Chapter 21

HUMAN ADAPTATION TO HIGH TERRESTRIAL ALTITUDE

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INTRODUCTION

Soldiers who deploy from sea-level bases for operations in the mountains or high plateaus will experience multiple environmental stressors, but the stress unique to high altitudes is the oxygen-deficient atmosphere. This chapter will focus on the physiological effects of acute and chronic exposure to that stressor. The emphasis will be on the effects experienced during altitude sojourns of the type that military units might conduct (ie, ascent to moderate altitudes [2,500–5,000 m] for a few days to several weeks), although effects of longer and more extreme ascents will also be considered. The mechanisms for these effects will be discussed with a view to explaining functional changes experienced by *lowlanders* (natives or acclimatized inhabitants of low-altitude regions) who are sojourning at altitude.

On arriving at high altitude, lowlanders will be incapable of as much physical exertion as they were at sea level. Further, they may not feel well, and may have impaired mentation. These effects are ultimately due to hypoxia. However, a series of physiological adjustments ensue that are directed at compensating for the reduction in ambient oxygen. These adjustments, which include increases in ventilation, hemodynamic and hematologic changes, altered hormone secretion, and metabolic and body water changes, to name a few, relieve some but not all of the physiological strain of continued residence at high altitude. The time required for altitude adaptations to become manifest varies with the different processes, with the altitude ascended, and with the speed of ascent. The progressive development of these adjustments, usually termed *acclimatization,* alleviates, to varying degrees, the symptoms and physical and mental limitations inflicted by hypoxia. The adjustments to hypoxia that begin immediately with acute hypoxic exposure, together with the continuing processes of acclimatization, collectively comprise the altitude adaptations that will be examined in this chapter.

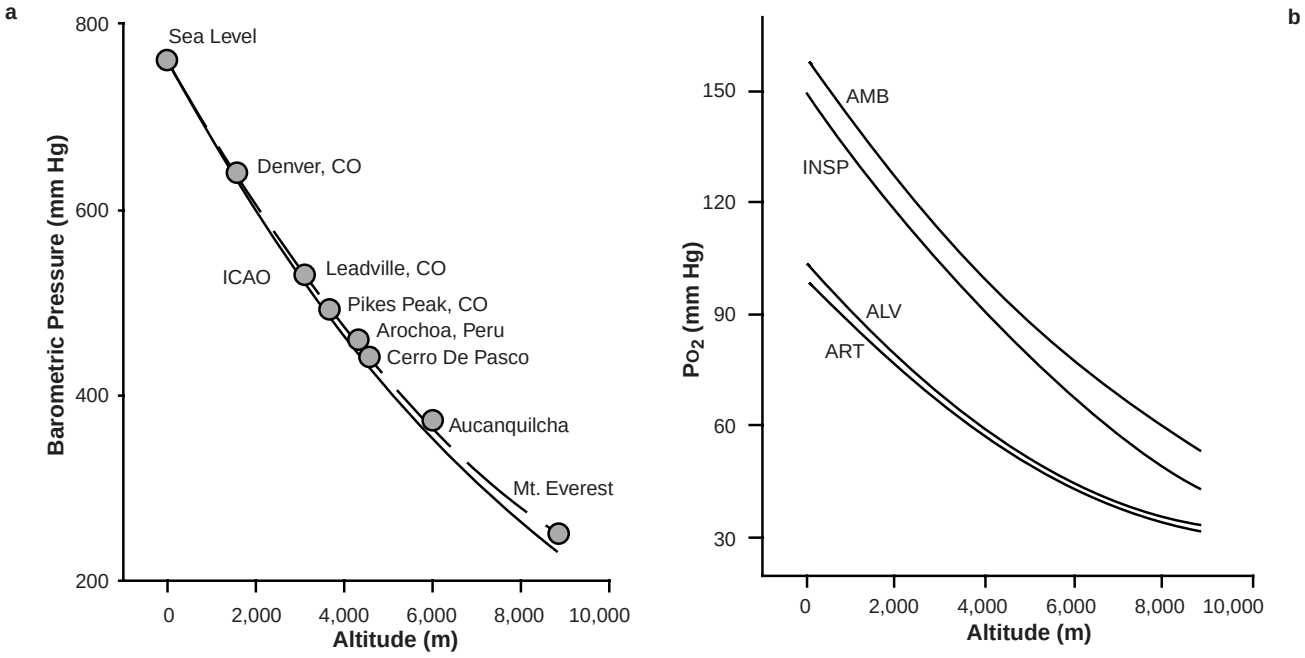

Fig. 21-1. Both atmospheric pressure and the partial pressure of oxygen decrease as functions of altitude. (**a**) The barometric pressure measured at various sites located at different elevations (closed circles and dashed line)[1,2] and the global average (solid line) reported[3] by the International Civil Aviation Organization (ICAO). (**b**) Partial pressures of oxygen (P_{O_2}) at increasing altitude are shown in ambient air (AMB), in the airways after inspired air has been warmed and humidified (INSP), in the alveolus after CO_2 has been added (ALV), and in the arterial blood (ART). Data sources: (1) West JB. Prediction of barometric pressures at high altitudes with the use of model atmospheres. *J Appl Physiol*. 1996;81:1850–1854. (2) Authors' personal unpublished observations. (3) Ward MP, Milledge JS, West JB. *High Altitude Medicine and Physiology*. New York, NY: Oxford University Press; 2000: 26, Table 2.1.

THE HYPOXIC ENVIRONMENT

Elevation, Barometric Pressure, and Inspired Oxygen

The surface of Earth's oceans, which we call sea level, is also the bottom of an ocean of air. Air, unlike water, is compressible. Therefore air is denser at sea level than at higher terrestrial elevations, and barometric pressure (P_B) is not directly proportional to elevation but is logarithmic. Thus, from sea level (P_B = 760 mm Hg) to the summit of Mount Everest (P_B = 253 mm Hg), the highest point on Earth, the relationship of pressure to elevation is a curved, and not a straight, line (Figure 21-1). Also, where P_B has actually been measured at various terrestrial elevations within the temperate zone, it is slightly higher than the "standard barometric pressure" indicated in the table published by the International Civil Aviation Organization (ICAO) to reflect mean conditions over the entire earth's surface.[1] In addition, the ambient barometric pressure is lower in winter than in summer, a decrease that over the years averages 8 mm Hg in Colorado.

Air is a mixture of gases, the summated partial pressures of which equal the P_B. The principal gases in air are oxygen and nitrogen. Their concentrations are essentially constant over Earth's terrestrial elevations. For example, when water vapor is absent, oxygen comprises 20.93% of the air at all elevations. The partial pressure of oxygen (P_{O_2}, in mm Hg) in the atmosphere falls as barometric pressure (P_B, in mm Hg) falls, as defined by Equation 1:

$$(1) \qquad P_{O_2} = P_B \bullet 0.2093$$

Thus, ambient P_{O_2} also depends on the terrestrial elevation, falling with P_B as elevation above sea level increases, as indicated in Figure 21-1b. The atmospheric P_{O_2} (in dry air) is 159 mm Hg at sea level (760 • 0.2093) and 53 mm Hg on the summit of Mount Everest (253 • 0.2093).

