PART 1

Mountain Medicine

CHAPTER 1

High-Altitude Physiology

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More than 40 million tourists visit recreation areas above 2400 meters (m), or 7874 feet, in the American West each year. Hundreds of thousands visit central and south Asia, Africa, and South America, many traveling to altitudes above 4000 m (13,123 feet). In addition, millions of persons live in large cities above 3000 m (9843 feet) in South America and Asia. The population in the Rocky Mountains of North America has doubled in the past decade; 700,000 persons live above 2500 m (8202 feet) in Colorado alone. Increasingly, physicians and other health care providers are confronted with questions of prevention and treatment of high-altitude medical problems, as well as the effects of altitude on pre existing medical conditions. Despite advances in high-altitude medicine, significant morbidity and mortality persist. Clearly, better education of the population at risk and those advising them is essential.

High-altitude medicine and physiology are discussed in the first three chapters of this textbook. In this chapter the reader is introduced to the basic physiology of high-altitude exposure. Chapter 2 describes the pathophysiology, recognition, management, and prevention of altitude illnesses and other clinical issues likely to be encountered in both "lowlanders" and high-altitude residents. Chapter 3 focuses on patients with preexisting medical problems who travel to high altitudes (Box 1-1).

DEFINITIONS

HIGH ALTITUDE (1500 to 3500 meters [4921 to 11,483 feet])

The onset of physiologic effects of diminished partial pressure of inspired oxygen (P_{IO_2}) includes decreased exercise performance and increased ventilation (lower arterial carbon dioxide partial pressure [Pa_{CO_2}]). Minor impairment exists in arterial oxygen transport (arterial oxygen saturation [Sa_{O_2}] at least 90%), but arterial oxygen partial pressure (Pa_{O_2}) is significantly diminished. Because of the large number of people who ascend rapidly to 2500 to 3500 m (8202 to 11,483 feet), high-altitude illness is common in this range of altitudes (see Chapter 2).

VERY HIGH ALTITUDE (3500 to 5500 meters [11,483 to 18,045 feet])

Maximal Sa_{O_2} falls below 90% as Pa_{O_2} falls below 50 mm Hg (Figure 1-1 and Table 1-1). Extreme hypoxemia may occur during exercise, sleep, and high-altitude pulmonary edema (HAPE) or other acute lung conditions. Severe altitude illness occurs most frequently in this range of altitudes.

EXTREME ALTITUDE (higher than 5500 meters [18,045 feet])

Marked hypoxemia, hypocapnia, and alkalosis characterize extreme altitude. Progressive deterioration of physiologic function eventually outstrips acclimatization. As a result, no permanent human habitation is above 5500 m (18,045 feet). A period of acclimatization is necessary when ascending to extreme altitude; abrupt ascent without supplemental oxygen for other than brief exposures invites severe altitude illness.

THE ENVIRONMENT OF HIGH ALTITUDE

Barometric pressure (P_B) falls with increasing altitude in a logarithmic manner (Table 1-2). Therefore, the partial pressure of oxygen (P_{O_2}, 21% of P_B) also decreases, resulting in the primary insult of high-altitude: hypoxia. At approximately 5800 m (19,029 feet), P_B is one-half that at sea level, and on the summit of Mt Everest (8848 m [29,029 feet]), P_{IO_2} is approximately 28% that at sea level (see Figure 1-1 and Table 1-1).

The relationship of P_B to altitude changes with distance from the equator. Thus, in addition to extreme cold, polar regions afford greater hypoxia at any given altitude. West[90] calculated that P_B on the summit of Mt Everest (27 degrees north latitude [N]) would be about 222 mm Hg instead of 253 mm Hg if Mt Everest were located at the latitude of Denali (62 degrees N). Such a difference, he claims, would be sufficient to render impossible an ascent without supplemental oxygen.

In addition to the role of latitude, fluctuations related to season, weather, and temperature affect the pressure-altitude relationship. Pressure is lower in winter than in summer. A low-pressure trough can reduce pressure 10 mm Hg in one night on Denali, making climbers awaken "physiologically higher" by 200 m (656 feet). The degree of hypoxia is thus directly related to P_B, not solely to geographic altitude.[90]

Temperature decreases with altitude (average of 6.5° C [11.7° F] per 1000 m [3281 feet]), and the effects of cold and hypoxia are generally additive in provoking both cold injuries and HAPE.[59,93] Ultraviolet (UV) light penetration increases approximately 4% per 300-m (984-foot) gain in altitude, increasing the risks for sunburn, skin cancer, and snowblindness. Reflection of sunlight in glacial cirques and on flat glaciers can cause intense radiation of heat in the absence of wind. We have observed temperatures of 40° to 42° C (104° to 107.6° F) in tents on both Mt Everest and Denali. Heat problems, primarily heat exhaustion, are often unrecognized in this usually cold environment. Physiologists have not yet examined the consequences of heat stress or rapid, extreme changes in environmental temperature combined with the hypoxia of high altitude.

Above the snow line is the "high-altitude desert," where water can be obtained only by melting snow or ice. This factor, combined with increased water loss through the lungs from increased respiration and through the skin, typically results in dehydration that may be debilitating. Thus, the high-altitude environment imposes multiple stresses, some of which may contribute to, or may be confused with, the effects of hypoxia.

