



MACON & JOAN BROCK VIRGINIA HEALTH SCIENCES

Eastern Virginia Medical School

AT OLD DOMINION UNIVERSITY

Sleep at Altitude

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Disclosures

I have no financial disclosures

Pictures are encouraged

Photos of mountains were taken by the presenter



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Objectives

Understand the physiology of sleep at altitude

- Describe how hypobaric hypoxia alters ventilation, oxygenation, and sleep architecture
- Explain mechanisms of periodic breathing and central sleep apnea in high-altitude environments and their impacts on sleep

Recognize clinical syndromes of altitude-related sleep disturbances

- Differentiate between acute mountain sickness, high-altitude periodic breathing, and central sleep apnea
- Identify risk factors that predispose individuals to sleep-disordered breathing and other medical conditions at altitude

Explore therapeutic strategies

- Evaluate evidence-based interventions (acetazolamide, supplemental oxygen, CPAP, ASV)
- Discuss non-pharmacologic measures (staged ascent, acclimatization strategies, behavioral modifications)

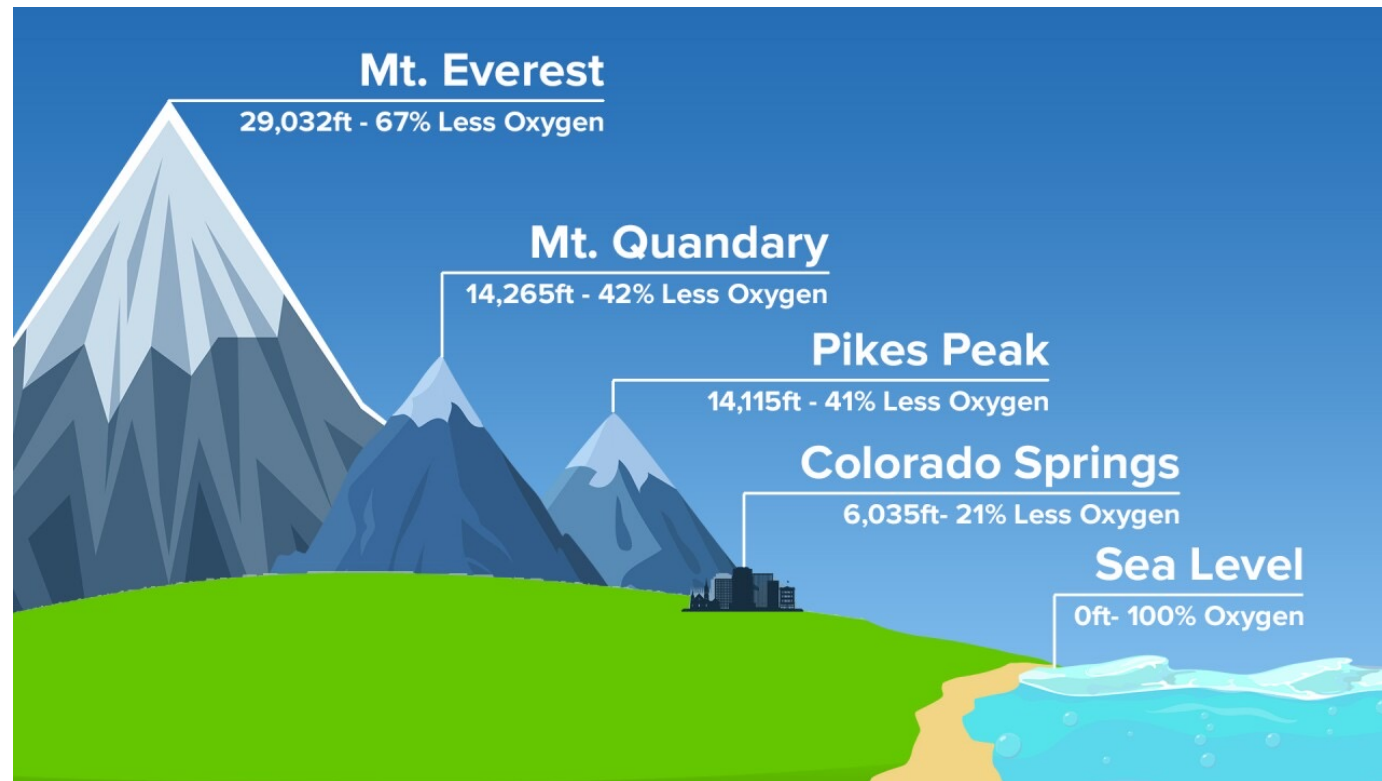


Mount Crested Butte
Gunnison, CO
12,168 feet (3,709 m)

Understand the physiology of sleep at altitude

Describe how hypobaric hypoxia alters ventilation, oxygenation

- **Barometric pressure** decreases with altitude
- **Functional concentrate** of oxygen (21%) is still the same as sea level
- **Oxygen tension** (product of functional concentrate and barometric pressure) reduces in ambient air with altitude