When air is inspired, it is warmed to body temperature and saturated with water vapor by the time it reaches the bifurcation of the trachea. The water vapor has a partial pressure, which is also a component of total pressure. At all altitudes, the partial pressure of water vapor (P_{H_2O}) in fully humidified air depends only on temperature, ranging (in mm Hg) from approximately 0.5 at 0°C and 760 at 100°C. At body temperature of 37°C, P_{H_2O} is 47 mm Hg. The dilution of inspired air by water vapor reduces the inspired oxygen pressure (P_{IO_2}) below the ambient P_{O_2}, as illustrated by Equation 2, where the P_{H_2O} is taken to be 47 mm Hg:

$$(2) \qquad P_{IO_2} = (P_B - 47) \bullet 0.2093$$

Thus, P_{IO_2} also falls with increasing elevation. As Figure 21-1(b) shows, P_{IO_2} is 149 mm Hg ([760 – 47] • 0.2093) at sea level and 43 mm Hg ([253 – 47] • 0.2093) on the summit of Mount Everest. Although the major determining factor of P_{IO_2} is P_B, body temperature can affect the P_{IO_2} somewhat. If body temperature falls, P_{H_2O} of saturated inspired air would also fall and P_{IO_2} would rise; conversely, if body temperature were to rise, P_{IO_2} would fall. At a given P_B, the oxygen pressure in the inspired air is therefore independent of ventilation and depends only on body temperature. (Alveolar temperature equals body temperature, but a detailed discussion of this point is beyond the scope of this chapter.)

Overview of the Oxygen-Transport Cascade at High Altitude

For health and even for life itself, oxygen must constantly be transported from the atmosphere to the mitochondria in sufficient quantities to meet tissue demands. Transport can be regarded as a series of steps in a cascade, because the P_{O_2} falls sequentially and progressively, much as cascading water flowing over steps must fall to each new level. The cascade has four steps (Figure 21-2a):

1. oxygen transport by the bellows action of the respiratory system, which brings oxygen from ambient air to the alveolus, from which
2. oxygen passively diffuses across the alveolar–capillary membrane into the blood, which then
3. convectively transports the oxygen via cardiac action to the systemic capillaries, where
4. the oxygen passively diffuses through the tissues to the cells' mitochondria.

Figure 21-2b illustrates the P_{O_2} fall for each step in the cascade during near maximal exercise. At sea level, where the P_{IO_2} is near 150 mm Hg, ventilation normally limits the P_{O_2} pressure fall during the first step in the cascade to approximately 40 mm Hg, resulting in an alveolar P_{O_2} of 110 mm Hg. During the second step in the cascade, the P_{O_2} falls as oxygen diffuses across the pulmonary–capillary

membrane from air in the alveolus to pulmonary capillary blood. During heavy exercise, where large amounts of oxygen are to be transported, the diffusion gradient may be large. This is because blood entering the pulmonary capillaries during heavy exercise has relatively little oxygen content to begin with, and the high circulatory flow rate ensures that oxygen is removed quickly after crossing the pulmonary–capillary membrane. In addition, venous shunts allow deoxygenated blood to bypass the lung capillaries and contribute to the P_{O_2} pressure gradient from alveolus to arterial blood. Figure 21-2b shows the cascade from alveolus to artery as a P_{O_2} pressure fall of about 30 mm Hg during near-maximal exercise at sea level. The third step, convective transport by the circulation, representing cardiac action, normally limits the P_{O_2} pressure fall to about 60 mm Hg (ie, from 80 mm Hg in arterial blood to 20 mm Hg in venous blood). In Figure 21-2b, venous P_{O_2} is assumed to reflect that in the systemic capillaries. The P_{O_2} in the mitochondria is considered to be near zero, so the fourth step in the cascade represents a P_{O_2} fall of about 20 mm Hg.

