (A). Panel (B) shows a normal response. The example in (C) shows a “hung-up” response typically seen if sweat production is excessive and no recovery is reached. Panel (D) shows a reduced sweat response with a delayed onset of sweat production.

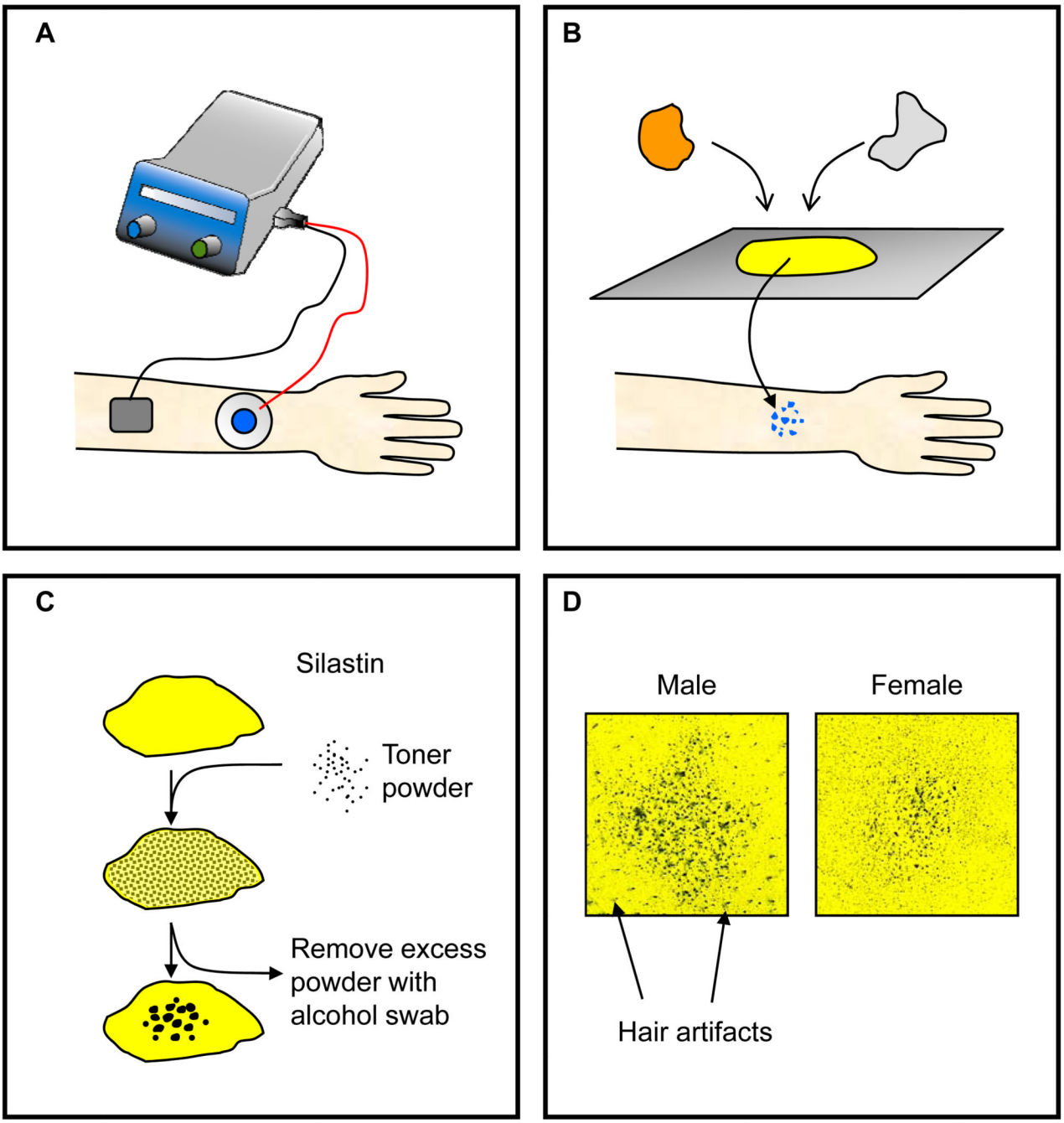

Figure 6. Silicone impressions

Sweat glands are stimulated via iontophoresis at 2mA for 5 minutes (A). Silicone compounds are mixed in equal parts, rolled out into a thin layer and applied on to the stimulated area until polymerization is reached (B). Toner powder is applied to the silicone imprint and the excess is removed by wiping the surface with alcohol swabs until only the sweat droplet imprints are stained (C). Panel (D) shows two typical imprints, with the male subject producing larger sweat output. Imprints are prone to artifacts, such as hair marks or air bubbles.