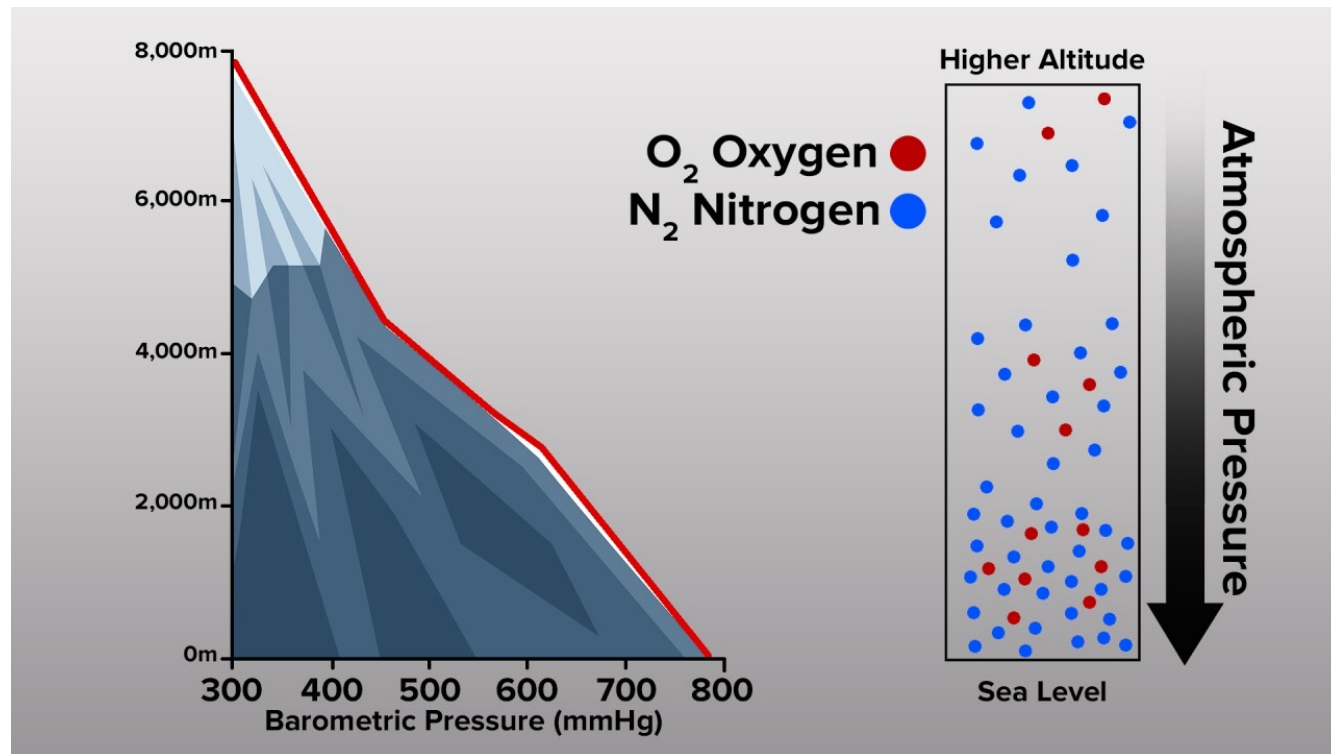


KOAA Weather

Understand the physiology of sleep at altitude

Describe how hypobaric hypoxia alters ventilation, oxygenation

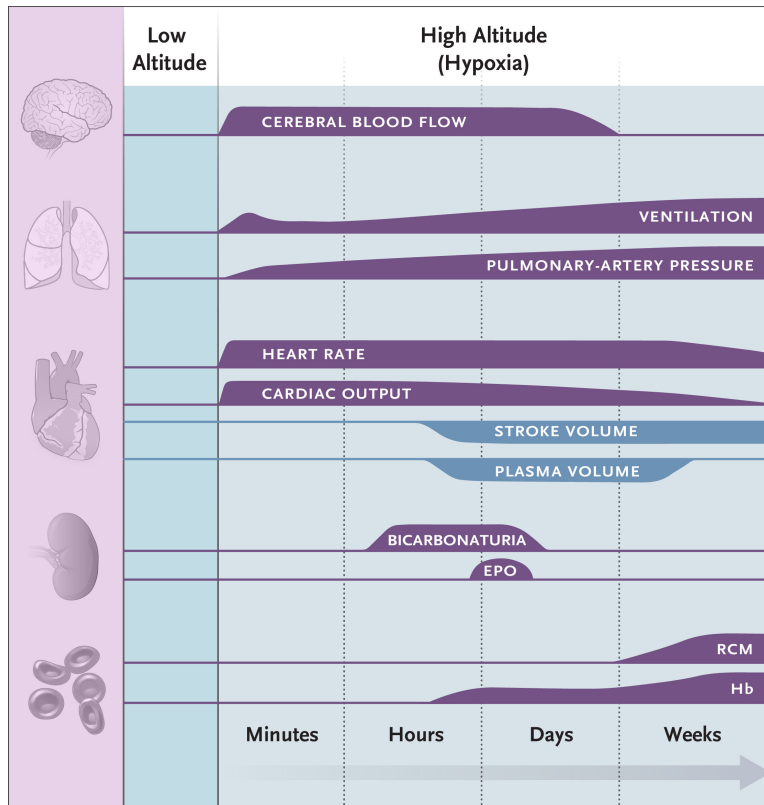
- Air always contains about 21% oxygen
- "Thinner" at altitude, "denser" at sea level
- At altitude, oxygen molecules have less barometric pressure to "push" them together
- Fewer oxygen molecules per volume of air



KOAA Weather

Understand the physiology of sleep at altitude

Describe how hypobaric hypoxia alters ventilation, oxygenation



Medical Conditions and High-Altitude Travel

Authors: Andrew M. Luks, M.D., and Peter H. Hackett, M.D.
January 26, 2022 N Engl J Med 2022;386:364-373

Hypobaric states → reduced Oxygen tension of ambient air → body response

- Reduces availability of arterial and tissue oxygenation
- Body response is to minimize hypoxia

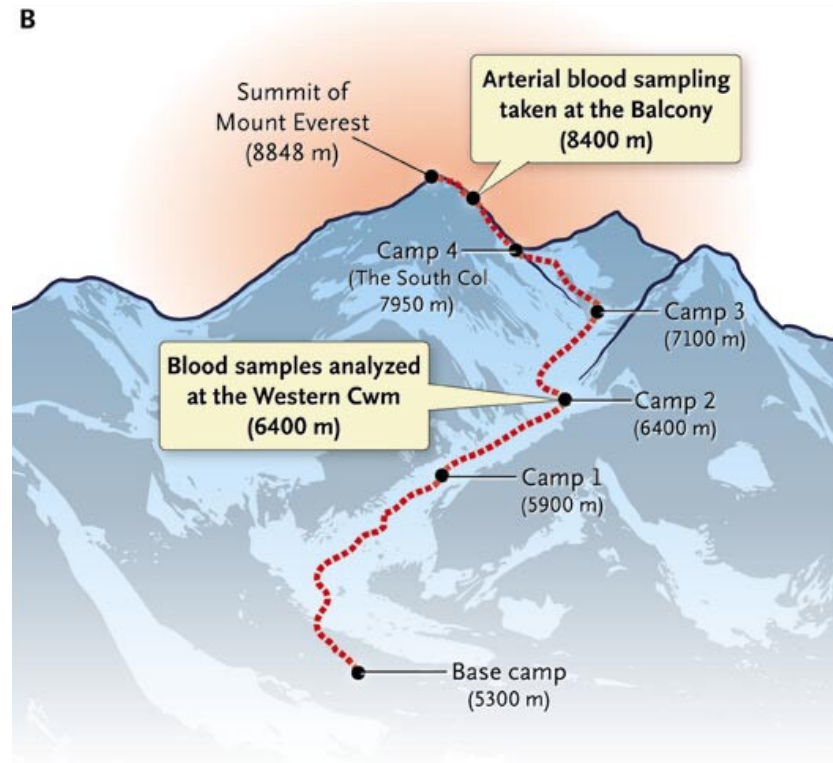
Body response ≥ 3000 m (9,842 ft)

- Increase cerebral blood flow
- Increase ventilation
- Increase cardiac output
- Eventually... increase RBC concentration and capillary/mitochondrial density