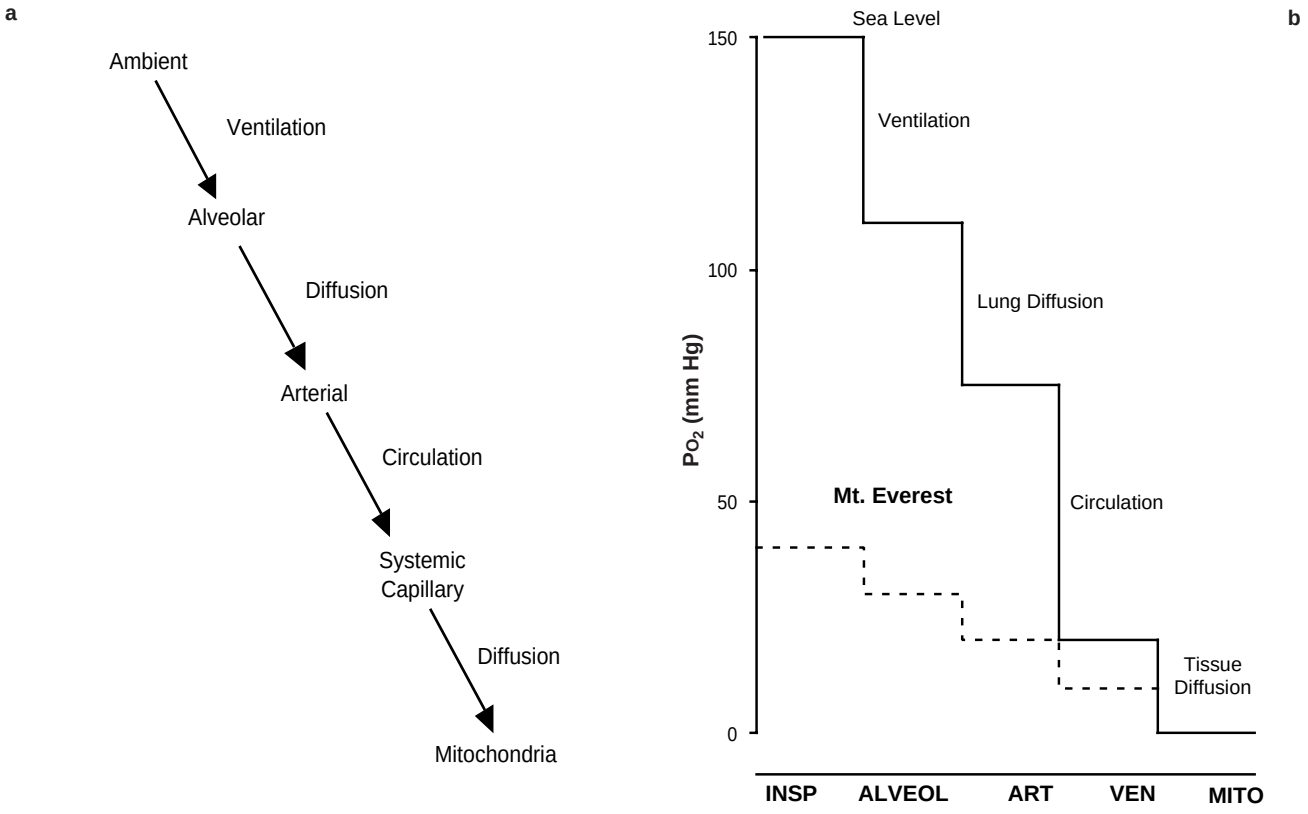

Fig. 21-2. In the oxygen transport cascade, oxygen moves from the atmosphere to the tissues down a decreasing pressure gradient. (**a**) The four steps in the oxygen transport cascade from ambient air to tissue mitochondria use either active (ventilation, circulation) or passive (diffusion) processes. (**b**) The average fall in the partial pressure of oxygen (P_{O_2}) was observed[1–4] at each step in the oxygen transport cascade during near-maximal exercise at sea level (solid line) and at the simulated summit of Mount Everest (dotted line).
INSP: inspired air, warmed and humidified; ALVEOL: in the alveoli, after CO_2 has been added; ART: in the arterial blood, convectively transporting oxygen to metabolically active tissue; VEN: in the venous blood draining from capillaries perfusing metabolically active tissue; MITO: in the mitochondria while oxygen is used in the regeneration of adenosophine triphosphate.
Data sources: (1) Sutton JR, Reeves JT, Wagner PD, et al. Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol.* 1988;64:1309–1321. (2) Wagner PD, Sutton JR, Reeves JT, Cymerman A, Groves BM, Malconian MK. Operation Everest II: Pulmonary gas exchange during a simulated ascent of Mt Everest. *J Appl Physiol*. 1987;63:2348–2359. (3) Cymerman A, Reeves JT, Sutton JR, et al. Operation Everest II: Maximal oxygen uptake at extreme altitude. *J Appl Physiol*. 1989;66:2446–2453. (4) Houston CS, Sutton JR, Cymerman A, Reeves JT. Operation Everest II: Man at extreme altitude. *J Appl Physiol*. 1987;63:877–882.

The overall P_{O_2} pressure gradient that drives oxygen down the transport chain during heavy exercise at sea level is approximately 150 mm Hg from inspired air to the mitochondria. The overall P_{O_2} gradient driving oxygen transport at the highest point on Earth, the summit of Mount Everest, is considerably less than at sea level, about 43 mm Hg from inspired air to the mitochondria, because the atmospheric P_{O_2} is so low at the top of Mount Everest. Nevertheless, men recently ascended Mount Everest successfully without using supplemental breathing oxygen.[2] As shown in Figure 21-2b, the P_{O_2} fall at each successive step in the oxygen-transport cascade is less on Mount Everest than at sea level. Clearly, humans must have a great capacity for physiological adjustments to compensate for the reduced pressure gradient that drives oxygen transport at high altitude. Not surprisingly, the most profound adjustments involve the active transport steps in the cascade, ventilation and circulation, but there are also adjustments affecting the passive transport steps. In the subsequent sections of this chapter, we will use experimental data reported from a variety of studies at high altitudes to focus on the physiology and implications involved in the altitude-related changes in each step in the oxygen-transport cascade, to better understand the normal responses to the combined stresses of exercise and hypoxia.

PULMONARY GAS EXCHANGE AT HIGH ALTITUDE

The Role of Increasing Ventilation

As we will discuss next in detail, one of the principal physiological responses to hypoxia is an increase in ventilation. However, in the preceding section it was pointed out that P_{IO_2} was independent of alterations in ventilation. Therefore, we need to consider what role increasing ventilation plays in adjusting oxygen transport in response to hypoxia.

The alveolus always contains carbon dioxide. Because ambient inspired air contains relatively little carbon dioxide, alveolar carbon dioxide (P_{ACO_2}) reflects the net balance between carbon dioxide diffusion into the alveolus from the capillary blood and removal of carbon dioxide from the alveolus by expiration. When the inspired air reaches the alveolus, it is diluted by the alveolar carbon dioxide, which causes the alveolar P_{O_2} (P_{AO_2}) to fall below the P_{IO_2} (see Figure 21-1b). For practical purposes one may consider that the alveolus contains essentially four gases: nitrogen (including the other inert gases), water vapor, oxygen, and carbon dioxide. When the glottis is open at the end of inspiration and expiration, the total pressure in the alveolus must equal the P_B, which is the sum of the partial pressures of the alveolar gases, as indicated in Equation 3:

$$(3) \qquad P_B = (P_{AN_2} + P_{AH_2O} + P_{ACO_2} + P_{AO_2})$$

Therefore, by rearranging Equation 3, an expression of the partial pressure of oxygen in the alveolus, Equation 4, is obtained:

$$(4) \qquad P_{AO_2} = P_B - (P_{AN_2} + P_{ACO_2} + P_{AH_2O})$$

So how can increasing ventilation at any altitude increase the partial pressure of oxygen in the alveolus? The P_B is determined by the altitude and the P_{AH_2O} is determined by body temperature (47 mm Hg at 37°C, as described above). Physiologically, nitrogen is an inert gas, being neither produced nor consumed by the body. Assuming that body temperature is 37°C and that equal volumes of oxygen leave and carbon dioxide enter the alveolus over time (ie, the respiratory exchange ratio, *R*, equals 1), the alveolar partial pressure of nitrogen (P_{AN_2}) may be expressed as follows in Equation 5:

$$(5) \qquad P_{AN_2} = (P_B - 47) \bullet 0.7907$$

where 0.7907 is the fraction of nitrogen in dry atmospheric air. Physiological variations in body temperature or R have only small effects on P_{AN_2}, which is relatively high, compared with pressures of other atmospheric gases. Thus, hyperventilation has little or no effect on the P_B, P_{AH_2O}, or P_{AN_2} components of Equation 4 but does have a profound effect on the two remaining components. Hyperventilation increases the rate of removal of carbon dioxide from the alveolus relative to the rate that it diffuses in from the blood. As hyperventilation lowers the P_{ACO_2}, the P_{AO_2} must rise.

Another expression of the steady state relation of P_{AO_2} and P_{ACO_2} is given by the alveolar air equation in Equation 6:

$$(6) \qquad P_{AO_2} = P_{IO_2} - P_{ACO_2} (F_{IO_2} + [1 - F_{IO_2}] / R)$$

where F_{IO_2} represents the fraction of oxygen in the inspired air (0.2093 during air breathing) and *R*, the respiratory exchange ratio, represents carbon dioxide production divided by oxygen uptake. As R varies within its usual physiological range of 0.8 to

1.2, P_{ACO_2} will be modified by a factor ranging, respectively, from approximately 1.20 to 0.87. Equation 7 illustrates the special case when R = 1:

$$P_{AO_2} = P_{IO_2} - P_{ACO_2} \quad (7)$$

It is clear from Equations 6 and 7 that if P_{IO_2} is constant, then P_{AO_2} must rise as P_{ACO_2} falls. Further, when R = 1, there is an equal exchange of O_2 for CO_2. Each mm Hg fall in P_{CO_2} is accompanied by a mm Hg rise in P_{O_2}. Thus, ventilation raises P_{O_2} to the extent that it lowers P_{CO_2}.

