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Physiology and pathophysiology at high altitude: considerations for the anesthesiologist

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Abstract
Millions of people live in, work in, and travel to areas of high altitude (HA). Skiers, trekkers, and mountaineers reach altitudes of 2500 m to more than 8000 m for recreation, and sudden ascents to high altitude without the benefits of acclimatization are increasingly common. HA significantly affects the human body, especially the cardiovascular and pulmonary systems, because of oxygen deprivation due to decreased ambient barometric pressure. Rapid ascents may lead to high-altitude diseases that sometimes have fatal consequences. Other factors, such as severe cold, dehydration, high winds, and intense solar radiation, increase the morbidity of patients at HA. Anesthesiologists working in or visiting areas of higher elevations should become familiar with the human physiology, altered pharmacology, and disease pattern of HA.

Key words High altitude · High altitude illness · Hypoxia · Hypoxic pulmonary vasoconstriction

Introduction

With an ever-growing world population, areas of high altitude (HA) are becoming increasingly inhabited. HA is defined as an elevation of 2700–5500 m above sea level, while extreme altitudes have an elevation beyond 5500 m [1]. More than 140 million people live above 2500 m, and millions more are visiting regions of HA every year, many of whom will require medical attention [2]. Moreover, many tourists, including anesthesiologists, are enjoying an open world to travel to higher elevations for skiing or hiking, or to become members on mountaineering expeditions to remote areas. Air travel has steadily increased, with an estimated 679 million people traveling on United States flights in 2008, exposing the passengers to a cabin altitude pressure of an equivalent of 2440 m (8000 feet) [3]. New hospitals are being built at higher elevations. Anesthesiologists work in these regions of HA and are faced with significant alterations in human physiology and the potentially unfamiliar pathophysiology of high-altitude illness (HAI), which is a set of syndromes that is generally divided into four categories: acute mountain sickness (AMS), high-altitude cerebral edema (HACE), high-altitude pulmonary edema (HAPE), and chronic mountain sickness (CMS).

There are many circumstances in which anesthesiologists might be challenged to take care of patients at HA. Anesthesia might be given electively within the hospital setting or emergently in the field with limited resources. The anesthesiologists' knowledge of pathophysiology and pharmacology and their ability to resuscitate critically ill patients puts them in the front line in HA incidents.

It is therefore important for many anesthesiologists to understand the human physiology and disease pattern at higher elevations and to become familiar with HAI.

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Physiological changes at high altitude

Hypoxia

People ascending to HA enter an environment with low ambient barometric pressure. Although the proportions of oxygen (O_2) and nitrogen (N_2) in the air remain the same, the low air pressure leads to a decrease in the partial pressure of oxygen (P_{O_2}), which makes it difficult for O_2 to diffuse into the lung capillaries, resulting in hypobaric hypoxemia. Table 1 lists the relationship between altitude, barometric pressure, and P_{O_2}. The alveolar P_{O_2}(Pa_{O_2}) can be calculated using the alveolar gas equation:

$$Pa_{O_2} = (F_{I_{O_2}} * (PB - P_{H2O})) - (Pa_{CO_2}/R)$$

Table 1. The relationship between altitude (m/feet[a]) and barometric pressure (P_B), estimated partial pressure of inspired oxygen ($P_{I_{O_2}}$), equivalent of the $P_{I_{O_2}}$ in percent at sea level (Eq $P_{I_{O_2}}$), estimated partial pressure of carbon dioxide (P_{CO_2}), estimated partial pressure of alveolar oxygen, inspired oxygen concentration ($F_{I_{O_2}}$), and the equivalent of the $F_{I_{O_2}}$ at sea level (Eq $F_{I_{O_2}}$) is demonstrated

m	Feet	P_B	$P_{I_{O_2}}$	Eq $P_{I_{O_2}}$ % at sea level	P_{CO_2}	Pa_{O_2}	$F_{I_{O_2}}$ %	Eq $F_{I_{O_2}}$ % at sea level
Sea level	Sea level	760	149	100	40	100	20.9	20.9
1000	3281	679	132	89	40	83	20.9	18.5
2000	6562	605	117	79	35	74	20.9	16.4
3000	9843	537	103	69	30	65	20.9	14.4
4000	13123	475	88	60	25	58	20.9	12.6
5000	16404	420	78	52	20	53	20.9	10.9
6000	19685	369	68	46	17.5	46	20.9	9.5
7000	22966	324	58	40	15	39	20.9	8.1
8000	26247	284	50	34	10	37	20.9	6.9
8850	29035	253	43	29	7.5	34	20.9	6.0
9000	29528	248	42	28	7	33	20.9	5.9
10000	32808	215	35	24	5	29	20.9	4.9