Understand the physiology of sleep at altitude

Describe how hypobaric hypoxia alters ventilation, oxygenation

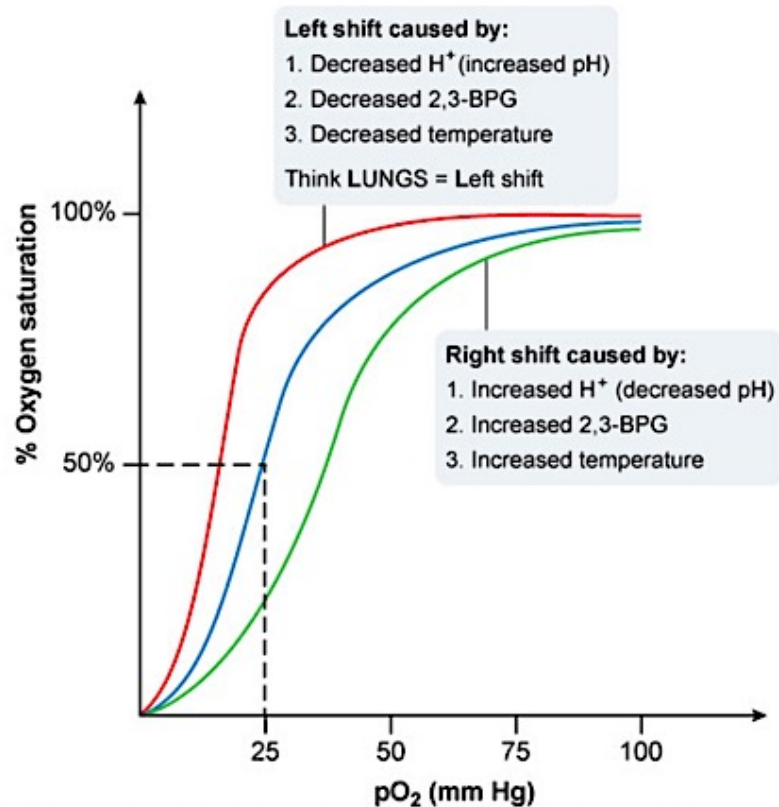
- **Arterial Blood Gases and Oxygen Content in Climbers on Mount Everest** (Grocott et al., NEJM 2009)
- ABG measurements of PaO₂, PaCO₂, SaO₂, Hgb
- PaO₂ fell with increasing altitude, whereas SaO₂ remained ~54-70%
- Extreme results
 - PaO₂ as low as 19 mmHg
 - PaCO₂ mean of 13 mmHg suggesting profound hyperventilation and resulting respiratory alkalosis
- Hemoglobin rose to boost oxygen carrying capacity to maintain SaO₂ until 7100 m



Understand the physiology of sleep at altitude

Describe how hypobaric hypoxia alters ventilation, oxygenation

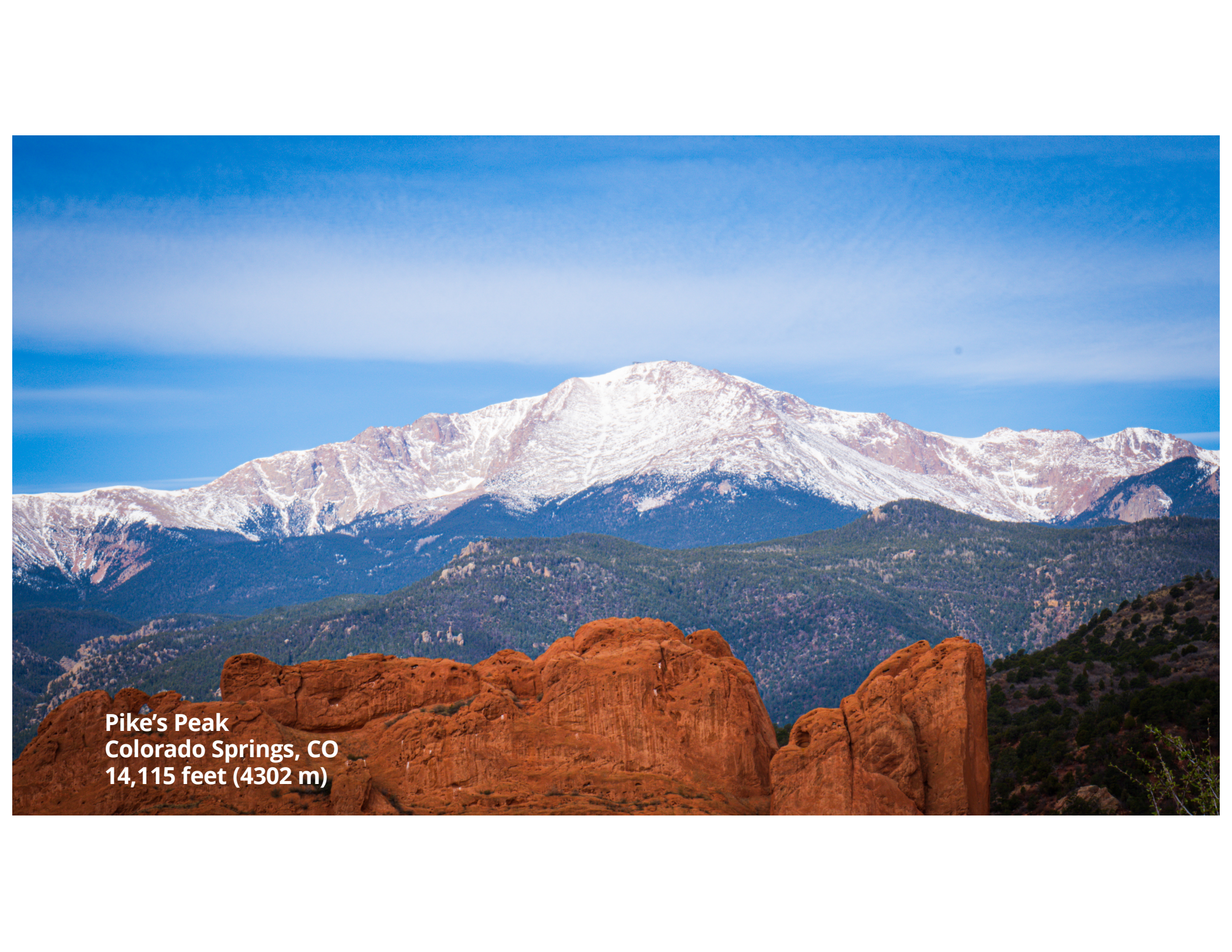
Oxygen-hemoglobin dissociation curve



2,3-BPG = 2,3-bisphosphoglycerate; pO₂ = partial pressure of oxygen in the blood.