It is important to understand that although the relationship between the ventilation expired (V_E) and P_{CO_2} depends on the volume of carbon dioxide to be expired, the expired volumes of ventilation and of carbon dioxide are reported differently. The ventilation expired is usually reported in liters per minute, measured at *b*ody *t*emperature, ambient *p*ressure, and *s*aturated with water vapor (BTPS, designated $V_{E\ BTPS}$). These measurements reflect the volume of gas expired under the conditions within the alveolus, and therefore the actual movement of the diaphragm and chest wall (ie, the bellows function of the respiratory system). But the volumes of carbon dioxide ($\dot{V}_{CO_2}$) are always reported under *s*tandard conditions of *t*emperature (0°C), *p*ressure (760 mm Hg), and *d*ry (P_{H_2O} = 0 mm Hg) (known as STPD) to reflect the number of molecules of gas. (Occasionally, ventilation is reported as $V_{E\ STPD}$ to designate the number of molecules transported into and out of the lungs, as will be discussed later in this chapter).

Equation 8 shows that the P_{ACO_2} falls as alveolar ventilation (V_A, total ventilation minus dead space ventilation) rises for any given volume of CO_2 produced ($\dot{V}_{CO_2}$):

$$P_{ACO_2} = (F \bullet \dot{V}_{CO_2\ STPD}) \,/\, V_{A\ BTPS} \quad (8)$$

where *F* is the factor that converts CO_2 from STPD to BTPS conditions, multiplied by the barometric pressure to allow the alveolar CO_2 to be expressed as a partial pressure rather than a fractional concentration.[3] Because F is nearly constant from sea level (1.21 • 760 mm Hg = 920 mm Hg) to the summit of Mount Everest (4.19 • 253 mm Hg = 1,060 mm Hg), the P_{ACO_2} for a given $\dot{V}_{CO_2}$ depends almost entirely on the V_A measured under BTPS conditions. Further, in normal subjects resting quietly at sea level, P_{ACO_2} and the ratio of $\dot{V}_{CO_2}$ / V_A remain stable over long periods,[4] demonstrating that even at rest, ventilation is tightly coupled to metabolic rate. The tight coupling of resting metabolic rate and ventilation also occurs at altitude, and decreases in P_{ACO_2} reflect altitude-related hyperventilation independent of changes in metabolic rate.[5] Also, carbon dioxide, being a water-soluble molecule, crosses the alveolar–capillary membrane with much greater facility than does oxygen. The result is that the resting alveolar–capillary P_{CO_2} gradient is so small that alveolar and arterial P_{CO_2} values are often used interchangeably. By convention, respiratory physiologists use the carbon dioxide partial pressure in either the alveolus (P_{ACO_2}) or the arterial blood (P_{aCO_2}) as convenient approximations of effective (alveolar) resting ventilation for the various altitudes.

Ventilatory Responses to Acute Hypoxia

Mechanism for Increasing Ventilation With Hypoxia

An increase in ventilation begins within seconds of exposure to hypoxia, but the subsequent time-dependent changes are complex. Figure 21-3 schematically depicts these sequential changes in stages that include a stimulation of ventilation known as the acute hypoxic ventilatory response, hypoxic ventilatory depression, ventilatory acclimatization, and finally hypoxic desensitization. The first two stages occur within minutes of hypoxic exposure, whereas ventilatory acclimatization is developed over the ensuing days to weeks that hypoxia continues and persists for many years of residence in a hypoxic environment. The final stage, hypoxic desensitization, is not usually observed until after decades of chronic hypoxic exposure.

The key sensors that initiate and sustain the increase in ventilation in response to hypoxia appear to be the peripheral chemoreceptor cells in the carotid bodies. The carotid bodies are about the size of the head of a pin and are located bilaterally in the wall of the internal carotid artery at its origin from the common carotid. Decreasing arterial oxygenation increases carotid body neural discharge. The carotid body neural discharge increases hyperbolically with decreasing P_{O_2}, and in inverse proportion to decreasing oxygen saturation below 96%.[6–8] With acute hypoxia, the carotid body neural discharge is tightly coupled with elevated phrenic nerve activity and increased ventilation.[8] Carotid bodies sense oxygen pressure rather than content, as they do not respond to carbon monoxide–induced reductions in arterial oxygen content

(Ca_{O_2}) where the arterial P_{O_2} remains high.[8] Carotid bodies have an extremely high blood flow relative to their size and metabolism (only a 5- to 15-mm Hg P_{O_2} gradient from arterial blood to the chemoreceptor cell), so small changes in arterial oxygenation can be rapidly sensed. Experiments with animals indicate that removal of the carotid bodies prevents ventilatory acclimatization to hypoxia.[9] Animals without carotid body function that are taken to high altitude do poorly and may die. Further, selective carotid body hypoxia induces acclimatization even when the rest of the body, including the brain, is normoxic. Thus, the acute and chronic ventilatory response to hypoxia resides in the carotid bodies.

When the arterial oxygen pressure (Pa_{O_2}) falls, nervelike cells (chemoreceptor cells, also called glomus type I cells) in the carotid body increase afferent impulses along the ninth cranial nerve to the respiratory system in the brainstem, resulting in increased respiratory effort. If a subject breathes oxygen-enriched mixtures, the reverse happens (ie, decreased nerve traffic and respiratory effort). Thus, an important mechanism controlling breathing is the Pa_{O_2}, where a decrease in P_{O_2} increases breathing, and an increase in P_{O_2} decreases breathing. In each case, the result is, in effect, the body's effort to maintain constant blood oxygen levels. This concept is fully developed in subsequent sections of this chapter.

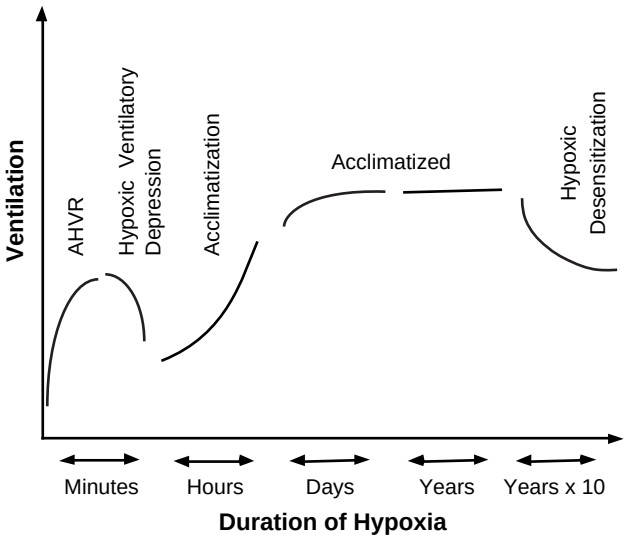

Fig. 21-3. Ventilation responses to hypoxia change as the exposure increases in duration. The acute hypoxic ventilatory response (AHVR) increases ventilation over the first 5 to 8 minutes. After about 10 minutes of hypoxia, some of the initial increase abates during hypoxic ventilatory depression. Over the next hours and days, ventilation increases as the ventilatory depression disappears, and ventilatory acclimatization occurs. Fully developed ventilatory acclimatization is characterized by hyperventilation, which is sustained for years at high altitude. A fall in ventilation that sometimes occurs after decades of altitude residence has been called hypoxic desentization. Adapted with permission from Weil JV. Ventilatory control at high altitude. In: Fishman AP, Cherniak NS, Widdicombe JG, Geiger SR, eds. *Handbook of Physiology. Section 3: The Respiratory System. Vol 2: Control of Breathing, Part 2.* Bethesda, Md: American Physiological Society; 1986: 704.