[a] Feet = m/3.2808

The $F_{I_{O_2}}$ is the concentration of inspired oxygen (~21% in dry atmospheric gas). The given pressure at sea level is due to atmospheric pressure (P_B = 760 mmHg) minus the partial pressure of water vapor (P_{H2O} = 47 mmHg), as alveolar gas is completely saturated with water. Pa_{CO_2} is the alveolar partial pressure of carbon dioxide (assumed to be equal to the measured arterial P_{CO_2}). R is the respiratory quotient (normally about 0.8). At sea level the equation is familiar:

$$Pa_{O_2} = 0.21(760\text{-}47) - 40/0.8 = 149.73\text{-}50 = 99.73 \text{ mmHg}$$

Conversely, on the summit of Mt. Everest the equation changes to:

$$Pa_{O_2} = 0.21(253\text{-}47) - 7.5/0.8 = 43.26\text{-}8.375 = 33.89 \text{ mmHg}$$

The calculated inspired P_{O_2} on top of Mt. Everest (8850 m/29035 feet) is less than 30% of its sea-level value, and life at the summit is sustainable only because of significant hyperventilation (P_{CO_2} = 7.5 mmHg), as reported by West [4]. In a recent study the mean Pa_{O_2} in subjects breathing ambient air was 24.6 mmHg at 8400 m (27559 feet) while the barometric pressure was 272 mmHg. The mean Pa_{CO_2} at rest was 13.3 mmHg [5].

Hypoxia at HA can be relieved by supplemental oxygen, or by increasing the barometric pressure in a pressure chamber or a portable pressure bag (Gamow bag) [6,7], and by descending to lower altitudes [4]. An increase of the $F_{I_{O_2}}$ to ~70 % would increase the Pa_{O_2} on top of Mt. Everest to values found at sea level (Fig. 1).

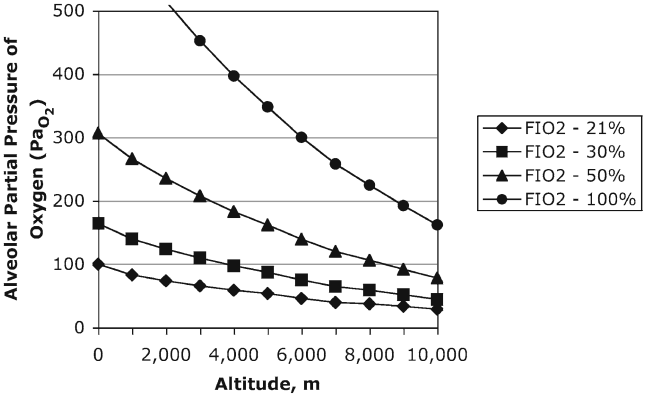

Fig. 1. An increase in inspired oxygen concentration ($F_{I_{O_2}}$) leads to significant improvement of the alveolar partial pressure of oxygen (Pa_{O_2}) at different altitudes

Physiological responses to HA hypoxia and acclimatization

Lack of O_2 at HA generally triggers physiological mechanisms, known as acclimatization, to improve O_2 transport and O_2 utilization. Particularly, respiratory, cardiovascular, and hematological adjustments occur. Genes coding for proteins involved in oxygen transport, growth of blood vessels, and erythropoiesis are activated [1].

Respiratory responses

An essential adaptation to acute HA hypoxia is hyperventilation [8,9]. The increase in respiratory rate and to a lesser degree the depth of breathing depends mainly on the stimulation of chemoreceptors within the carotid body, which are activated by changes in arterial blood O_2 concentration and relay sensory information to the brainstem [4,10,11]. Hyperventilation increases the alveolar and hence arterial P_{O_2}, as reflected in the alveolar gas equation [1]. Above an altitude of about 7000 m, alveolar P_{O_2} did not decrease further in one report, but remained at a level of about 35 mmHg by increasing hyperventilation [12]. The increase in breathing reduces the alveolar carbon dioxide partial pressure (P_{CO_2}),