©UWorld

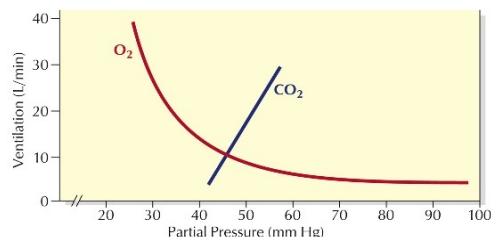
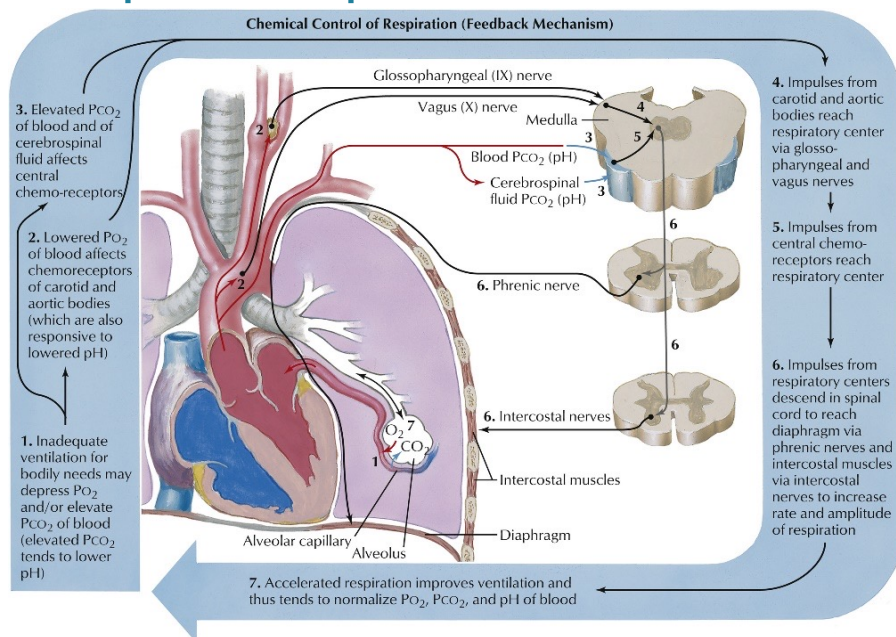
- Grocott et al. continued
- Lowest PaO₂ ever documented in a human 19mmHg!!
- Profound respiratory alkalosis to maintain oxygen loading despite low ambient oxygen
- Hemoglobin rose over time
- Arterial oxygen saturation was compensated due to optimized Hgb-O₂ desaturation curve



Pike's Peak
Colorado Springs, CO
14,115 feet (4302 m)

Understand the physiology of sleep at altitude

Explain mechanisms of periodic breathing and central sleep apnea in high-altitude environments and their impacts on sleep



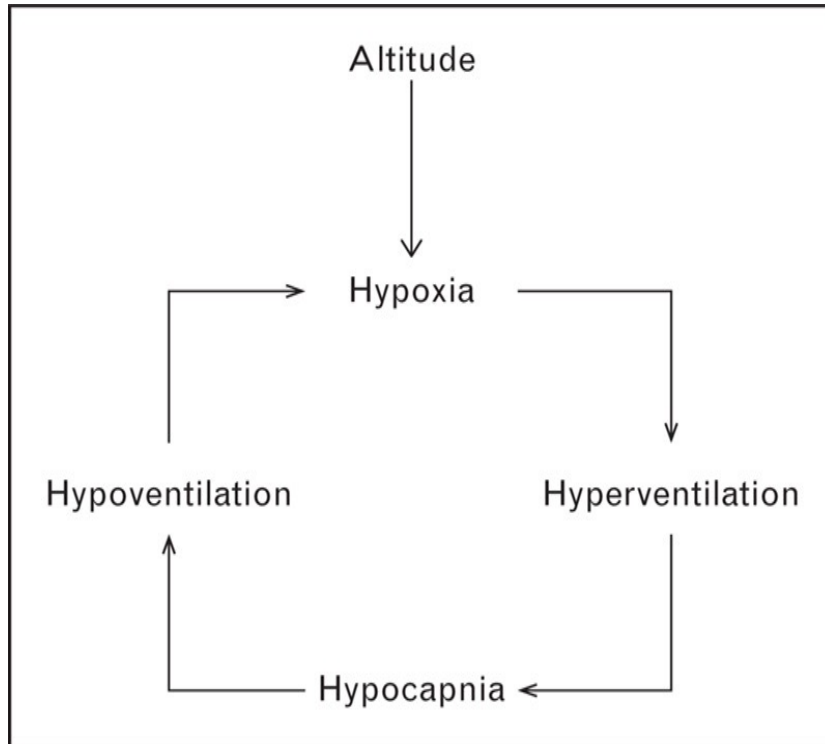
Lee-Chiong et al. **Respiratory Physiology During Sleep** Sleep Med Clin 7 (2012) 497–505

- As hypoxic exposure triggers hyperventilation, potentiating **periodic breathing** (repeated central apneas)
 - First described in 1913 by C.G. Douglas et al. while sleeping on Pike's Peak
- When asleep, wakefulness drive is lost and thus respiration depends on this **3-part system**
- **Central controllers**
 - Pons and medulla
- **Sensors (peripheral chemoreceptors)**
 - Carotid body, glossopharyngeal nerve, vagus nerve, aortic body
- **Effectors**
 - Respiratory motor neurons and muscles
- Primary influence on ventilation is from $PaCO_2$, PaO_2 (when hypoxia is severely impacted e.g., altitude), and pH

Understand the physiology of sleep at altitude

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Respiratory Response to Altitude



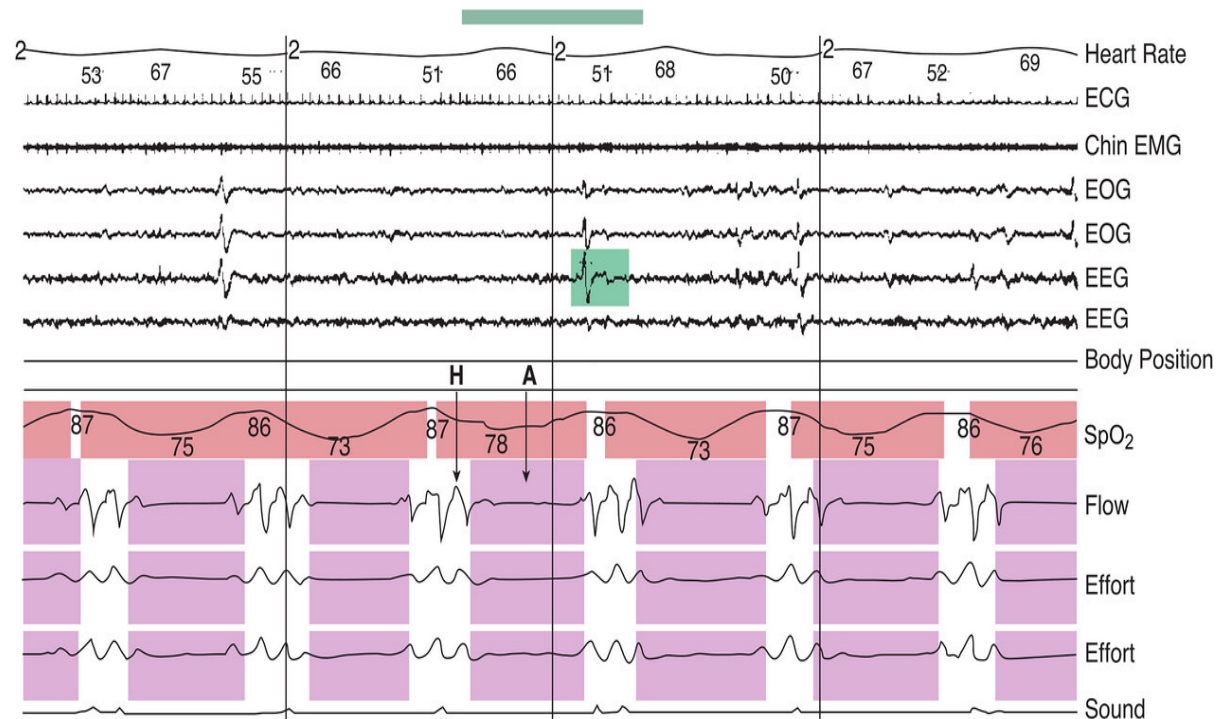
- Hypoxia-hypocapnia opposing effects on respiratory drive
- Hypoxic drive primarily peripheral sensors
- Hypocapnic response primarily central sensors
- Increased sensitivity to hypocapnia in setting of hypoxia