How the carotid body senses oxygen levels has been intensively investigated. Following the initial report from Lopez-Barneo,[10] there is increasing evidence that the glomus type I cells have voltage-gated K^+ channels that are altered by oxygen pressure over the physiological range (see review by Benot[11]). When the P_{O_2} is high, the channels are open, allowing the egress of K^+ to maintain the negative transmembrane potential in the interior of the cell, which under these conditions is quiescent. As the P_{O_2} falls, the outward K^+ current is progressively inhibited, causing the interior of the cell to become less negative and thereby inducing membrane depolarization. A reduction in P_{O_2} thus induces electrical discharge of the glomus type I cells, which send afferent impulses up the ninth cranial nerve to the respiratory center in the medulla, resulting in an increase in ventilation within seconds. Whether changing P_{O_2} directly affects the K^+ channels by changing the configuration of key proteins, or whether it alters mitochondrial activity, or works through some other mechanism is not clear.

Many complex factors act on this basic control mechanism to modulate the resultant level of ventilation. For one thing, hypercapnia augments and hypocapnia inhibits the hypoxic response. Changes in P_{CO_2} exert direct effects on the respiratory center as well as acting indirectly by affecting chemoreceptor function.[12] Although changing P_{CO_2} levels appear to be foremost, other factors also modulate the hypoxic ventilatory response. Dopamine is thought to profoundly inhibit carotid body chemoreceptor activity, probably via effects on the Na^+ and Ca^{++} channels and the levels of cyclic adenosine monophosphate (AMP) in the glomus type I cells, which modulate the firing rate.[13] Somatic neural impulses to the central nervous system, including those from the lungs, also contribute to regulation of ventilation. With so many influences, ventilation is both highly regulated and variable from one individual to another. The interplay of these various influences within an individual account for changes in ventilation over time at altitude (see Figure 21-3).

The Acute Hypoxic Ventilatory Response

When sea-level residents are made progressively more hypoxemic over 10 minutes, the stimulus–response curve of P_{O_2} to ventilation is hyperbolic (Figure 21-4a). That the curve indeed reflects a stimulus-response relationship is theoretically likely, because P_{O_2} may be considered the actual stimulus for the carotid body, as already discussed. The acute ventilatory response can be described by Equation 9[8,14]:

$$\dot{V}_E = V_o + A \,/\, (P_{O_2} - B) \tag{9}$$

where $\dot{V}_E$ represents minute ventilation (in L/min), and V_o, the asymptote along the abscissa, represents the minute ventilation (in L/min) when the P_{O_2} is high (ie, when there is no hypoxic stimulation of ventilation). The constant *B*, empirically determined to equal 32 mm Hg,[8,14] represents the P_{O_2} below which there is no further increase in carotid body neural discharge, and ventilation is assumed to become asymptotic along the ordinate.[6,7] P_{O_2}, by convenience, usually represents the alveolar oxygen pressure (P_{AO_2}, in mm Hg), and *A* represents the shape parameter for the curve. Figure 21-4a shows clearly that a higher A value corresponds with a greater "drive" to breathe, whereas a lower A value characterizes individuals with a less-sen-

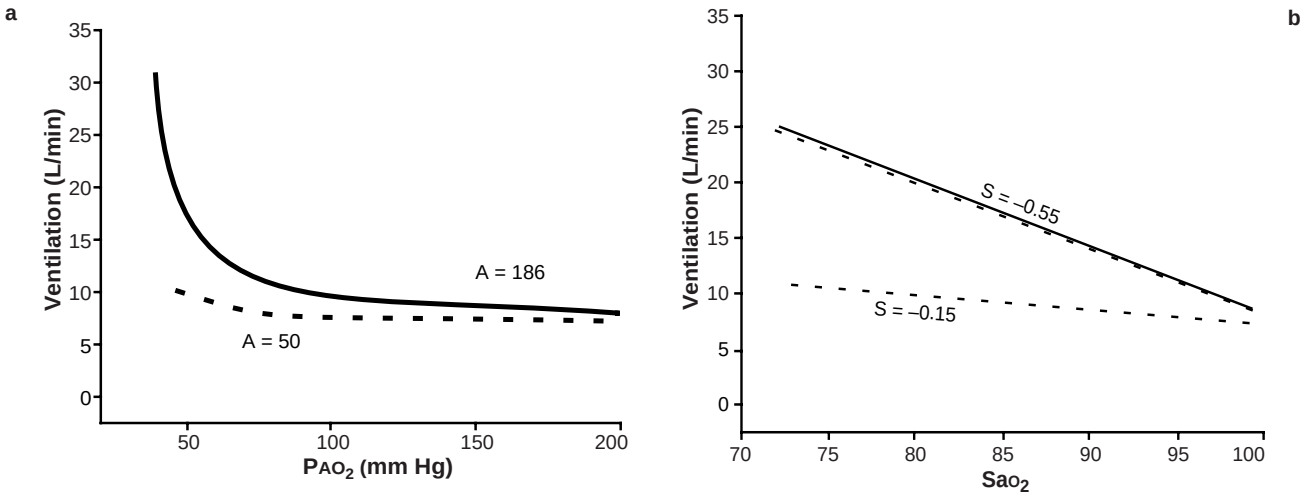

Fig. 21-4. The acute hypoxic ventilatory response is quantified by the increase in ventilation measured as alveolar oxygen pressure (P_{AO_2}) is decreased. (**a**) The stimulus-response curve is generated by plotting minute ventilation as P_{AO_2} is progressively lowered over 5–8 minutes from a high value to about 45 mm Hg. The shape parameter, A, from the response curve's equation, quantifies an individual's "drive" to ventilate ($\dot{V}_E = V_o + A \,/\, P_{O_2} - B$), where $\dot{V}_E$ represents minute ventilation (in L/min), and V_o, the asymptote along the abscissa, represents the minute ventilation (in L/min) when the P_{O_2} is high (ie, when there is no hypoxic stimulation of ventilation). The constant *B*, empirically determined to equal 32 mm Hg, represents the P_{O_2} below which there is no further increase in carotid body neural discharge, and ventilation is assumed to become asymptotic along the ordinate.[1,2] P_{O_2}, by convenience, usually represents the alveolar oxygen pressure (P_{AO_2}, in mm Hg).

The average response (solid line) for 44 normal men and women has a shape parameter equal to 186 (the shape parameter's units are generally ignored), whereas in a subgroup of individuals whose response to hypoxia was at the low end of the normal range (broken line), the value of A is 50.[3,4] (**b**) For the tests plotted in panel (a), the corresponding relationship between minute ventilation and the arterial oxygen saturation (Sa_{O_2}) is linear with a negative slope.