which increases the arterial pH. During a climb to the top of Mt. Everest the P_{CO_2} was 7.5 mmHg, serum bicarbonate had decreased from 22.2 to 9.9 mMol, and the pH was 7.56 [13]. The alkaline pH gradually returns toward normal due to the renal excretion of sodium bicarbonate or potassium bicarbonate and this can be accelerated by acetazolamide or other carbonic anhydrase inhibitors [14]. Furthermore, ventilatory acclimatization to hypoxia involves an increase in the hypoxic ventilatory response, as well as a re-setting of the arterial P_{CO_2} "set point" that results in persistent hyperventilation and hypocapnia when normoxia is restored [15]. Conversely, HA residents typically show a blunted hypoxic ventilatory response and tend to have larger lung volumes with increased vital and total lung capacities [15]. This raises lung diffusing capacity and preserves arterial oxygen saturation [16].

Hemoglobin dissociation and polycythemia

At altitudes above 3000 m the arterial P_{O_2} falls into the steep portion of the hemoglobin dissociation curve, resulting in lower hemoglobin O_2 saturation [1]. An alkaline pH shifts the hemoglobin dissociation curve towards the left, which facilitates loading of O_2 in the lung, but decreases unloading of O_2 at the tissue level. Moreover, levels of 2,3-diphosphoglycerate (2,3-DPG) increase rapidly during acute hypoxia and continued to rise in one study during a 3-week sojourn at HA [16]. Increases in 2,3-DPG shift the hemoglobin dissociation curve to the right, allowing for more effective oxygen extraction in the capillaries [17].

Polycythemia develops in response to erythropoietin secretion by kidney cells at HA [9,17]. In one study it took 40 days until complete hematocrit adaptation to 3500 m was achieved and 57 days for an altitude of 8812 m [18]. Therefore, polycythemia does not play a major role in short-term visits to HA, but it does so during chronic adaptation and is a component of CMS [18].

Cardiovascular responses

Systemic blood pressure increases in response to acute hypoxia during early HA adaptation [19]. The enhanced blood pressure response is likely caused by higher activity of arterial chemoreceptors and an increase of the sympathetic nervous tone [20]. In addition, during ascent the heart rate and thus cardiac output is increased to restore the systemic O_2 transport [19,21–23]. The cardiac output tends to decrease again after a few days at HA due to diuresis and a lower plasma volume [24]. Furthermore, the peak heart rate during exhaustive exercise decreases with increasing severity of acute hypoxia in a linear manner up to 6300 m [20,25]. As a consequence of the decreased peak heart rate, the maximal cardiac output is also reduced at HA, resulting in a reduction in maximum oxygen delivery to the tissues [20]. Echocardiography of subjects at simulated extreme HA has demonstrated an improved left ventricular (LV) ejection fraction despite pulmonary hypertension and severe arterial hypoxemia [26,27]. LV systolic function is therefore not limiting the exercise capacity at HA [26].

Cardiac and cerebral blood flow is selectively increased by the direct vasodilatory effects of arterial hypoxia, which may contribute to HACE [28,29]. Hypocarbia-induced cerebral vasoconstriction counteracts this vasodilatation [1]. Increased pulmonary blood flow reduces capillary transit time and may lead to the failure of erythrocytes to fully equilibrate with alveolar gas, worsening arterial hypoxemia [30]. As part of chronic adaptation, Tibetan highlanders were found to achieve normal O_2 delivery by a tenfold increase in circulating nitric oxide (NO) plasma concentration, which leads to vasodilatation and increased tissue blood flow [31].

A relationship exists between exposure to HA, polycythemia, and increased coagulability [32]. Platelets are activated at HA, which leads to platelet aggregation and platelet consumption [32]. A decrease in partial thromboplastin time, and an increase in prothrombin fragments, thrombin-antithrombin complexes, and factor VIIa activity have been reported [33]. A higher incidence of stroke, myocardial infarction, arrhythmia, pulmonary thromboembolism, and sudden cardiac death at HA has been linked to hypoxia, hypoxia-induced hypercoagulability, and hyperviscosity syndrome [34–37]. Prior myocardial infarction, known coronary artery disease, diabetes, hypercholesterolemia, and deconditioning have been identified as risk factors for sudden cardiac death during mountain hiking [36,38]. Conversely, one study found patients 6 months after cardiac revascularization, who had a normal exercise stress test at sea level, at low cardiac risk during a rapid ascent and submaximal exercise at 3454 m [39].