ACCLIMATIZATION TO HIGH ALTITUDE

Although rapid exposure from sea level to the altitude at the summit of Mt Everest (8848 m [29,029 feet]) causes loss of consciousness in a few minutes and death shortly thereafter, climbers can ascend Mt Everest over a period of weeks without supplemental oxygen because of a process termed *acclimatization*. A complex series of physiologic adjustments increases oxygen delivery to cells and also improves their hypoxic tolerance. The severity of hypoxic stress, rate of onset, and individual physiology determine whether the body successfully acclimatizes or is

BOX 1-1 Glossary of Physiologic Terms*

P_B	Barometric pressure
P_{O_2}	Partial pressure of oxygen
P_{IO_2}	Inspired P_{O_2} (0.21 × [P_B – 47 mm Hg]) (47 mm Hg = vapor pressure of H_2O at 37°C [98.6°F])
P_{AO_2}	P_{O_2} in alveolus
P_{ACO_2}	P_{CO_2} in alveolus
P_{aO_2}	P_{O_2} in arterial blood
P_{aCO_2}	P_{CO_2} in arterial blood
S_{aO_2}	Arterial oxygen saturation (HbO_2 ÷ total Hb × 100)
RQ	Respiratory quotient (CO_2 produced ÷ O_2 consumed)
Alveolar gas equation	$P_{AO_2} = P_{IO_2} - (P_{ACO_2}/RQ)$

*Pressures are expressed as millimeters of mercury (1 mm Hg = 1 torr).

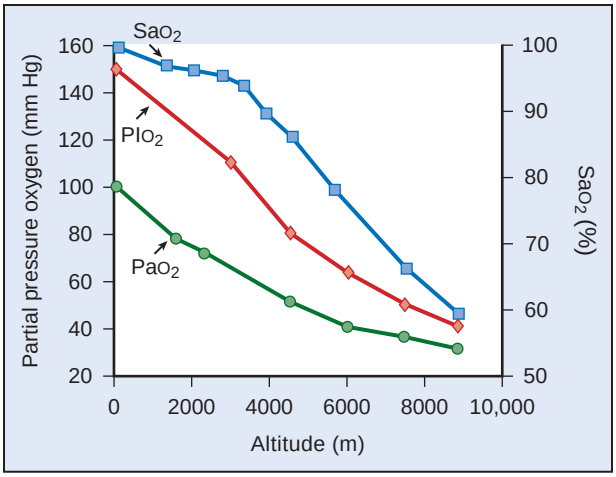

FIGURE 1-1 Increasing altitude results in decreasing inspired oxygen partial pressure (P_{IO_2}), arterial P_{O_2} (P_{aO_2}), and arterial oxygen saturation (S_{aO_2}). Note that the difference between P_{IO_2} and P_{aO_2} narrows at high altitude because of increased ventilation, and that S_{aO_2} is well maintained while awake until over 3000 m (9843 feet). *(Data from Morris A:* Clinical pulmonary function tests: A manual of uniform lab procedures, *Salt Lake City, 1984, Intermountain Thoracic Society; and Sutton JR, Reeves JT, Wagner PD, et al: Operation Everest II: Oxygen transport during exercise at extreme simulated altitude,* J Appl Physiol *64:1309, 1988.)*

overwhelmed. Importantly, acclimatization is the only known means to improve physical and cognitive performance at high altitude.

The recent revolution in our understanding of the molecular mechanisms of human responses to hypoxia has focused on *hypoxia-inducible factor* (HIF). This transcription factor modulates the expression of hundreds of genes, including those involved in apoptosis, angiogenesis, metabolism, cell proliferation, and permeability processes.[20,27,67,69,88] In chronic hypoxia, HIF activation by hypoxia has the positive effect of elevating oxygen delivery by boosting hemoglobin mass. However, HIF also plays a role in carotid body sensitivity to hypoxia, which in turn largely determines the ventilatory response to hypoxia.[55,56,70] As a master regulator of the hypoxia response in humans, HIF has beneficial and harmful effects at different stages during human exposure to hypoxia and in different cells in the body.[36,47] Figure 1-2 provides an overview of some of the hundreds of processes by which the response to hypoxia is modulated by HIF.

Individuals vary in their ability to acclimatize, reflecting certain genetic polymorphisms, including HIF. Some adjust quickly, without discomfort, whereas acute mountain sickness (AMS) develops in others, who go on to recover. A small percentage fail to acclimatize even with gradual exposure over weeks. The tendency to acclimatize well or to become ill is consistent on repeated exposure if rate of ascent and altitude gained are similar, supporting the role of important genetic factors and an individual's predisposition. Successful initial acclimatization protects against altitude illness and improves sleep. Longer-term acclimatization (weeks) primarily improves aerobic exercise ability. These adjustments disappear at a similar rate on descent to low altitude. A few days at low altitude may be sufficient to render a person susceptible to altitude illness, especially HAPE, on reascent. The improved ability to do physical work at high altitude, however, persists for up to 3 weeks.[43,77] Persons who live at high altitude during growth and development appear to realize the maximum benefit of acclimatization changes; for

TABLE 1-1 Arterial Blood Gases and Altitude*

Population	Altitude		P_B (mm Hg)	P_{aO_2} (mm Hg)	S_{aO_2} (%)	P_{aCO_2} (mm Hg)
	Meters	Feet				
Altitude residents	1646[1]	5400	630	73.0 (65.0-83.0)	95.1 (93.0-97.0)	35.6 (30.7-41.8)
Acute exposure	2810[2]	9219	543	60.0 (47.4-73.6)	91.0 (86.6-95.2)	33.9 (31.3-36.5)
	3660[2]	12,008	489	47.6 (42.2-53.0)	84.5 (80.5-89.0)	29.5 (23.5-34.3)
	4700[2]	15,420	429	44.6 (36.4-47.5)	78.0 (70.8-85.0)	27.1 (22.9-34.0)
	5340[2]	17,520	401	43.1 (37.6-50.4)	76.2 (65.4-81.6)	25.7 (21.7-29.7)
	6140[2]	20,144	356	35.0 (26.9-40.1)	65.6 (55.5-73.0)	22.0 (19.2-24.8)
Subacute exposure	6500[3]	21,325	346	41.1 ± 3.3	75.2 ± 6	20 ± 2.8
	7000[3]	22,966	324			
	8000[3]	26,247	284	36.6 ± 2.2	67.8 ± 5	12.5 ± 1.1
	8400[4]	27,559	272	24.6 ± 5.3	54	13.3
	8848[3]	29,029	253	30.3 ± 2.1	58 ± 4.5	11.2 ± 1.7
	8848[5]	29,029	253	30.6 ± 1.4		11.9 ± 1.4