Understand the physiology of sleep at altitude

Explain mechanisms of periodic breathing and central sleep apnea in high-altitude environments and their impacts on sleep

- **Periodic breathing** usually present in **N1 and N2 sleep**, and during wakefulness (during periods of drowsiness)
- Reduced PB in REM sleep may be due to wider PCO₂ reserves in REM sleep
 - This is also observed in PB associated with CHF
- Cycle length characterized as being short cycle (12-34 seconds) compared to long cycle lengths with CHF (40-90 seconds)

Pictured: 2 min epoch from one subject at 5050 m

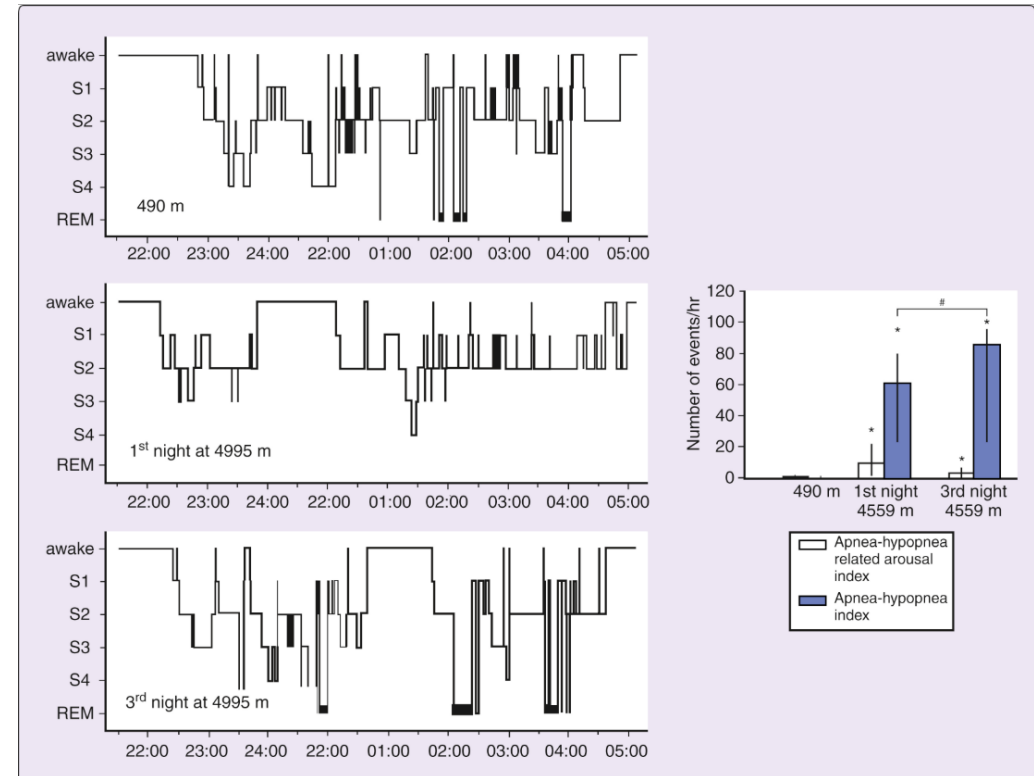


Ainslie PN, Lucas SJ, Burgess KR. Breathing and sleep at high altitude. *Respir Physiol Neurobiol.* 2013;188:233–56.

Understand the physiology of sleep at altitude

Explain mechanisms of periodic breathing and central sleep apnea in high-altitude environments and their impacts on sleep

- **Sleep disruption** at altitude is common, especially during **first two nights after ascent**
- **Reduced** TST, N3 sleep ("deep" sleep), and REM sleep*
- **Increased** N1, N2 and arousals
- Sleep quality seems to **improve after third night** at the same altitude
- **Complaints of persistent sleeplessness** despite this improvement (may be due to sleep fragmentation)
- Periodic breathing persists beyond night 3, suggesting it **may not be the predominant** cause of sleep disturbances



Nussbaumer-Ochsner Y, Ursprung J, Siebenmann C, et al. Effect of short-term acclimatization to high altitude on sleep and nocturnal breathing. *Sleep*. 2012;35:419–23.



Zugspitze
(highest mountain in Germany)
Bavaria, Germany
2,962 meters (9,718 feet)

Recognize clinical syndromes of altitude-related sleep disturbances

Differentiate between acute mountain sickness, high-altitude periodic breathing, and central sleep apnea

- **Unacclimatized** lowlanders ascending to terrestrial high altitude may experience altitude related conditions beginning at **2500 m (8,202 ft)**
- **Predisposing medical** conditions (cardiac and pulmonary especially) **may precipitate symptoms at lower altitudes** and thus increase risk of developing altitude related conditions
- In addition to absolute altitude reached, **time at altitude** and **physical exertion** impact risk
- How could these other altitude related conditions impact sleep?

Table 1. Clinical Problems at High Altitude.*		
Illness and Clinical Presentation	Prevention	Treatment
High-altitude headache Common above 2500 m Onset within 4–24 hr after ascent Dull or pulsating bifrontal, temporal, or diffuse headache, often worsened by movement	Allow time for proper acclimatization For moderate- or high-risk ascent profiles: acetazolamide, 125 mg every 12 hr, or dexamethasone, 2 mg every 6 hr	Stop ascent and rest at current elevation NSAIDs or acetaminophen Consider dexamethasone (4 mg once) for severe headache If headache persists or worsens, descend or use
Acute mountain sickness Common Onset within 4–24 hr after ascent Headache, anorexia, nausea, and/or fatigue Headache may be severe and may persist Normal neurologic status	The NEW ENGLAND JOURNAL of MEDICINE REVIEW ARTICLE C. Corey Hardin, M.D., Ph.D., Editor	
High-altitude cerebral edema Unusual but can be fatal Onset within 1–3 days after ascent Global neurologic deficits Status, ataxia, or both; focal neurologic deficits uncommon Can progress to coma	Medical Conditions and High-Altitude Travel N ENGL J MED 386;4 NEJM.ORG JANUARY 27, 2022	
High-altitude pulmonary edema Unusual below 3000 m Onset 2–4 days after ascent Early signs: increasing dyspnea with activity, decreased exercise performance, dry cough Late signs: dyspnea with simple activities or at rest, cyanosis, cough with pink frothy sputum, respiratory distress	Allow time for proper acclimatization Sustained-release nifedipine, 30 mg every 12 hr, for travelers with history of high-altitude pulmonary edema	In resource-limited settings: descend if feasible; otherwise, use supplemental oxygen or portable hyperbaric chamber Sustained-release nifedipine, 30 mg every 12 hr if oxygen is not feasible In well-resourced settings, supplemental oxygen and