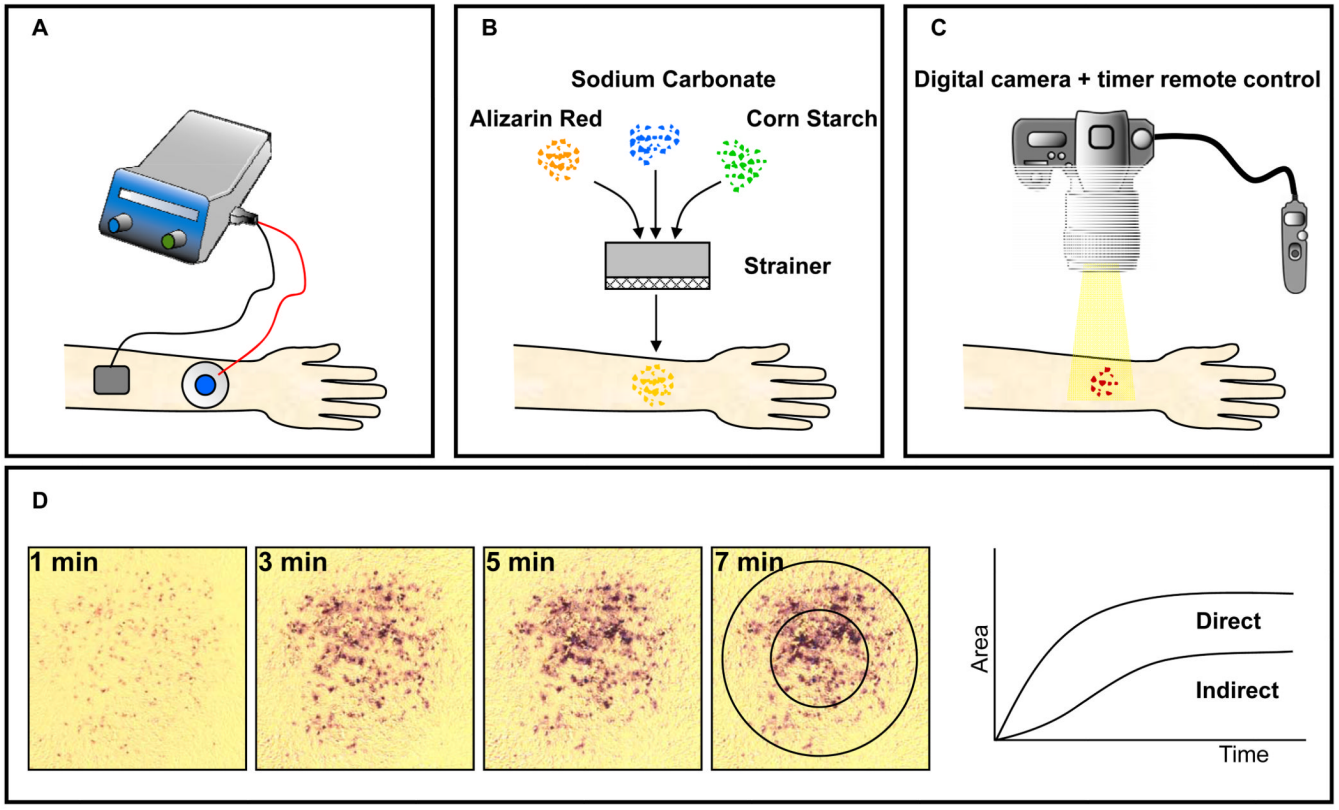

Figure 7. QDIRT: Quantitative direct and indirect reflex testing of sudomotor function

Sweat glands are stimulated via iontophoresis at 2mA for 5 minutes (A). Alizarin red powder is applied in a thin layer onto the stimulated area (B). Immediately, digital pictures are taken every 15 seconds for 7 minutes (C). The results can be quantified by droplet number, size, location and response latency in both direct and indirect testing regions.