[1]Data from Loeppky JA, Caprihan A, Luft UC: VA/Q inequality during clinical hypoxemia and its alterations. In: Shiraki K, Yousef MK, editors. *Man in stressful environments,* Springfield, Ill, 1987, Thomas; pp 199-232.
[2]Data from McFarland RA, Dill DB: A comparative study of the effects of reduced oxygen pressure on man during acclimatization, *J Aviat Med* 9:18-44, 1938.
[3]Data for chronic exposure during Operation Everest II from Sutton JR, Reeves JT, Wagner PD, et al: Operation Everest II: Oxygen transport during exercise at extreme simulated altitude, *J Appl Physiol* 64:1309-1321, 1988.
[4]Data from near the summit of Mt Everest from Grocott MP, Martin DS, Levett DZ, et al: Arterial blood gases and oxygen content in climbers on Mount Everest, *N Engl J Med* 360:140-149, 2009.
[5]Data from the simulated summit of Mt Everest from Richalet JP, Robach P, Jarrot S, et al: Operation Everest III (COMEX '97): Effects of prolonged and progressive hypoxia on humans during a simulated ascent to 8,848 m in a hypobaric chamber, *Adv Exp Med Biol* 474:297-317, 1999.
P_B, Barometric pressure; P_{aCO_2}, arterial partial pressure of carbon dioxide; P_{aO_2}, arterial partial pressure of oxygen; S_{aO_2}, arterial oxygen saturation.
*Data are mean values and (range) or ±SD (standard deviation), where available. All values are for people age 20 to 40 years who were acclimatizing well.

TABLE 1-2 Altitude Conversion: Barometric Pressure,* Estimated Partial Pressure of Inspired Oxygen,† and the Equivalent Oxygen Fraction at Sea Level‡

Meters	Feet	P_B	P_{IO_2}	F_{IO_2} at SL
Sea level	Sea level	759.6	149.1	0.209
1000	3281	678.7	132.2	0.185
1219	4000	661.8	128.7	0.180
1500	4921	640.8	124.3	0.174
1524	5000	639.0	123.9	0.174
1829	6000	616.7	119.2	0.167
2000	6562	604.5	116.7	0.164
2134	7000	595.1	114.7	0.161
2438	8000	574.1	110.3	0.155
2500	8202	569.9	109.4	0.154
2743	9000	553.7	106.0	0.149
3000	9843	536.9	102.5	0.144
3048	10,000	533.8	101.9	0.143
3353	11,000	514.5	97.9	0.137
3500	11,483	505.4	95.9	0.135
3658	12,000	495.8	93.9	0.132
3962	13,000	477.6	90.1	0.126
4000	13,123	475.4	89.7	0.126
4267	14,000	460.0	86.4	0.121
4500	14,764	446.9	83.7	0.117
4572	15,000	442.9	82.9	0.116
4877	16,000	426.3	79.4	0.111
5000	16,404	419.7	78.0	0.109
5182	17,000	410.2	76.0	0.107
5486	18,000	394.6	72.8	0.102
5500	18,045	393.9	72.6	0.102
5791	19,000	379.5	69.6	0.098
6000	19,685	369.4	67.5	0.095
6096	20,000	364.9	66.5	0.093
6401	21,000	350.7	63.6	0.089
6500	21,325	346.2	62.6	0.088
6706	22,000	337.0	60.7	0.085
7000	22,966	324.2	58.0	0.081
7010	23,000	323.8	57.9	0.081
7315	24,000	310.9	55.2	0.077
7500	24,606	303.4	53.7	0.075
7620	25,000	298.6	52.6	0.074
7925	26,000	286.6	50.1	0.070
8000	26,247	283.7	49.5	0.069
8230	27,000	275.0	47.7	0.067
8500	27,887	265.1	45.6	0.064
8534	28,000	263.8	45.4	0.064
8839	29,000	253.0	43.1	0.060
8848	29,029	252.7	43.1	0.060
9000	29,528	247.5	42.0	0.059
9144	30,000	242.6	40.9	0.057
9500	31,168	230.9	38.5	0.054
10,000	32,808	215.2	35.2	0.049

F_{IO_2}, fraction of inspired oxygen; *P_B*, barometric pressure; *P_{IO_2}*, partial pressure of inspired oxygen; *SL*, sea level.
*P_B is approximated by Exponent (6.6328 – {0.1112 × altitude – [0.00149 × altitude^2]}), where altitude is terrestrial altitude in meters/1000 or kilometers (km).
†P_{IO_2} is calculated as P_B – 47 × fraction of O_2 in inspired air, where 47 is water vapor pressure at body temperature.
‡The equivalent F_{IO_2} at sea level for a given altitude is calculated as P_{IO_2} ÷ (760 – 47). Substituting ambient P_B for 760 in the equation allows similar calculations for F_{IO_2} at different altitudes.

example, their exercise performance matches that of persons at sea level.[8,50]