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High altitude headache

- **Presents at 2500 m, within 4-24 hours of ascent**
- **Symptoms:** Dull, pulsating, temporal, bifrontal, or diffuse; worse w/ movement
- **Prevention:** allow time for acclimatization, acetazolamide 125 mg Q12H, dexamethasone 2 mg q6H
- **Treatment:** stop at current elevation, rest, NSAIDs
- **Severe symptoms:** dexamethasone 4 mg x1, descend to lower altitude, oxygen

Recognize clinical syndromes of altitude-related sleep disturbances
Differentiate between acute mountain sickness, high-altitude periodic breathing, and central sleep apnea

Acute mountain sickness

- **Common above 2500 m, 1-2 days after ascent**
- **Symptoms:** Headache, plus at least 1:
 - Poor appetite, nausea, vomiting, lethargy, lightheadedness
- **Prevention:** allow time for acclimatization, acetazolamide 125 mg Q12H, dexamethasone 2 mg q6H
- **Treatment:** stop at current elevation, rest, NSAIDs, acetaminophen, antiemetics
- **Mild symptoms:** acetazolamide 250 mg q12H
- **Severe symptoms:** dexamethasone 4 mg q6H x1 day, plus acetazolamide, descend to lower altitude, oxygen

Recognize clinical syndromes of altitude-related sleep disturbances
Differentiate between acute mountain sickness, high-altitude periodic breathing, and central sleep apnea

High altitude cerebral edema (HACE)

- **Uncommon below 3500 m, a few days after ascent**
- **Symptoms:** Preceded by acute mountain sickness, followed by altered mental status +/- ataxia (global encephalopathy) → can progress to coma
- Focal neurological deficits uncommon
- **Prevention:** allow time for acclimatization, acetazolamide 125 mg Q12H, dexamethasone 2 mg q6H
- **Treatment:** descend to lower altitude, supplemental oxygen, hyperbaric chamber
- Dexamethasone 8 mg x1 day, then 4 mg q6H until descent achieved or symptoms resolve

Recognize clinical syndromes of altitude-related sleep disturbances
Differentiate between acute mountain sickness, high-altitude periodic breathing, and central sleep apnea

High altitude pulmonary edema (HAPE)

- **Uncommon below 3000 m, 2-4 days after ascent**
- **Symptoms:** Early signs include dyspnea with exertion, decreased exercise capacity, dry cough
- Late: dyspnea at rest, cyanosis, pink frothy sputum, respiratory distress
- **Prevention:** allow time for acclimatization, sustained release nifedipine 30 mg q12H for individuals with history of altitude pulmonary edema
- **Treatment:** descend to lower altitude, supplemental oxygen, rest, hyperbaric chamber, sustained release nifedipine 30 mg q12H if unable to descend or apply oxygen

Recognize clinical syndromes of altitude-related sleep disturbances
Differentiate between acute mountain sickness, high-altitude periodic breathing, and central sleep apnea

Central sleep apnea

- **Common above 2500 m, first night after ascent**
- **Symptoms:** reduced sleep quality, frequent awakenings, panic upon awakening common
- **Prevention:** Prophylaxis generally unnecessary, but can use acetazolamide 125 mg q12H or nocturnal oxygen
- **Treatment:** Treatment reserved for severe sleep disruption impacting daytime symptoms
- Acetazolamide 125 mg q12H, nocturnal oxygen improve CSA
- Hypnotics such as zolpidem, zaleplon, temazepam may improve perceived sleep quality but does not reduce CSA

Recognize clinical syndromes of altitude-related sleep disturbances
Identify risk factors that predispose individuals to sleep-disordered breathing and other medical conditions at altitude

- **Conditions contraindicated above 2500m**
 - Sickle cell disease
 - Inadequately controlled coronary artery disease or heart failure
 - High-risk pregnancy
 - Advanced lung diseases
- Note that **obstructive sleep apnea** is not a contraindication
 - Continue treatment with CPAP or OAT
 - Central apneas are likely to be present on PAP downloads
 - Exaggerated hypoxemia with apneas
 - Consider acetazolamide

Table 2. Contraindications to Travel above 2500 m.*

Advanced COPD (FEV_1 <30% of predicted value or requirement for continuous oxygen therapy)
Advanced cystic fibrosis (FEV_1 <30% of predicted value)
Advanced restrictive lung disease (TLC <50% of predicted value or requirement for continuous oxygen therapy)
Decompensated heart failure
High-risk pregnancy
Myocardial infarction or stroke within the past 90 days
Poorly controlled seizure disorder
Pulmonary hypertension (systolic PAP >60 mm Hg)
Sickle cell disease
Unstable angina
Untreated, high-risk cerebrovascular abnormality (aneurysm or arteriovenous malformation)

* COPD denotes chronic obstructive pulmonary disease, FEV_1 forced expiratory volume in 1 second, PAP pulmonary-artery pressure, and TLC total lung capacity.



Arapahoe Basin (A-Basin)
Summit County, CO
Base: 10,520 to 10,780 ft
Summit: 13,050 ft (3,980m)

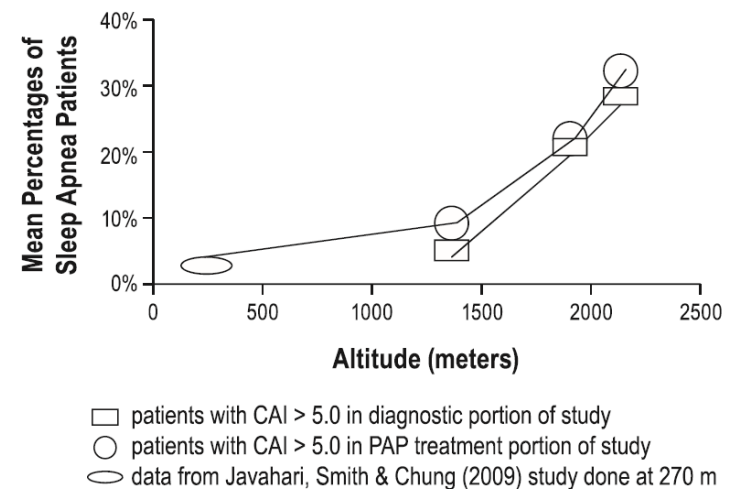
Review diagnostic approaches

Discuss the role of polysomnography and portable sleep testing at altitude

Understand challenges in interpretation of sleep studies under hypoxic conditions

- Mountain West Study evaluated OSA and CAI at Altitude
- 450 patients living at 3 different altitudes
- Split night study
- Increasing % with CAI > 5 with increasing altitude
- Similar susceptibility to CAI in diagnostic and treatment

Figure 1—Comparison of mean percentages of sleep apnea patients with CAI > 5.0 in diagnostic portion of study and CAI > 5.0 in PAP treatment portion of study graphed versus altitude (including treatment data from Javaheri, Smith & Chung [2009] study done at 270 m)



Pagel et al. **Effects of Altitude Associated Central Apnea on the Diagnosis and Treatment of Obstructive Sleep Apnea: Comparative Data from Three Different Altitude Locations in the Mountain West.** J Clin Sleep Med 2011 Dec 15; 7(6): 610–615

Review diagnostic approaches

Discuss the role of polysomnography and portable sleep testing at altitude

Understand challenges in interpretation of sleep studies under hypoxic conditions

Table 1—Site comparison

Altitude, meters (Site)	N	%	Community Population	Lab Beds	Site	Monitor System	Age (SD)	% Female	BMI (SD)
1421 (1)	150	34	145000	6	Hosp	Embla	58.34 (10.3)	36.4	34.98 (8.0)
1808 (2)	150	34	425000	4	IMRT	Alice-5	55.26 (9.61)	33.1	33.34 (6.82)
2165 (3)	142	32	8500	2	Hosp	Alice-5	62.34 (9.50)	35.2	32.74 (6.63)
Sig dif.							p = 0.01		

Data are shown as means.