Hypoxic pulmonary vasoconstriction

Hypoxic pulmonary vasoconstriction (HPV) is a vasomotor response to alveolar hypoxia, brought about by the active vasoconstriction of small, muscular pulmonary arteries (PA), also termed resistance PA [40]. HPV shunts blood from poorly oxygenated areas to better ventilated lung segments, thereby optimizing ventilation-perfusion matching, optimizing systemic O_2 delivery, and reducing shunt fraction [40,41]. Beginning within seconds of hypoxia, HPV plateaus within minutes and may persist for hours after exposure [42]. HPV increases pulmonary vascular resistance by 50%–300% and contributes to significant pulmonary hypertension during global hypoxia, as occurs at HA or in the fetal lung [40,42]. On the other hand, an increase in dispersion of pulmonary blood flow that occurs during exercise at HA may counteract HPV, worsen ventila-

tion-perfusion mismatch, and thus contribute to the development of HAPE [43]. Furthermore, HPV is significantly impaired by hyperventilation and respiratory alkalosis, which reduce pulmonary hypertension [40].

Cerebral function

Noticeable changes caused by HA hypoxia include a decrease in physical and mental performance, increased fatigue, and impaired sleep [44,45]. The detrimental effects of hypoxia on reasoning skills and judgment during acute exposures to extreme HA often persist for several days even after descent to lower altitudes [1]. Anesthesiologists need to be aware that their own mental performance, concentration, and judgment may be altered at HA [44–46]. In one study of healthy volunteers at 5050 m the cerebral oxygen saturation decreased more significantly than in the periphery [47]. Thus, peripheral oxygen saturation monitors might overestimate cerebral oxygen saturation [47]. Magnetic resonance imaging (MRI) in 12 out of 13 climbers who successfully climbed Mt. Everest showed evidence of significant brain damage, including cortical atrophy and irreversible subcortical lesions [48] (Fig. 2).

Cellular function and gene activation

Hypoxemia alters normal cellular function by decreasing the mitochondrial P_{O_2}, the mitochondrial electron transport chain, and the production of adenosine triphosphate (ATP) [4]. O_2 deprivation rapidly reduces the supply of ATP [1]. The activation of oxygen-responsive genes is regulated by the activation of transcriptional factors, which results in the expression of various genes controlling the molecular response to hypoxia [1,49]. Moreover, the cellular response to hypoxia is multifactorial and includes an increase in hypoxia-inducible factor 1 (HIF-1), which regulates cytochrome oxidase subunits to optimize the efficiency of respiration in hypoxic cells [1,50]. O_2 sensors in blood vessels activate the expression of vascular endothelial growth factor-1, which initiates angiogenesis especially in the heart and probably in the brain [51].

Furthermore, hypoxia-induced malnutrition and malabsorption, with subsequent weight loss, is believed to be significant at altitudes of more than 5000 m [52]. Substrate metabolism at HA favors carbohydrate oxidation and thus the body is in greater dependence on blood glucose levels, because carbohydrate oxidation generates more ATP per molecule of O_2 than fat utilization [53].

Fig. 2. Mount Everest, Nepal. High-altitude illness, severe temperature and weather conditions, and poor judgment caused by hypobaric hypoxia have led to the deaths of many mountaineers attempting to reach the top of Mt. Everest. Between 1990–2005, the overall odds of summiting were 30.7% ($n = 722$) and those of dying were 1.5% ($n = 36$). The death rate of mountaineers descending from the summit (2.35%; $n = 17$) was roughly twice that of those who did not summit (1.2%; $P = 0.048$). The total success rate (probability of summiting and surviving) was 29.9% [114]

High-altitude illness (HAI)

The risk of HAI is directly proportional to the rate of ascent and the altitude reached. A gradual ascent to promote acclimatization may be the best strategy to prevent HAI [54]. Guidelines suggest that above an altitude of 2500 m, the altitude at which one sleeps should not be increased by more than 600 m per day and that an extra day should be added for acclimatization for every increase of 600 to 1200 m [54,55]. Treatment strategies for HAI are listed in Table 2.