VENTILATION

By reducing alveolar carbon dioxide, increased ventilation raises alveolar oxygen, improving oxygen delivery (Figure 1-3). This response begins at altitudes as low as 1500 m (4921 feet) (P_{IO_2} = 124.3 mm Hg; see Table 1-2) and within the first few minutes to hours of high-altitude exposure. The carotid body, sensing a decrease in P_{aO_2}, through a HIF-mediated process, signals the central respiratory center in the medulla to increase ventilation.[3,51,57] This carotid body function, the *hypoxic ventilatory response* (HVR), is genetically determined[89] but is influenced by a number of extrinsic factors. Respiratory depressants such as alcohol and soporific drugs, as well as fragmented sleep, depress HVR. Agents that increase general metabolism, such as caffeine and coca, as well as specific respiratory stimulants, such as progesterone[37] and almitrine,[25] increase HVR. Acetazolamide, a respiratory stimulant, acts on the central respiratory center rather than on the carotid body. Physical conditioning apparently has no effect on HVR. Numerous studies have shown that a good ventilatory response enhances acclimatization and performance,[77] and that a very low HVR may contribute to illness[61] (see Acute Mountain Sickness and High-Altitude Pulmonary Edema in Chapter 2).

As ventilation increases, hypocapnia produces alkalosis, which acts as a braking mechanism on the central respiratory center and limits a further increase in ventilation. To compensate for the alkalosis, within 24 to 48 hours of ascent, the kidneys excrete bicarbonate, decreasing the pH toward normal; ventilation increases as the braking effect of the alkalosis is removed. Ventilation continues to increase slowly, reaching a maximum only after 4 to 7 days at the same altitude (see Figure 1-3). The plasma bicarbonate concentration continues to drop and ventilation continues to increase with each successive increase in altitude. Persons with lower oxygen saturation at altitude have higher serum bicarbonate values. Whether the kidneys might be limiting acclimatization or whether this reflects poor respiratory drive is not clear.[16] This process is greatly facilitated by acetazolamide (see Acetazolamide Prophylaxis in Chapter 2).

The paramount importance of hyperventilation is readily apparent from the following calculation: the alveolar P_{O_2} on the summit of Mt Everest (approximately 33 mm Hg) would be reached at only 5000 m (16,404 feet) if alveolar P_{CO_2} stayed at 40 mm Hg, limiting an ascent without supplemental oxygen to near this altitude. Table 1-1 lists the measured arterial blood gas values resulting from acclimatization to various altitudes.

CIRCULATION

The circulatory pump is the next step in the transfer of oxygen, moving oxygenated blood from the lungs to the tissues.

Systemic Circulation

Increased sympathetic activity on ascent causes an initial mild increase in blood pressure, moderate increases in heart rate and cardiac output, and increase in venous tone. Stroke volume is low because of decreased plasma volume, which drops as much as 12% over the first 24 hours[95] as a result of the bicarbonate diuresis, a fluid shift from the intravascular space, and suppression of aldosterone.[7] Resting heart rate returns to near sea level values with acclimatization, except at extremely high altitude. Maximal heart rate follows the decline in maximal oxygen uptake with increasing altitude. As the limits of hypoxic acclimatization are approached, maximal and resting heart rates converge. During Operation Everest II (OEII), cardiac function was appropriate for the level of work performed, and cardiac output was not a limiting factor for performance.[58,76] Interestingly, myocardial ischemia at high altitude has not been reported in healthy persons, despite extreme hypoxemia. This is partly because of reduction in myocardial oxygen demand from reduced maximal heart rate and cardiac output. Pulmonary capillary wedge pressure is low, and catheter studies have shown no evidence of left ventricular dysfunction or abnormal filling pressures in humans at rest.[24,29] On echocardiography, the left ventricle is smaller than normal because of decreased stroke volume, whereas the right ventricle may become enlarged.[76] The abrupt increase in pulmonary artery pressure can cause a change in left ventricular diastolic function, but because of compensatory increased atrial contraction, no overt diastolic dysfunction results.[2] In trained