References for the figure legend: (1) Hornbein TF. The relation between stimulus to chemoreceptors and their response. In: Torrance RW, ed. *Arterial Chemoreceptors*. Oxford, Edinburgh, Scotland: Blackwell Scientific Publications; 1968: 65–78. (2) von Euler US, Liljestrand G, Zotterman Y. The excitation mechanism of the chemoreceptor in the carotid body. *Scand Arch Physiol*. 1939;83:132–152. (3) Weil JV, Byrne-Quinn E, Sodal IE, Filley GF, Grover RF. Hypoxic ventilatory drive in normal man. *J Clin Invest*. 1971;50:186–195. (4) Hirschman CA, McCullough RE, Weil JV. Normal values for hypoxic and hypercapnic ventilatory drives in man. *J Appl Physiol*. 1975;38:1095–1098.
Data sources for the graphs: (1) Weil JV, Byrne-Quinn E, Sodal IE, Filley GF, Grover RF. Hypoxic ventilatory drive in normal man. *J Clin Invest*. 1971;50:186–195. (2) Hirschman CA, McCullough RE, Weil JV. Normal values for hypoxic and hypercapnic ventilatory drives in man. *J Appl Physiol*. 1975;38:1095–1098.

sitive response to falling P_{AO_2}. In a group of 44 normal Denver residents, V_o and A were measured and found to be (mean ± 1 SD) 6.9 ± 2.4 L/min, and 186 ± 85 L • mm Hg/min, respectively.[8,14] The large standard deviation for A indicates the large variability among individuals observed in the normal population.

The strength of an individual's acute ventilatory response during the 10-minute progressive hypoxia test can also be quantified using the relationship between $\dot{V}_E$ and the arterial oxygen saturation (Sa_{O_2}) (Figure 21-4b). As Sa_{O_2} falls, $\dot{V}_E$ rises linearly, such that the slope, *S*, is negative, as calculated in Equation 10:

$$S = \Delta\dot{V}_E / \Delta Sa_{O_2} \quad (10)$$

Sa_{O_2} is frequently and conveniently measured using commercial oximeters. Thus, the negative slope of the relation of $\dot{V}_E$ to Sa_{O_2} is a measure of the strength of the hypoxic ventilatory response, where the strength of an individual's hypoxic ventilatory response increases as the slope becomes more negative. The curvilinear relation of $\dot{V}_E$ (and carotid body neural discharge) to P_{AO_2}, as shown in Equation 9 and Figure 21-4a, have been thought to reflect the shape of the oxyhemoglobin dissociation curve (ODC). Therefore, using Sa_{O_2} rather than P_{AO_2} to describe ventilatory responsiveness linearizes the relationship between stimulus and response, although the stimulus to the carotid body is thought to be oxygen pressure rather than hemoglobin saturation. Another advantage of using Sa_{O_2} rather than P_{AO_2} is that arterial blood (and not alveolar air) bathes the carotid chemoreceptor.

Regardless of whether the hypoxic ventilatory response is quantified using oxygen pressure to measure A, or hemoglobin saturation to measure S, it is an inherent characteristic of an individual that provides an accurate index of the strength of the ventilatory response to acute hypoxia. Because there is greater concurrence between identical than fraternal twins, the response may have a familial component.[15] When P_{CO_2} is maintained at normal values during the hypoxic breathing (isocapnia), the response is greater than when P_{CO_2} is allowed to fall.[6,16] The hypoxic ventilatory response correlates with P_{CO_2} at sea level and may be a determinant of ventilation in subjects acclimatized to 4,300 m.[17] The response is increased when the metabolic rate is increased, as with eating, exercise, and hyperthyroidism. The strength of the ventilatory response to hypoxia correlates with the strength of the ventilatory response to hypercapnia,[14] suggesting that the ventilatory responses to low oxygen and high carbon dioxide are linked.

Hypoxic Ventilatory Depression

The strength of the initial hypoxic response is not sustained (Figure 21-5). For example, at P_{AO_2} of approximately 45 mm Hg, the ventilatory response during acute hypoxia rises to a maximum between 5 and 10 minutes, and then over the next 20 minutes partially declines toward the normoxic, control value. This ventilatory depression is not a response to hypocapnia, because it occurs both when P_{CO_2} is held constant (isocapnia) and when it is allowed to vary (poikilocapnia).

This hypoxic ventilatory depression may not originate from the carotid body. Studies using anesthetized cats have demonstrated that when the ventilation falls, the carotid body neural traffic does not decrease.[9] In other studies using cats, selective hypoxia of the brain stem produced the ventilatory depression, indicating that the depression is central in origin.[18] Recent research has focused on the possibility that hypoxic ventilatory depression is mediated by γ-aminobutyric acid (GABA). GABA is a central neurotransmitter released by inhibitory interneurons within the brain and spinal cord during hypoxia and is implicated in the hypoventilation of hibernating and diving animals.[19] Further, GABA administration depresses ventilation, and administration of antagonists to GABA prevents the hypoxic ventilatory depression.[20] Possibly, GABA release is a vestigial remnant of a central mechanism that was active in the aquatically adapted fetus.[21] However, anesthetized animals may not provide an appropriate model of ventilatory control in awake humans, in whom the carotid body may still regulate the ventilatory depression.[22]

Ventilation Arrival at High Altitude

Thus, in subjects rapidly transported to high altitude, opposing factors alter ventilation on arrival. On the one hand, hypoxia stimulates ventilation; on the other, the ventilatory response is limited by the development of both hypocapnia and hypoxic depression.[16] When all three factors—hypoxic stimulation, hypocapnia, and hypoxic depression—were measured over 30 minutes in a group of individuals at low altitude, these factors largely accounted for the level of ventilation observed on arrival (day 1) at high altitude (see Figure 21-5a). Approximately half of the ventilatory inhibition that occurred on arrival could be attributed to hypoxic depression, and half to the development of hypocapnia. Both inhibitory factors abated over the