Acute mountain sickness (AMS) and high-altitude cerebral edema (HACE)

AMS and HACE refer to the cerebral abnormalities of HAI and usually affect people who rapidly ascend to an altitude above 2500 m. According to the Lake Louise AMS symptom score, there are five main symptoms of AMS: headache, gastrointestinal disturbance (anorexia, nausea, and vomiting), dizziness, fatigue, and insomnia [54–56]. Mostly the symptoms remain mild, but in severe cases fluid collects in the brain, causing HACE, a life-threatening acute encephalopathy characterized by ataxia and a depressed level of consciousness [54,57,58]. Although the exact mechanisms of AMS and HACE remain incompletely understood, the pathophysiological process includes hypoxia-induced cerebral vasodilatation, overperfusion of capillaries, capillary leak, vasospasms, and increasing amounts of vasogenic cerebral edema, which can lead to death if left untreated [58,59].

The treatment of HACE is a medical emergency. A rapid reduction in altitude is the single most important

Table 2. Currently recommended treatment options for high-altitude illness

Treatment of high-altitude illness
Mild acute mountain sickness and high-altitude headache • Stop ascent, rest, and acclimatize at same altitude for at least 1 day • Acetazolamide, 125 to 250 mg bid • Symptomatic treatment as necessary with analgesics (aspirin, ibuprofen) and antiemetics • Descend 500 m or more
Moderate to severe acute mountain sickness • Low-flow oxygen, if available • Acetazolamide, 250 mg bid • Consider dexamethasone, 4 mg PO, IM, or IV q6h • Hyperbaric therapy • Descend 500–1000 m
High-altitude cerebral edema • Immediate descent or evacuation • Oxygen, 2 to 4 $l \cdot min^{-1}$ • Dexamethasone, 4 mg PO, IM, or IV q6h • Acetazolamide, 250 mg bid • Hyperbaric therapy • Minimize exertion and keep warm • Consider tracheal intubation to protect airway or if respiration inadequate
High-altitude pulmonary edema • Immediate descent or evacuation • Oxygen, 4 to 6 $l \cdot min^{-1}$ until improving, then 2 to 4 $l \cdot min^{-1}$ • Nifedipine, 10 mg PO q4 h by titration to response, or 10 mg PO once, followed by 30 mg extended release q12 to 24 h • Hyperbaric therapy • Minimize exertion and keep warm • Consider tracheal intubation to protect airway or if respiration inadequate • Nitric oxide therapy if available in an ICU • Tadalafil 10 mg twice daily or sildenafil 50 mg every 8 h are experimental treatments

ICU, intensive care unit

treatment and may be life-saving. A descent of 500 to 1000 m is typically effective for AMS, but HACE may require descent to a much lower altitude. Supplemental O_2 should be administered and the patient should be evacuated to a lower altitude as soon as possible. Use of a pressure chamber or a Gamow bag in the field may be effective [54]. Aspiration is a risk in the Gamow bag, in which the patient is difficult to reach during pressurization, and positioning in the lateral position might be advisable [6,7]. Recommended medical treatment includes dexamethasone (8 mg followed by 4 mg every 6 h) and acetazolamide (250 mg twice daily) [54,60,61]. Diuresis with furosemide and mannitol may be helpful, but these agents are currently not recommended [54,58]. Acetazolamide and, controversially, dexamethasone or ginkgo biloba, may be attempted as prophylaxis against AMS, and aspirin and ibuprofen may decrease the associated headache [14,54,62,63].

High-altitude pulmonary edema (HAPE)

HAPE typically occurs the second night at a higher altitude, but rarely appears after 4 days at a given altitude [54]. HAPE is characterized initially by fatigue, dyspnea, cough, and cyanosis, and progresses to a life-threatening condition if left untreated [54,56,64]. The predominant pathophysiological mechanism of HAPE is excessive, uneven HPV leading to increased pulmonary capillary pressure [64,65]. Inhomogeneous HPV leads to lung areas that are subjected to very high pressure and flow, with mechanical overdistension of pulmonary capillaries and capillary leak [64,66,67]. MRI has demonstrated uneven HPV, particularly in HAPE-susceptible individuals, which is accompanied by a greater increase in pulmonary artery pressure compared with control subjects [66]. Excessive pulmonary capillary pressure leads to the extravasation of fluid, plasma proteins, and blood cells into the interstitial and alveolar spaces [68]. Adult respiratory distress syndrome secondary to HAPE has been described [69]. Chest radiographs and computed tomography scans of early HAPE show a patchy, peripheral distribution of edema. The radiographic appearance is more homogeneous in advanced cases and during recovery [64].