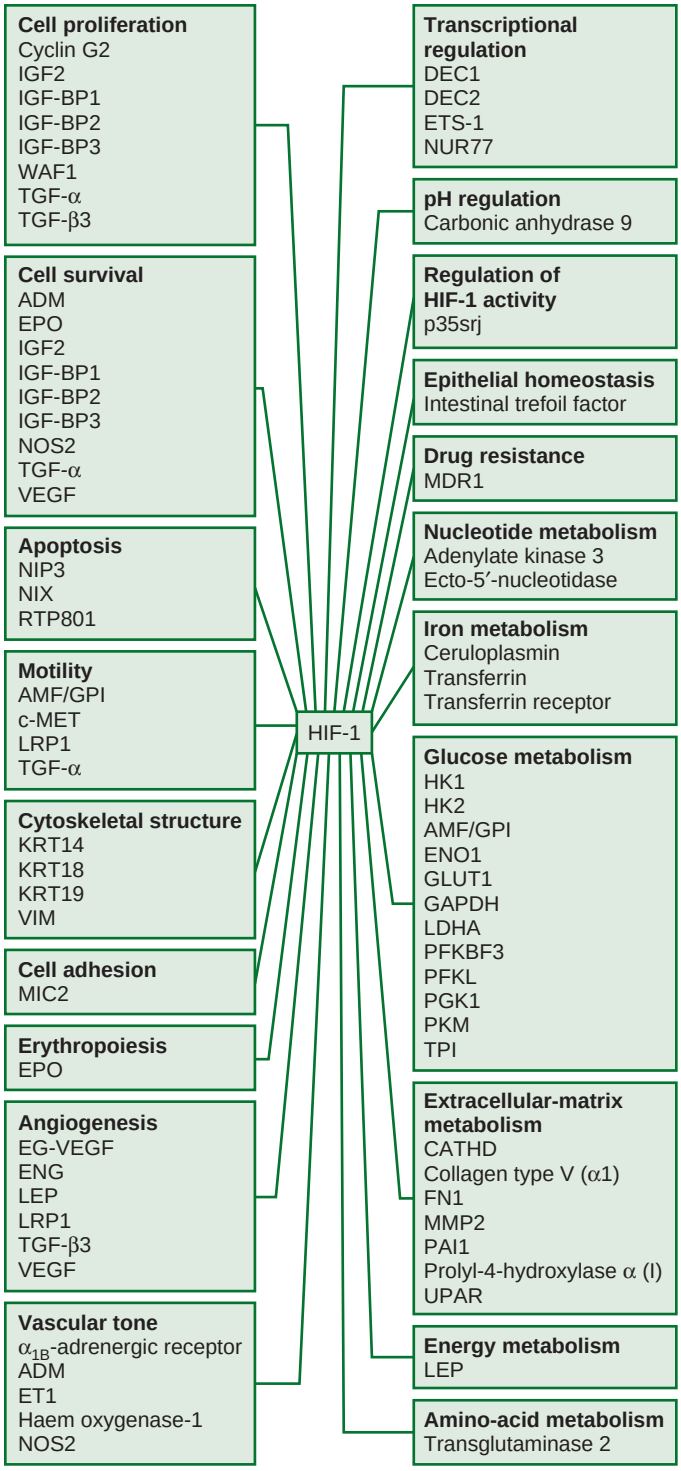

FIGURE 1-2 Regulation of oxygen sensing by hypoxia-inducible factor (HIF). HIF is produced constitutively, but in normoxia the α subunit is degraded by the proteasome in an oxygen-dependent manner. Hypoxic conditions prevent hydroxylation of the α subunit, enabling the active HIF transcription complex to form at the hypoxia-response element (HRE) associated with HIF-regulated genes. A range of cell functions are regulated by the target genes, as indicated. ADM, adrenomedullin; AMF, autocrine motility factor; CATHD, cathepsin D; EG-VEGF, endocrine gland–derived vascular endothelial growth factor; ENG, endoglin; ENO1, enolase 1; EPO, erythropoietin; ET1, endothelin-1; FN1, fibronectin 1; GAPDH, glyceraldehyde-3-phosphate-dehydrogenase; GLUT1, glucose transporter (1, 3); HK1, hexokinase 1; HK2, hexokinase 2; IGF2, insulin-like growth factor 2; IGF-BP, IGF-binding protein (1, 2, 3); KRT, keratin (14, 18, 19); LDHA, lactate dehydrogenase A; LEP, leptin; LRP1, LDL receptor–related protein 1; MDR1, multidrug resistance gene 1; MMP2, matrix metalloproteinase 2; NOS2, nitric oxide synthase 2; PFKBF3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase-3; PFKL, phosphofructokinase L; PGK 1, phosphoglycerate kinase 1; PAI1, plasminogen-activator inhibitor 1; PKM, pyruvate kinase M; TGF-β3, transforming growth factor-β3; TPI, triosephosphate isomerase; VEGF, vascular endothelial growth factor; UPAR, urokinase plasminogen activator receptor; VIM, vimentin. *(Modified from Semenza G: Targeting HIF-1 for cancer therapy,* Nat Rev Cancer *3[10]:721-732, 2003.)*

athletes doing an ultramarathon, the strenuous exercise at high altitude did not result in left ventricular damage; however, wheezing, reversible pulmonary hypertension, and right ventricular dysfunction occurred in one-third of those completing the race and resolved within 24 hours.

Pulmonary Circulation

On ascent to high altitude, a prompt but variable increase in pulmonary vascular resistance (PVR) from hypoxic pulmonary vasoconstriction increases pulmonary artery pressure (PAP). Mild pulmonary hypertension is greatly augmented by exercise, with PAP reaching near-systemic values,[24] especially in persons with a prior history of HAPE.[6,19] During OEII, Groves and colleagues[24] demonstrated that even with a mean PAP of 60 mm Hg, cardiac output remained appropriate, and right atrial pressure did not rise above sea level values. Thus, right ventricular function was intact despite extreme hypoxemia and pulmonary hypertension in these well-acclimatized individuals.

Administration of oxygen does not completely restore PAP to sea level values,[45] likely because of vascular remodeling with medial hypertrophy. (See Stenmark and associates[71,72] for excellent recent reviews of molecular and cellular mechanisms of the pulmonary vascular response to hypoxia, including remodeling.) PVR returns to normal within a few weeks after descent to low altitude.

Cerebral Circulation

Cerebral oxygen delivery, the product of arterial oxygen content and cerebral blood flow (CBF), depends on the net balance between hypoxic vasodilation and hypocapnia-induced vasoconstriction. Despite hypocapnia, CBF increases when Pa_{O_2} is less than 60 mm Hg (altitude >2800 m [9186 feet]). In a classic study, CBF increased 24% on abrupt ascent to 3810 m (12,500 feet) and returned to normal over 3 to 5 days.[68] These findings have been confirmed by positron emission tomography (PET) and brain magnetic resonance imaging (MRI) studies showing both elevations in CBF in hypoxia in humans and striking heterogeneity of the CBF, with CBF rising up to 33% in the hypothalamus and 20% in the thalamus, and with other areas showing no significant change.[9,54] Cerebral autoregulation, the process by which cerebral perfusion is maintained as blood pressure varies, is impaired in hypoxia. Interestingly, this occurs with acute ascent,[31,41,81,84] after successful acclimatization,[79,82] and in natives to high altitude.[31] The uniform "impairment" in all humans who become hypoxic raises questions about the importance of cerebral autoregulation, specifically as it pertains to altitude illness (see Chapter 2 for advanced discussion on AMS and cerebral autoregulation). Overall, global cerebral metabolism seems well maintained with moderate hypoxia.[1,17,49]

BLOOD

Hematopoietic Responses to Altitude

Ever since the observation in 1890 by Viault[85] that hemoglobin concentration was higher than normal in animals living in the Andes, scientists have regarded the hematopoietic response to increasing altitude as an important component of the acclimatization process. On the other hand, hemoglobin values apparently have no relationship to susceptibility to high-altitude illness.