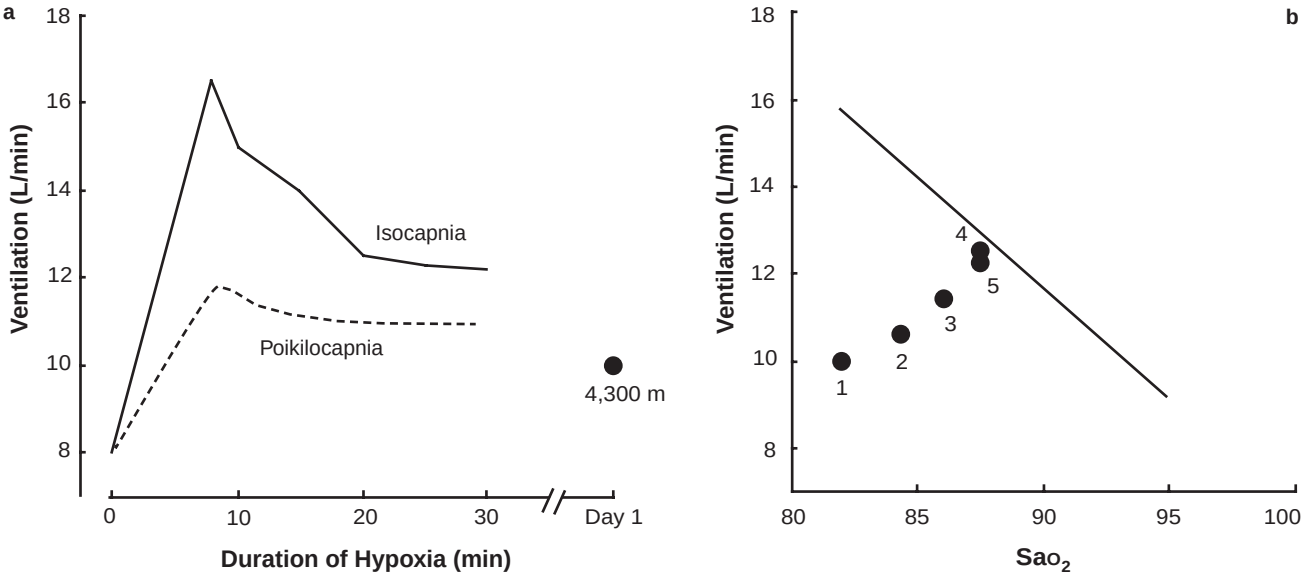

Fig. 21-5. When hypoxia is sustained for more than a few minutes, the increase in ventilation observed with acute hypoxia abates owing to ventilatory depression. (**a**) The acute ventilatory response to hypoxia (partial pressure of alveolar oxygen [P_{AO_2}] ~ 45 mm Hg) and the ventilatory response to hypoxia sustained over the next 30 minutes were measured in 11 male residents of 1,600 m. Ventilation is greater when the partial pressure of alveolar carbon dioxide (P_{ACO_2}) is held constant (isocapnia, solid line) than when it is allowed to fall (poikiolcapnia, dotted line) during the hypoxia. However, ventilatory depression begins after about 10 minutes of hypoxia, regardless of whether the partial pressure of carbon dioxide (P_{CO_2}) is maintained or allowed to fall. Resting ventilation in these subjects on arrival at 4,300 m was near that observed during sustained poikilocapnic hypoxia at 1,600 m. (**b**) For the same 11 subjects at 1,600 m (solid line), the mean values of resting ventilation and the corresponding arterial oxygen saturation (SaO_2) were measured on each of the first 5 days during acclimatization at 4,300 m (closed circles, days 1–5). These observations suggest that ventilation on arrival at altitude could be predicted from low altitude hypoxic tests when there was hypocapnia and hypoxic depression, whereas the acclimatized ventilation could be predicted from the acute isocapnic hypoxic ventilatory response at low altitude. Adapted with permission from Huang SY, Alexander JK, Grover RF, et al. Hypocapnia and sustained hypoxia blunt ventilation on arrival at high altitude. *J Appl Physiol*. 1984;56:604.

next several days at altitude, and the ventilation observed was that predicted by the acute ventilatory response to isocapnic hypoxia at low altitude (see Figure 21-5b). The loss, over several days, of the factors inhibiting ventilation at altitude may contribute to the process of ventilatory acclimatization, as will be discussed in the next section of this chapter.

The increase in ventilation at altitude is a true hyperventilation, in that ventilation increases out of proportion to metabolic requirements. However, resting metabolic rate increases on arrival at altitude,[5,23] and this increased metabolic rate is another contributing factor signaling for an increase in ventilation. This is demonstrated by the findings that propranolol treatment to induce dense β-adrenergic blockade prevented the increase in metabolic rate and lowered ventilation at altitude compared to placebo treatment.[5] However, ventilation rose progressively and P_{aCO_2} fell progressively in both propranolol- and placebo-treated subjects.[5] Thus, these data were interpreted to indicate that the increase in metabolic rate on arrival at altitude does stimulate ventilation; however, this effect was separate from the process of ventilatory acclimatization.

Ventilatory Acclimatization to High Altitude

Ventilation increases during the first days after arrival at high altitude through a poorly understood process termed "ventilatory acclimatization." As ventilation increases, P_{CO_2} falls and arterial pH and Sa_{O_2} rise (Figure 21-6). More time is required for full development of ventilatory acclimatization (evidenced by plateauing of these responses) when the altitude ascended increases (Figure 21-7). The rise in ventilation develops progressively over several days following arrival at altitude, even though hypoxemia—a ventilatory stimulus—progressively decreases, and hypocapnic alkalosis—usually con-

sidered a ventilatory inhibitor—increases. Concomitantly, the hypoxic ventilatory response increases.[4,24] Paradoxically therefore, both ventilation and the acute ventilatory response to hypoxia increase under conditions not usually considered conducive to such an increase.

Simultaneously defending both arterial Pa_{O_2} and acid–base balance presents a physiological dilemma for the lowlander on arrival at altitude. The dilemma is that a large increase in ventilation to raise Pa_{O_2} would cause severe alkalosis, whereas constraining ventilation at altitude to maintain normal sea-level Pa_{CO_2} and pH would result in severe hypoxemia. The dilemma arises because the ventilatory response to hypoxia occurs immediately, but the renal compensation to respiratory alkalosis requires several days. The body resolves the dilemma with a compromise where the initial increase in ventilation is incomplete on arrival at altitude, thus the acid–base derangement is minimal. The passage

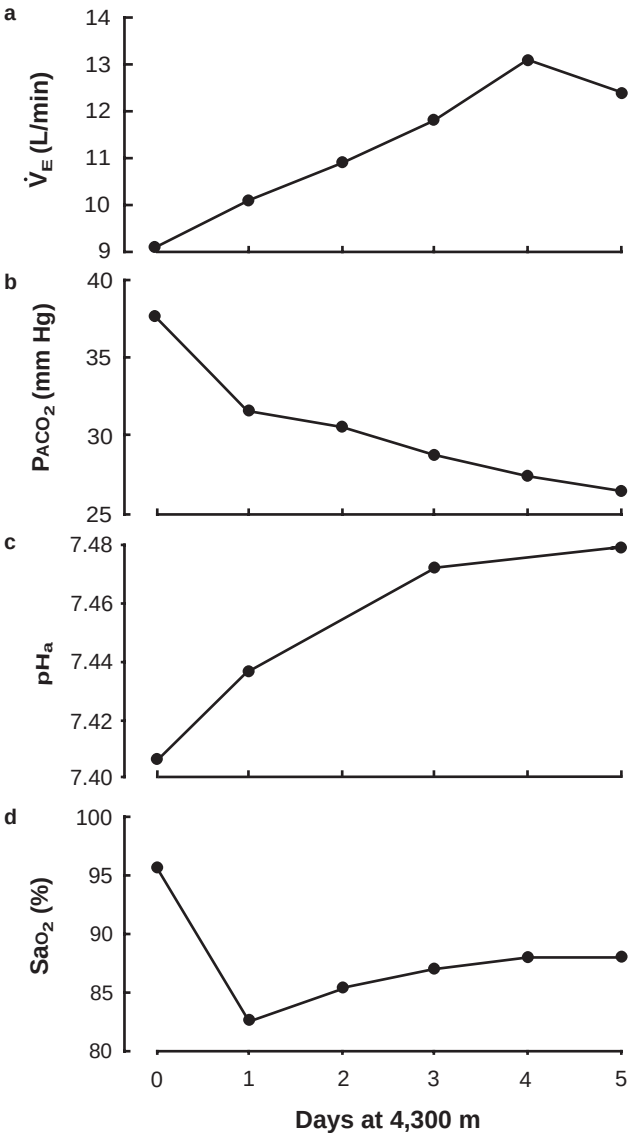

Fig. 21-6. Ventilatory acclimatization at altitude is characterized by time-dependent changes in ventilation. The four panels in this figure show (**a**) ventilation ($\dot{V}_E$), (**b**) the partial pressure of alveolar carbon dioxide (P_{ACO_2}), (**c**) arterial pH (pHa), and (**d**) oxygen saturation of arterial blood (Sa_{O_2}) measured in 11 normal men at their residence altitude of 1,600 m and on days 1 through 5 after arriving at 4,300 m. Adapted with permission from Huang SY, Alexander JK, Grover RF, et al. Hypocapnia and sustained hypoxia blunt ventilation on arrival at high altitude. *J Appl Physiol*. 1984;56:603.