Treatment of HAPE consists of immediate, rapid descent, supplemental oxygen, and hyperbaric therapy [54,60] (see Fig. 3). Pharmacologically, nifedipine (10 mg sublingually, followed by 20 mg of a slow-release pre-

Fig. 3. Khumbu Glacier, Mount Everest National Park, Nepal. Clouds are approaching rapidly, making descent from higher altitudes a difficult and dangerous endeavor

paration every 6 h) and dexamethasone have been recommended for prophylaxis and treatment [54,70,71]. The PA pressure can also be lowered in patients with HAPE by administering acetazolamide, hydralazine, phentolamine, tadalafil, sildenafil, or nitric oxide [54,60,71–74].

Chronic mountain sickness (CMS)

CMS or Monge's syndrome is a public health problem in the Andean populations, as well as in other HA regions of the world. CMS is characterized by severe chronic hypoxemia leading to excessive erythrocytosis (females, hemoglobin 19 $g \cdot dl^{-1}$; males, hemoglobin 21 $g \cdot dl^{-1}$), cyanosis, and significant pulmonary hypertension, which may evolve to cor pulmonale, leading to congestive heart failure (HF) [19,75,76]. Preventive measures include modifying risk factors such as smoking, obesity, air pollution, and lung diseases. Bloodletting and isovolemic hemodilution are palliative procedures [19]. The definite treatment of CMS is descent to lower altitudes, which typically relieves the symptoms [19]. Calcium-channel blockers such as nifedipine and sildenafil, and inhaled NO may reduce pulmonary hypertension in CMS [19].

Anesthesia at high altitude

Anesthesia management at HA depends greatly on the setting in which the anesthetic is given and whether HAI and other coexisting conditions are present. In mountainous regions of the world elective anesthesia is commonly given within hospitals at HA. On the other hand, anesthesia in the field at extreme HA is difficult to administer and should be avoided except for life-threatening situations.

Anesthetics and anesthesia equipment at HA

The effects of volatile anesthetic vapors and nitrous oxide have been studied at decreased ambient pressures [77–82]. The potency of anesthetic gases is proportional to their partial pressure. It has been demonstrated that nitrous oxide causes less analgesia and is a less potent anesthetic at HA, because its concentration remains fixed and its partial pressure decreases as barometric pressure drops [79–80,83]. Therefore, it has been advised to avoid nitrous oxide at HA [62]. Conversely, halothane has been successfully used in a hyperbaric chamber at an equivalent altitude of 5490 m [62]. Moreover, the partial pressure of anesthetic vapors is dependent on temperature, not barometric pressure, and in an extremely cold environment more anesthetic vapor might be required [73,82]. In one study, the delivered concentration of halothane increased with altitude, but its alveolar partial pressure remained constant [81]. Although the concentration of the inspired volatile anesthetic was increased, the anesthetic effect remained unchanged at the given vaporizer setting [81,82]. In other words, halogenated hydrocarbon vapors are delivered at a constant potency at constant temperature irrespective of altitude. Desflurane is the only exception to this rule. Unlike variable-bypass vaporizers, the Datex-Ohmeda (Steeton, UK) Tec 6 and Tec 6 plus vaporizers require manual adjustments of the concentration control dial at altitudes other than sea level to maintain a constant partial pressure of anesthetic [84].

Floating-bobbin or floating-ball gas flow meters are affected by HA. Both O_2 and nitrous oxide flow meters tend to under-read the actual flow rate. It may therefore be hazardous to mix a low flow of O_2 with a higher flow of nitrous oxide [62,81]. An O_2 analyzer calibrated at HA is advisable under these circumstances. While using the O_2 analyzer it needs to be remembered that 21% O_2 becomes a relatively hypoxic mixture at HA (see Table 1). In addition, the decreased gas density and viscosity at HA make some ventilators deliver lower than set tidal volumes during volume control ventilation [85]. Venturi-type facemasks deliver a slightly higher percentage of O_2 at HA when they are calibrated at sea level and are therefore safe to use [81].