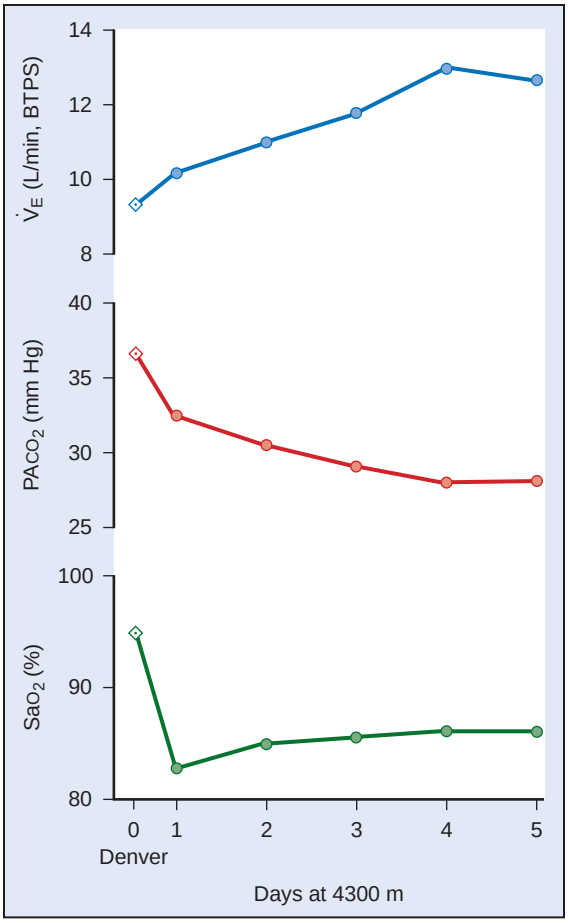

FIGURE 1-3 Change in minute ventilation ($\dot{V}_E$), alveolar (end-tidal) carbon dioxide partial pressure ($PACO_2$), and arterial oxygen saturation (SaO_2) during 5 days' acclimatization to 4300 m (14,108 feet). *BTPS,* Body temperature pressure saturated. *(Modified from Huang SY, Alexander JK, Grover RF, et al: Hypocapnia and sustained hypoxia blunt ventilation on arrival at high altitude,* J Appl Physiol *56:602-606, 1984.)*

In response to hypoxemia, erythropoietin is secreted by the kidneys and stimulates bone marrow production of red blood cells (RBCs).[66] The hormone is detectable within 2 hours of ascent, nucleated immature RBCs can be found on a peripheral blood smear within days, and new RBCs are in circulation within 4 to 5 days. Over weeks to months, RBC mass increases in proportion to the degree of hypoxemia. Iron supplementation can be important; women who take supplemental iron at high altitude approach the hematocrit values of men at altitude[26] (Figure 1-4). The field of erythropoietin and iron metabolism has exploded in recent years, with discovery of two new iron-regulating hormones, hepcidin[23] and erythroferrone,[10,22,34,38] and a novel, soluble erythropoietin receptor with function directly linked to performance at high altitude.[86] How all these new findings are integrated and their responses during acclimatization to hypoxia remain to be determined.

The increase in hemoglobin seen 1 to 2 days after ascent is caused by hemoconcentration secondary to decreased plasma volume, rather than by a true increase in RBC mass. This results in a higher hemoglobin concentration at the cost of decreased blood volume, a trade-off that might impair exercise performance. Longer-term acclimatization leads to an increase in plasma volume as well as in RBC mass, thereby increasing total blood volume. Overshoot of the hematopoietic response causes excessive polycythemia, which may impair oxygen transport because of increased blood viscosity. Although the "ideal" hematocrit at high altitude is not established, phlebotomy is often recommended when hematocrit values exceed 60% to 65%. During the American Medical Research Expedition to Mt Everest (AMREE), hematocrit was reduced by hemodilution from 58% ±1.3% to 50.5% ±1.5% at 5400 m (17,717 feet) with increased cerebral functioning and no decrement in maximal oxygen uptake.[65]

Oxyhemoglobin Dissociation Curve

The oxygen dissociation curve (ODC) plays a crucial role in oxygen transport. The sigmoidal shape of the curve allows SaO_2 to be well maintained up to 3000 m (9843 feet), despite significant decreases in PaO_2 (see Figure 1-1). Above 3000 m, small changes in PaO_2 cause large changes in SaO_2 (Figure 1-5). Because PaO_2 determines diffusion of oxygen from capillary to cell, small changes in PaO_2 can have clinically significant effects. This is often confusing for clinicians because SaO_2 appears relatively well preserved. At high altitude, small changes in PaO_2 lead to lower oxygen uptake that can have a large effect on systemic

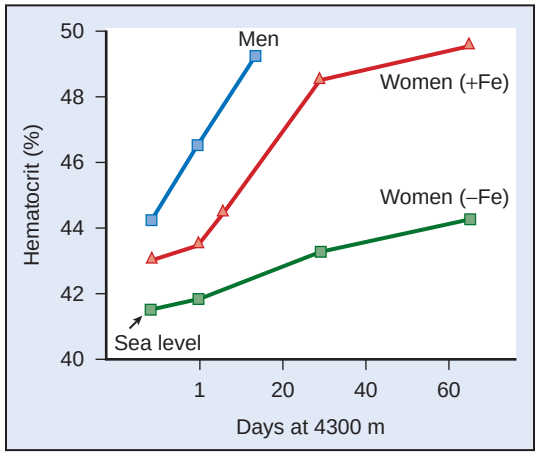

FIGURE 1-4 Hematocrit changes on ascent to altitude in men and in women with (+Fe) and without (–Fe) supplemental iron. *(Modified from Hannon JP, Klain GJ, Sudman DM, Sullivan FJ: Nutritional aspects of high-altitude exposure in women,* Am J Clin Nutr *29:604-613, 1976.)*