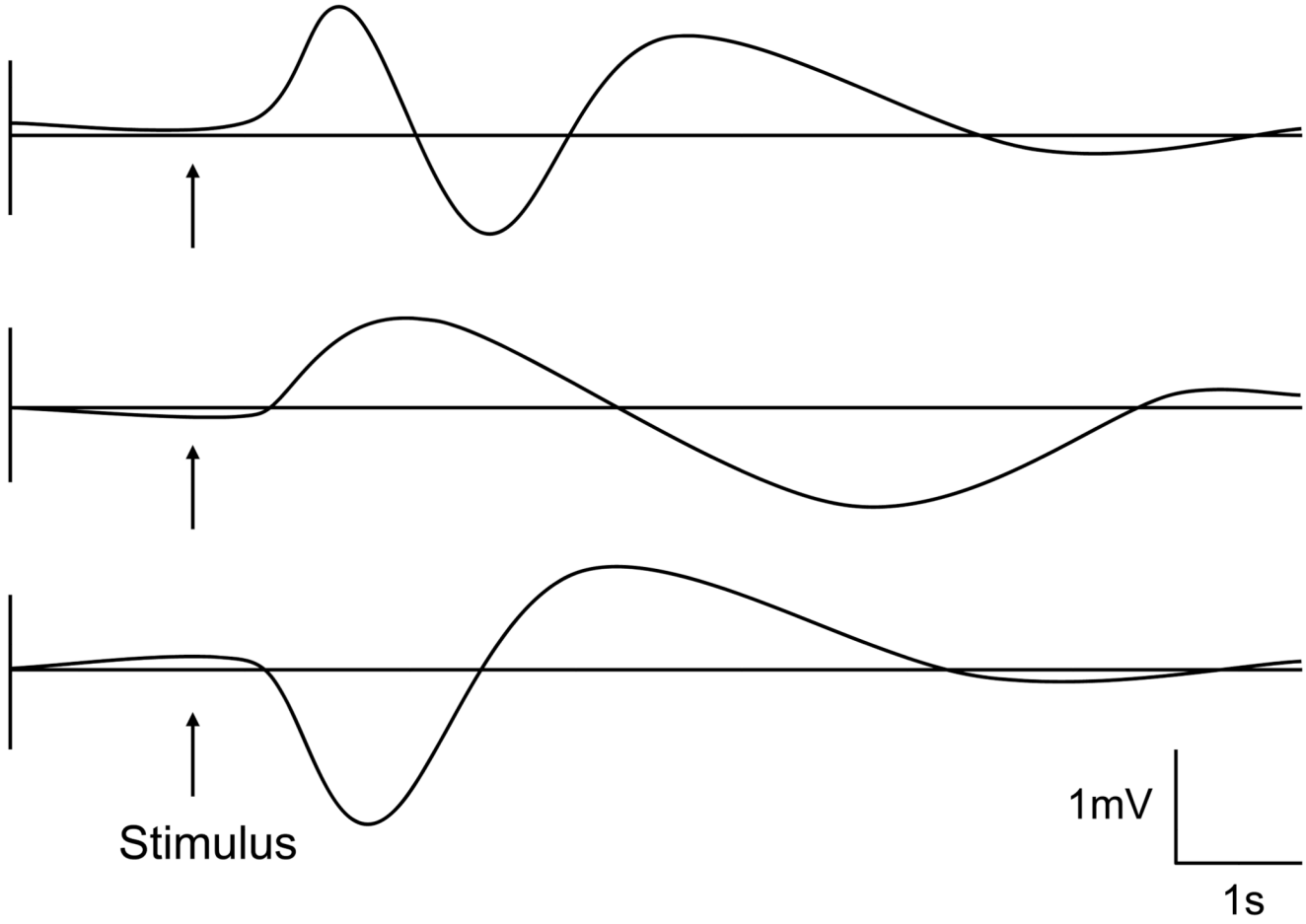

Figure 8. The sympathetic skin response (SSR)

The figure shows examples of three normal recordings. After a stimulus (e.g. a deep breath) any deviation from the baseline is reported. If no change is seen, a stronger stimulus is applied (e.g. electrical stimulation) and if there is still no change seen, an “absent response” is reported. The onset latency and magnitude of response can be quantified, although the results are highly variable within and between subjects.