Barometric pressure also affects the function of capnographs, which need to be recalibrated at the ambient pressure [86]. Capnograph malfunction is common at HA, possibly due to reduced gas flow rates through the sample chamber, the effect of low barometric pressure on the calibration, or the effect of the reduced barometric pressure on the computer software [86]. Furthermore, significant hyperventilation and low P_{CO_2} levels may make colorimetric P_{CO_2} detectors unreliable [87].

Pressures in an air-filled tracheal tube cuff or within a laryngeal mask airway (LMA) may increase signifi-

cantly during rapid ascent to altitudes commonly experienced during aeromedical transport and may cause ischemic injury to the tracheal or pharyngeal mucosa [88]. Removal of air from the cuff or filling the cuff with water may be indicated [88]. Conversely, cuff pressures may decrease, causing a leak, when a patient is rapidly evacuated to lower altitude. Further challenges of monitoring patients during aeromedical evacuation have been described in detail [85].

Anesthesia management at HA

Supplemental oxygen is the single most important therapy to be administered, because the reduced inspired P_{O_2} at HA increases the risk of perioperative hypoxia. Anesthetics, analgesics, and tranquilizers potentially decrease the ventilatory drive and need to be used with caution. Benzodiazepines impair respiration at HA at doses that have insignificant effects on respiration at low altitude [89,90]. Similar results were demonstrated after 50 g alcohol at moderate altitude [91]. These reports found an impaired function of peripheral chemoreceptors in the carotid bodies under the influence of sedating substances at altitude. Low-dose ketamine resulted in sustained apnea, possibly by central medullary chemoreceptor impairment, in one report [92]. Conversely, one small study of 11 patients at 3840 m found that low-dose ketamine (~2.0 $mg \cdot kg^{-1}$) with midazolam produced dissociative anesthesia that did not depress the hypoxic respiratory drive significantly, nor did it interfere with the pharyngeal or laryngeal reflexes [93]. Supplemental O_2 had to be administered to 3 of these 11 patients when the O_2 saturation fell below 80% and was not corrected by a jaw thrust or stimulation [93]. Maharjan [94] suggest that ketamine anesthesia for cleft lip repair is practical and cost-effective in remote areas in Nepal. On the other hand the pharmacologic effects of ketamine and nitrous oxide may enhance pulmonary vascular resistance and, theoretically, worsen HAPE [80,95].

Puri et al. [83] reported a significantly higher need for intravenous propofol to achieve a similar target bispectral index (BIS) during induction of HA residents at 3505 m altitude compared to lowlanders at 304 m. Moreover, the study concluded propofol anesthesia to be safe at HA [83]. Unfortunately, propofol has not been studied in newcomers to HA. In addition, Puri et al. [83] found a normal blood pressure response to skin incision in natives to HA, but an attenuated heart rate response to the stresses of endotracheal intubation and surgical incision in the same group, compared to patients at low altitude.

Desaturation following induction of anesthesia and apnea is more rapid at HA, because the O_2 reservoir in the lungs' functional residual capacity is decreased [96]. Anesthetics should be carefully titrated to effect during induction and maintenance of anesthesia because of variable effects of the anesthesia drugs at HA [62,83,89,90,92–94,97]. Both narcotic analgesics and anesthetics blunt the hypoxic ventilatory drive and may therefore precipitate hypoxia during spontaneous ventilation [83,89]. An anesthetic technique that is least likely to suppress ventilation should be chosen, especially in remote locations where perioperative monitoring and supplemental O_2 may not be readily available. Prior to the induction of anesthesia a chest radiograph can give valuable information about HAPE [64].

All patients need to be deemed at risk for aspiration and rapid sequence induction and full stomach precautions should be considered, because gastric emptying is significantly delayed at HA [98,99]. Glucose levels should be checked because HA may increase glucose consumption [53].

Maintenance of temperature homeostasis can be challenging at HA. Hypothermia can be a leading cause of coagulopathy and hypothermia-induced vasoconstriction can mask hypovolemia [100,101]. Frostbite, a severe form of cold injury, is common at HA. Frostbite damage is caused by cellular ice crystal formation with cellular dehydration and microvascular occlusion [101]. Because repeated bouts of freezing and thawing worsen the injury, it is best to begin rewarming after removing the patient from the cold environment. The operating room should be warm upon arrival of the patient. Intravenous (IV) fluids should be warmed, warm-water baths should be prepared for areas of frostbite, and warming blankets applied [101]. Humidification of inspired gases reduces evaporative heat loss and helps to warm the patient. Furthermore, heated peritoneal, bladder, or colonic lavage, and extracorporeal circulatory rewarming may be applied [101,102]. Patients with significant hypothermia and frostbite need to be monitored carefully during rewarming, because of potential cardiac arrhythmia due to cold blood returning to the heart and peripheral vasodilation leading to hypotension and shock [100,101]. Once started, rapid rewarming is the goal. Excessive heat is often disastrous and should be avoided [101].