Table 2—Comparison of initial split-night study data between sites

Altitude, meters (Site)	N	AHI (SD)	Low SpO ₂ (SD)	% CAI > 5.0 in Dx portion	Split-night titration adequacy (SD)	% CAI > 5.0 in Tx portion	Split-night titration rated adequate or unacceptable & 2nd titration requested	# Having second titration
1421 (1)	150	45.8 (29.7)	73.5 (11.3)	4.7	1.44 (0.82)	4.1	9/150 (6%)	4/150 (3%)
1808 (2)	150	50.1 (35.05)	75.5 (10.7)	22.7	1.57 (0.96)	22.6	26/150 (17%)	12/150 (8%)
2165 (3)	142	46.7 (26.8)	74.2 (9.61)	33.8	1.78 (1.025)	38.7	33/142 (23%)	15/142 (11%)
Sig. dif.				3 > 1 (p < 0.05)	3 > 1 (p < 0.01)	3 > 1 (p = 0.01) 2 > 1 (p = 0.02)	3 > 1 (p = 0.01) 2 > 1 (p = 0.02)	p = 0.025

Analysis of covariance comparing titration adequacy across 3 altitude levels, controlling for age, was significant for the effect of altitude; p = 0.017.

Pagel et al. **Effects of Altitude Associated Central Apnea on the Diagnosis and Treatment of Obstructive Sleep Apnea: Comparative Data from Three Different Altitude Locations in the Mountain West.** J Clin Sleep Med 2011 Dec 15; 7(6): 610–615



Haleakalā summit
Haleakalā National Park, Maui, HI
10,023 feet (3,055 meters)

Explore therapeutic strategies

Evaluate evidence-based interventions (acetazolamide, supplemental oxygen, CPAP, ASV)

CPAP

- 10 OSA patients evaluated at both 1,320 m and 2,750 m simulated altitude on stable CPAP (median 10 cmH₂O)
- Underwent PSGs on PAP at both altitudes
- AHI was higher (11 vs. 2 events/h; P , 0.01)
- Mean oxygen saturations were lower (88 vs. 93%; P , 0.01)
- Conclusion: PAP at same settings may not be as effective initially, CSA may dominate OSA at altitude



A multiplace hyperbaric/hypobaric chamber

Grissom et al Ann Am Thorac Soc Vol 12, No 7, pp 1072–1078, Jul 2015

Explore therapeutic strategies

Evaluate evidence-based interventions (acetazolamide, supplemental oxygen, CPAP, ASV)

Acetazolamide

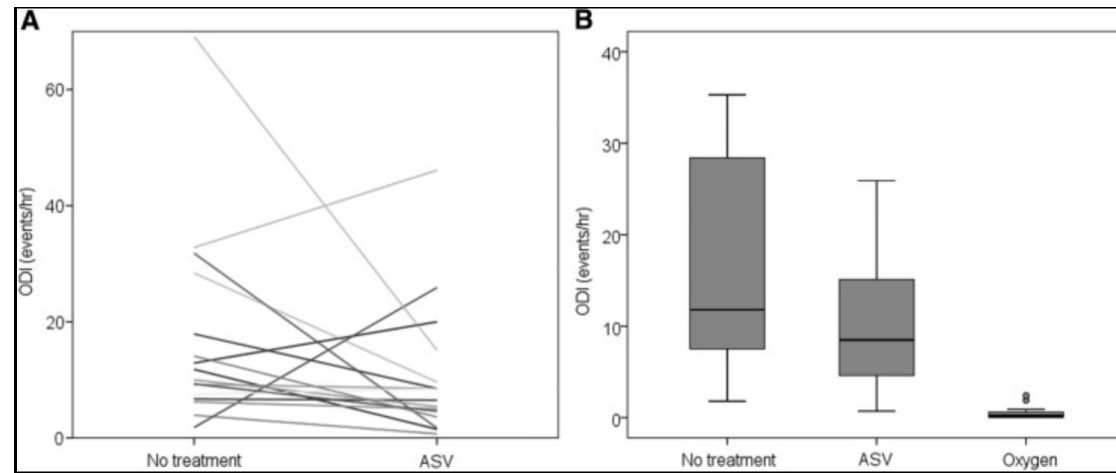
- Carbonic anhydrase inhibitor
- Respiratory stimulant via metabolic acidosis (renal excretion of bicarbonate) and hyperventilation
- Improves mean level of arterial oxygenation and reduces periodic breathing
- Prophylactic dosing: 125 mg BID (24H before ascent, continued 2 days after sleeping highest altitude)
- **Malhotra et al Acetazolamide for OSA and Central Sleep Apnea: A Comprehensive Systematic Review and Meta-Analysis. Chest. 2020 Dec;158(6):2632-2645.**
 - **28 studies**
 - **Showed that AHI was improved by 37.7%** with improved oxygen saturation nadir, with greater efficacy at higher doses (up to 500 mg/day)
- Side effects: paresthesias (most commonly in the hands and feet), impaired taste of carbonated beverages, gastrointestinal symptoms, tinnitus, metabolic acidosis, electrolyte imbalance, drowsiness, and increased nocturnal diuresis

Explore therapeutic strategies

Evaluate evidence-based interventions (acetazolamide, supplemental oxygen, CPAP, ASV)

Low flow supplemental oxygen

- Reduces hypoxic drive:** PaO_2 stays higher, so carotid body chemoreceptors are less activated
- Stabilizes ventilation:** With reduced hypoxic sensitivity, the ventilatory control system is less "over-reactive"
- Raises CO_2 closer to apneic threshold:** Breathing doesn't overshoot as much, so PaCO_2 doesn't dip below the apneic threshold
- Suppresses central apneas & periodic breathing:** Ventilation becomes more steady, oxygen desaturation cycles are prevented



Orr, et al. Adaptive Servoventilation as Treatment for Central Sleep Apnea Due to High-Altitude Periodic Breathing in Nonacclimatized Healthy Individuals. High Alt Med Biol. 2018;19(2):178-84

Explore therapeutic strategies

Evaluate evidence-based interventions (acetazolamide, supplemental oxygen, CPAP, ASV)