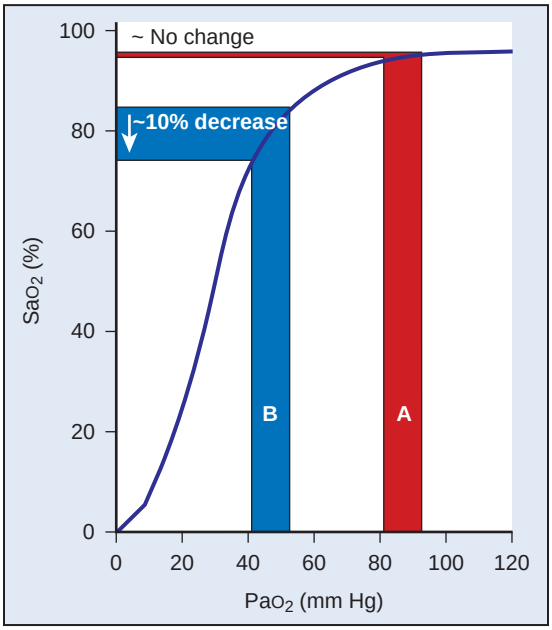

FIGURE 1-5 Oxygen-hemoglobin dissociation curve showing effect of 10–mm Hg decrement in arterial partial pressure of oxygen (PaO_2) on arterial oxygen saturation (SaO_2) at sea level *(A)* and near 4400 m (14,436 feet) *(B).* Note the much larger drop in SaO_2 at high altitude. *(Modified from Severinghaus JW: Blood gas calculator,* J Appl Physiol *21:1108-1116, 1966.)*

hypoxemia, and thus on clinical status, while Sa_{O_2} may appear relatively unchanged.

In 1936, Ansel Keys and colleagues[35] demonstrated an in vitro right shift in position of the ODC at high altitude, favoring release of oxygen from blood to tissues. This change, caused by increased 2,3-diphosphoglycerate, is proportional to the severity of hypoxemia. In vivo, however, the alkalosis at moderate altitude offsets this, and no net change occurs. In contrast, the marked alkalosis of extreme hyperventilation, as measured on the summit and simulated summit of Mt Everest (Pa_{CO_2} = 8 to 10 mm Hg; pH >7.5), shifts the ODC to the left, facilitating oxygen-hemoglobin binding in the lung, which raises Sa_{O_2} and is advantageous.[64] Persons with a very left-shifted ODC caused by an abnormal hemoglobin (Andrew-Minneapolis), when taken to moderate (3100 m [10,171 feet]) altitude, had less tachycardia and dyspnea and remarkably no decrease in exercise performance.[28] High-altitude–adapted animals also have a left-shifted ODC.

TISSUE CHANGES

The next link in the oxygen transport chain is tissue oxygen transfer, which depends on capillary perfusion, diffusion distance, and driving pressure of oxygen from the capillary to the cell. Banchero[5] has shown that capillary density in dog skeletal muscle doubles in 3 weeks at P_B of 435 mm Hg. A recent study in humans noted no change in capillary density or in gene expression thought to enhance muscle vascularity.[42] Ou and Tenney[53] revealed a 40% increase in mitochondrial number but no change in mitochondrial size, whereas Oelz and colleagues[52] showed that high-altitude climbers had normal mitochondrial density. A significant decrease in muscle size is often noted after high-altitude expeditions because of net energy deficit, resulting in increased capillary density and ratio of mitochondrial volume to contractile protein fraction as a result of the atrophy. Although there is no de novo synthesis of capillaries or mitochondria, the net result is a shortening of diffusion distance for oxygen.[42,44]

EXERCISE

Maximal oxygen consumption drops dramatically on ascent to high altitude.[21,62] Maximal oxygen uptake ($\dot{V}O_2max$) falls from sea level value by approximately 10% for each 1000 m (3281 feet) of altitude gained above 1500 m (4921 feet). Persons with the highest $\dot{V}O_2max$ values at sea level have the largest decrement in $\dot{V}O_2max$ at high altitude, but overall performance at high altitude is not consistently related to sea level $\dot{V}O_2max$.[52,60,91] In fact, many of the world's elite mountaineers, in contrast to other endurance athletes, have quite average $\dot{V}O_2max$ values.[52] Acclimatization at moderate altitudes enhances submaximal endurance time but does not enhance $\dot{V}O_2max$ (Figure 1-6).[21] Two groups recently confirmed that acclimatization leads to improvement in submaximal work capacity using field tests,[39,77] and Subudhi and associates[77] showed that adaptation to submaximal work performance persists for up to 3 weeks after descent to low altitude. This occurs despite a marked drop in hemoglobin concentration, suggesting that other factors are involved.