Fluid management can also be a challenge. Hypobaric hypoxemia elevates the set point of the plasma osmolality-to-plasma vasopressin relationship, thereby causing hypovolemia and hyperosmolarity [24]. In addition, aldosterone secretion is decreased, mediated through the release of atrial natriuretic factor (ANF). The interaction of these two hormones results in enhanced renal salt and water excretion, worsening hypovolemia during hypoxemic conditions [103]. Hypovolemia may also be caused by insufficient water intake, a dry environment, and prolonged sun expo-

sure. A fluid bolus may therefore be necessary before the induction of anesthesia in the hypovolemic patient. On the other hand, fluid overload must be avoided because of the potential of worsening respiratory status in patients with HAPE, whereas suboptimal resuscitation may exacerbate tissue hypoperfusion [104,105]. Fluid therapy should be geared to maintain renal perfusion, especially in patients with crush injury, in order to avoid myoglobin-induced renal failure [106]. In addition, IV lines should be completely cleared of air bubbles, because right-to-left shunts develop frequently through a patent foramen ovale (PFO) in the setting of pulmonary vasoconstriction [107]. A PFO was found to be four to five times more frequent in subjects with HAPE than in those without, and the size of the PFO was directly related to the hypoxemia [108].

Antithrombotic prophylaxis should be strongly considered for postsurgical patients or for those with a septal defect such as PFO, because hypercoagulability produced as a result of acclimatization to HA increases risk for stroke, transient ischemic attacks, and deep venous thrombosis [40]. No surgical or anesthetic complications were encountered during simple cardiac surgical procedures such as ligation of a patent ductus arteriosus at HA [109]. On the other hand, the reduction in the ambient P_{O_2} has a significant deleterious effect on the performance of oxygenators used for cardiopulmonary bypass. One retrospective study evaluated the efficiency and reliability of oxygenators at an altitude of 5200 feet [110]. During hypothermia, the authors found all of the oxygenators used provided safe oxygenation of all patients. However, during the rewarming phase, the low barometric pressure became a critical factor for adequate oxygenation. The study concluded an oxygenator should have a low priming volume, low pressure drop, and sufficient gas transfer to provide safe oxygenation at HA [110].

Regional anesthesia at HA

Regional anesthesia techniques at HA have been reported to be feasible, with onset and offset times for sensory and motor effects similar to those seen with these techniques performed at sea level [82,111,112]. Care needs be taken not to cause phrenic nerve paresis during interscalene brachial plexus, stellate ganglion, and supra- and infraclavicular nerve blocks, because diaphragmatic paralysis or lung injury may lead to respiratory decompensation [112,113]. Safar and Tenicela [78] reported, in 1964, a high incidence of post-dural puncture headache following spinal anesthesia at HA. No recent data regarding the safety and feasibility of neuraxial anesthesia at HA are available.

Conclusion

Anesthesiologists routinely manage critically ill patients and trauma victims. Their detailed knowledge of pathophysiology and pharmacology and their ability to resuscitate and manage the airway of seriously ill patients are factors that make anesthesiologists well prepared in coping with HA incidents. Anesthesiologists working in and traveling to regions of HA need to be familiar with the physiological and pathophysiological changes that occur in response to hypobaric hypoxia. The anesthesiologist's main concern is to maintain adequate respiratory gas exchange, to maintain adequate circulation, and to preserve central nervous system function. If either HAPE or HACE is present supplemental O_2, rapid descent to a lower altitude, or hyperbaric therapy may be life-saving.

Anesthesia management highly depends on available resources as well as on the patient's injuries and type of surgery. Because all anesthetics and opiates potentially depress the respiratory drive, an anesthetic technique that is least likely to suppress ventilation should be applied in locations where perioperative monitoring and supplemental O_2 may not be readily available.

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