Hypnotics (temazepam, zolpidem, zaleplon)

- Several studies exist examining the effects of the above at altitude
- Impact:
 - Shortened sleep latency
 - Decreased arousals
 - Increased sleep efficiency
 - Increased REM sleep
 - **No significant impact on respiratory pattern, SaO₂, daytime cognitive or physical performance**
- Possibility of cognitive dysfunction and balance during early awakenings due to prolonged half life

Explore therapeutic strategies

Discuss non-pharmacologic measures (staged ascent, acclimatization strategies, behavioral modifications)

- Staged gradual ascent can blunt sleep-related symptoms and acute mountain sickness
 - Spending 6–7 days at moderate altitude (2,200–3,000 m) before ascending higher should allow physiological adaptation and reduce the risk of acute mountain sickness (AMS) and high-altitude cerebral edema (HACE)

Am Fam Physician. 2020;101(8):505-507

Explore therapeutic strategies

Discuss non-pharmacologic measures (staged ascent, acclimatization strategies, behavioral modifications)

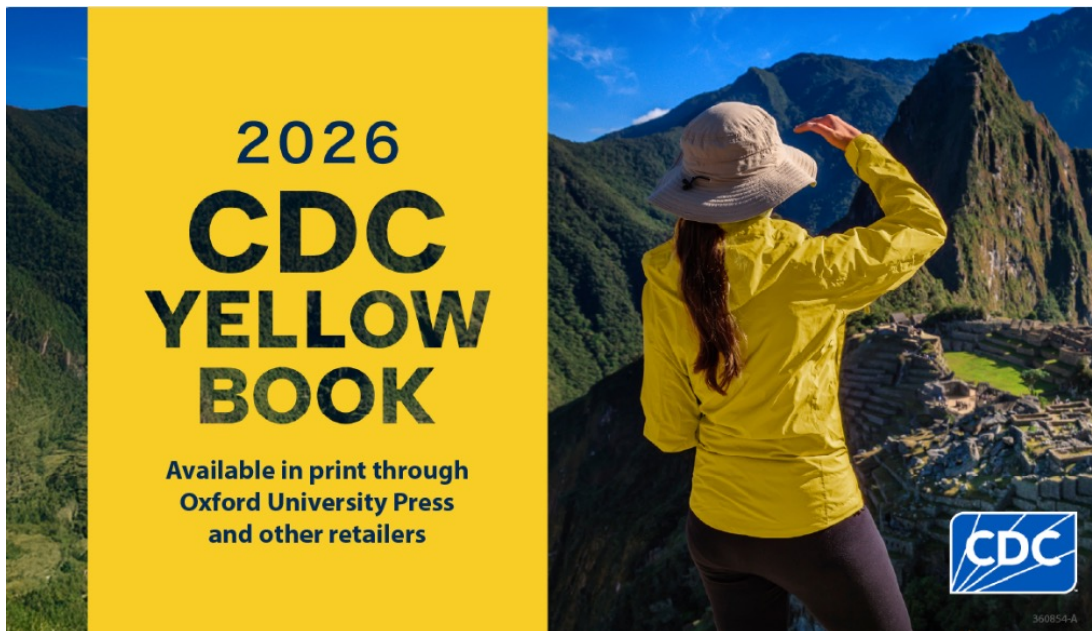
- Maintaining adequate hydration is advised, as dehydration symptoms can mimic AMS
- Short-term supplemental oxygen (such as oxygen bars or prefilled canisters) or over-the-counter products (e.g., powdered drink mixes) for prevention of AMS is controversial
 - Mixed to low/no significant evidence

Am Fam Physician. 2020;101(8):505-507

Explore therapeutic strategies

Discuss non-pharmacologic measures (staged ascent, acclimatization strategies, behavioral modifications)

- Behavioral recommendations also include avoiding alcohol for the first 48 hours at altitude, maintaining regular caffeine intake for habitual users, and limiting strenuous exercise during the initial acclimatization period



Explore therapeutic strategies

Table 2—Summary of recommendations.

Intervention	Recommendation	Overall Certainty of the Evidence	Population
CPAP versus no CPAP	Conditional for	⊕⊕○○	- Primary CSA - CSA due to heart failure - CSA due to medication or substance use - Treatment-emergent CSA - CSA due to a medical condition or disorder
BPAP with a backup rate versus no BPAP with a backup rate	Conditional for	⊕○○○	- Primary CSA - CSA due to medication or substance use - Treatment-emergent CSA - CSA due to a medical condition or disorder
BPAP without a backup rate	Conditional against	⊕○○○	- Primary CSA - CSA due to heart failure - CSA due to medication or substance use - Treatment-emergent CSA - CSA due to a medical condition or disorder
ASV versus no ASV	Conditional for	⊕⊕○○	- Primary CSA - CSA due to heart failure - CSA due to medication or substance use - Treatment-emergent CSA - CSA due to a medical condition or disorder
Low-flow oxygen versus no low-flow oxygen	Conditional for	⊕⊕○○	CSA due to heart failure
Low-flow oxygen versus no low-flow oxygen	Conditional for	⊕○○○	High altitude*
Acetazolamide versus no acetazolamide	Conditional for	⊕⊕○○	- Primary CSA - CSA due to heart failure - CSA due to medication or substance use - Treatment-emergent CSA - CSA due to a medical condition or disorder
Acetazolamide versus no acetazolamide	Conditional for	⊕○○○	High altitude*
TPNS versus no TPNS	Conditional for	⊕○○○	- Primary CSA - CSA due to heart failure

*Recent ascent to high altitude (at least 2,500 meters [8,202 feet]).

GRADE certainty of evidence: ⊕⊕○○ = low, ⊕○○○ = very low.

CSA = central sleep apnea, CPAP = continuous positive airway pressure, ASV = adaptive servo ventilation, BPAP = bilevel positive airway pressure, TPNS = transvenous phrenic nerve stimulation.

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Treatment of central sleep apnea in adults: an American Academy of Sleep Medicine clinical practice guideline

M. Safwan Badr, MD, MBA, Rami N. Khayat, MD, J. Shirine Allam, MD, Suzanne Hyer, PhD, RN, Reem A. Mustafa, MD, MPH, PhD, Matthew T. Naughton, MBBS, MD, FRACP, ATSF, FERS, Susheel Patil, MD, PhD, FAASM, Grace Pien, MD, MSCE, Winfried Randerath, MD, FAASM, Christine Won, MD, MSc [SEE FEWER AUTHORS](#) ^

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Summary

- Hypobaric hypoxia induced respiratory changes can present at 5000 ft but become more severe at 9000 ft
- When traveling to high altitudes, sleep fragmentation occurs in the first several days acutely with reduced N3 and REM sleep
- Sleep disordered breathing increases with increasing altitude
- OSA likely worsens acutely with altitude
- Severe OSA at altitude is generally dominated by severe CSA
- Acetazolamide appears to be affective in CSA due to altitude
- Low flow oxygen may be beneficial as well
- Sedatives may improve sleep quality, but do not improve sleep breathing