Oxygen transport during exercise at high altitude becomes increasingly dependent on the ventilatory pump. The marked rise in ventilation produces a sensation of breathlessness, even at low work levels. The following quotation is from a high-altitude mountaineer:[48]

> ***After every few steps, we huddle over our ice axes, mouths agape, struggling for sufficient breath to keep our muscles going. I have the feeling I am about to burst apart. As we get higher, it becomes necessary to lie down to recover our breath.***

In contrast to the increase in ventilation with exercise, at increasing altitudes in OEII, cardiac function and cardiac output were maintained at or near sea level values for a given oxygen consumption (workload).[58] Recent work attributed the altitude-induced drop to the lower P_{IO_2}, impairment of pulmonary gas exchange, and reduction of maximal cardiac output and peak leg blood flow, each explaining about one-third of the

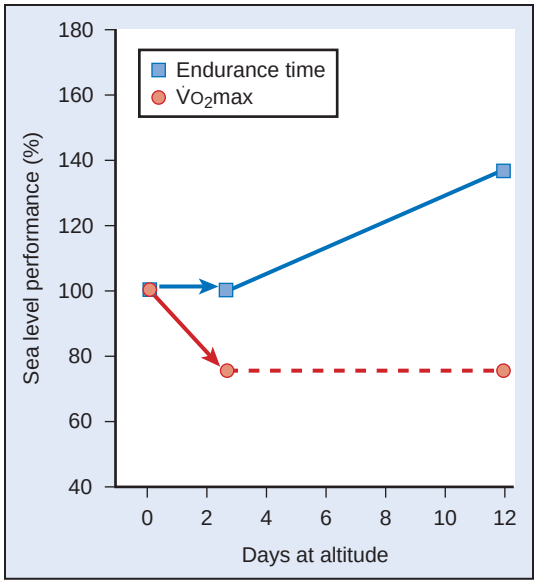

FIGURE 1-6 On ascent to altitude, maximal oxygen consumption ($\dot{V}O_2max$) decreases and remains suppressed. In contrast, endurance time (minutes to exhaustion at 75% of altitude-specific $\dot{V}O_2max$) increases with acclimatization. *(Modified from Maher JT, Jones LG, Hartley LH: Effects of high-altitude exposure on submaximal endurance capacity of men,* J Appl Physiol *37:895-898, 1974.)*

loss in $\dot{V}O_2max$.[11] However, mechanisms to explain impaired gas exchange and lower blood flow remain elusive. Wagner[87] proposes that the pressure gradient for diffusion of oxygen from capillaries to the working muscle cells may be inadequate. Others propose that increased cerebral hypoxia from exercise-induced desaturation is the limiting factor.[15,30,78,80] Mountaineers, for example, become lightheaded and their vision dims when they move too quickly at extreme altitude (Figure 1-7).[92]

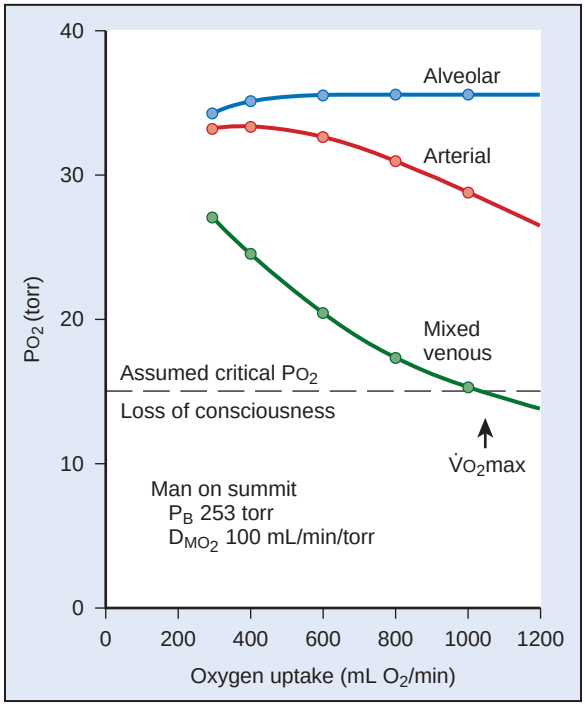

FIGURE 1-7 Calculated changes in the oxygen partial pressure (P_{O_2}) of alveolar gas and arterial and mixed venous blood as oxygen uptake is increased for a climber on the summit of Mt Everest. Unconsciousness develops at a mixed venous P_{O_2} of 15 mm Hg. P_B, Barometric pressure; D_{MO_2}, muscle-diffusing capacity; $\dot{V}O_2max$, maximal oxygen consumption (intake). *(Modified from West J: Human physiology at extreme altitudes on Mount Everest,* Science *223[4638]:784-788, 1984.)*

Training at High Altitude

Optimal training for increased performance at high altitude depends on the altitude of residence and the athletic event. For aerobic activities (events lasting >3 minutes) at altitudes above 2000 m (6562 feet), acclimatization for 10 to 20 days is necessary to maximize performance.[18] For events occurring above 4000 m (13,123 feet), acclimatization at an intermediate altitude is recommended. Highly anaerobic events at intermediate altitudes require only arrival at the time of the event, although AMS may become a problem.

The benefits of training at high altitude for subsequent performance at or near sea level depend on choosing the training altitude that maximizes the benefits and minimizes the inevitable "detraining" when $\dot{V}O_2max$ is limited (altitude >1500 to 2000 m [4921 to 6562 feet]). Therefore, data from training above 2400 m (7874 feet) have shown no increase in subsequent sea level performance. Also, intermittent exposures to hypoxia seem to have no benefit.[33,83] Runners returning to sea level after 10 days' training at 2000 m (6562 feet) had faster running times and an increase in aerobic power, plasma volume, and hemoglobin concentration.[4] The "live high–train low" approach pioneered by Levine and Stray-Gundersen[40,74] has been adopted by many endurance athletes. The optimal dose for specific sports is still being determined,[12,13,94] but overall, endurance athletes believe and science supports a small but significant improvement in sea level performance after participating in a live high–train low training camp.[75] The benefit appears to result from enhanced erythropoietin production and increased RBC mass, which requires adequate iron stores and thus usually iron supplementation.[46,63,73] Some individuals do not respond to the live high–train low approach, perhaps related to genetic polymorphisms and inability to increase erythropoietin levels sufficiently to increase RBC mass and thus increase oxygen-carrying capacity.[12,14,32]

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