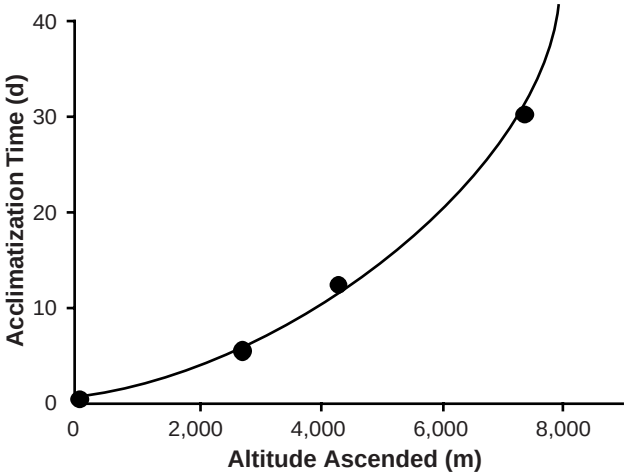

Fig. 21-7. The time required for ventilatory acclimatization varies with elevation ascended above residence altitude. The curve was drawn from three points reflecting altitude gains of 2,700 m (Denver to Pikes Peak[1]), 4,300 m (sea level to Pikes Peak[2]), and 7,380 m (sea level to simulated altitude[3]). The time indicated for ventilatory acclimatization to an ascent of 8,100 m (30 d) should be considered hypothetical because the data at this point were derived from a progressively staged ascent (as opposed to a continuous ascent as in the other data points), and a continous ascent to that elevation is not physiologically tolerable.

Data sources: (1) Huang SY, Alexander JK, Grover RF, et al. Hypocapnia and sustained hypoxia blunt ventilation on arrival at high altitude. *J Appl Physiol*. 1984;56:602–606. (2) Green HJ, Sutton JR, Wolfel EE, Reeves JT, Butterfield GE, Brooks GA. Altitude acclimatization and energy metabolic adaptations in skeletal muscle during exercise. *J Appl Physiol*. 1992;73:2701–2708. (3) Reeves JT, Groves, BM, Sutton R, et al. Adaptations to hypoxia: Lessons from Operation Everest II. In: Simmons DH, ed. *Current Pulmonology*. St Louis, Mo: Mosby–Year Book; 1991: 23–50.

of time for development of the large increase in ventilation that is characteristic of full acclimatization provides time for renal compensation by bicarbonate excretion to limit alkalosis. Although other factors may play a role, the principal mechanisms mediating this ventilatory acclimatization involve the central chemoreceptors (pH receptors in the medulla) and the peripheral chemoreceptors (P_{O_2} receptors in the carotid body).

Central (Medullary) Chemoreceptor Mechanisms

Ventilation is sensitive to small changes in medullary pH, increasing with increased concentration of hydrogen ions [H^+], and decreasing with decreased [H^+]. An early view considered that ventilatory acclimatization reflected a progressive withdrawal of the inhibitory effects exerted by the central chemoreceptor in response to hypocapnic alkalosis. As acclimatization proceeds, the concentration of bicarbonate [HCO_3^-] in the blood and cerebral spinal fluid falls due to renal compensation concomitant with the decline in P_{CO_2}, thus limiting the fall in [H^+]. In addition, hypoxia may increase metabolic production of lactate in the brain, which could increase [H^+] concentration near the medullary chemoreceptor. Either mechanism would tend to restore normal pH in or near the medullary chemoreceptor, despite decreased arterial P_{CO_2}. The ventilatory response to carbon dioxide is shifted to lower P_{CO_2} values, and the slope of the response becomes somewhat steeper. While this early view implicating the central chemoreceptor in the acclimatization process is attractive and may be correct, there is little direct evidence to support it.[12,25]

Peripheral (Carotid) Chemoreceptor Mechanisms

An alternative view attributes ventilatory acclimatization to an increase in hypoxic sensitivity of the carotid (ie, peripheral) chemoreceptor. Studies with animals show neural activity from the carotid body progressively increasing over time at altitude.[26] In goats, acclimatization occurs within hours when the hypoxia is limited to the carotid bodies, but does not occur when the hypoxia is limited to the central nervous system.[9] Further, acclimatization occurs with carotid body hypoxia whether or not there is accompanying hypocapnia.[12,25] The studies have suggested that acclimatization occurs within the carotid body, possibly independent of the changes within the central nervous system.

Experiments involving human subjects appear to confirm the conclusions from those with animals. In one study, maintaining normocapnia reportedly prevented ventilatory acclimatization in humans who were exposed for 100 hours to hypobaric hypoxia[27]; however, these experiments appeared flawed[4,9,25] in that there was poor control of carbon dioxide, particularly during the first 24 hours of altitude exposure, during which time only one measurement was made. In more-recent and better-controlled human studies, ventilation and the ventilatory response to acute hypoxia were observed to increase progressively during the first 8 hours of hypoxia—even though P_{CO_2} was tightly maintained at sea-level values.[4,24] These results indicate that in man, as in the goat, ventilatory acclimatization to hypoxia can develop in the absence of hypocapnia and, therefore, is not merely a matter of overcoming central hypocapnic alkalosis. Still, ventilation appears to rise more rapidly during hypoxia with normocapnia than with hypocapnia,[4,27] so the possibility of some role for the central chemoreceptor in the process of ventilatory acclimatization cannot be entirely ruled out.[4,24] Nevertheless, the weight of current evidence suggests that acclimatization results primarily from a progressive effect of hypoxia on the carotid body.

Acclimatization to Altitude: Rest

The reduction in P_{aCO_2} and the increase in P_{AO_2} with ventilatory acclimatization at altitude becomes more pronounced with increasing altitude (Figure 21-8). For ethical reasons, unacclimatized subjects are not studied at altitudes above approximately 4,500 m. In unacclimatized subjects, P_{aCO_2} values observed at 4,300 to 4,500 m were approximately 10 mm Hg higher than in acclimatized subjects at the same altitudes. The higher P_{aCO_2} values maintained in the unacclimatized subjects dictate lower P_{AO_2} values than in acclimatized subjects, thus limiting the altitude to which the unacclimatized are able to ascend. Inspection of Figure 21-8b indicates that the unacclimatized subjects at 4,300 to 4,500 m had P_{AO_2} values similar to the values in acclimatized subjects above 7,000 m.

The increasing importance of ventilatory acclimatization with increasing altitude was first noted by Fitzgerald,[28] and later by Rahn and Otis,[29] who illustrated this relationship by plotting their observations on a $P_{ACO_2} - P_{AO_2}$ diagram. This classical representation of the effects of ventilatory acclimatization is depicted in Figure 21-9, in which the early observations by Rahn and Otis[29] are displayed along with more-recent data that were obtained during the American Medical Research Expedition to Everest (AMREE)[1]

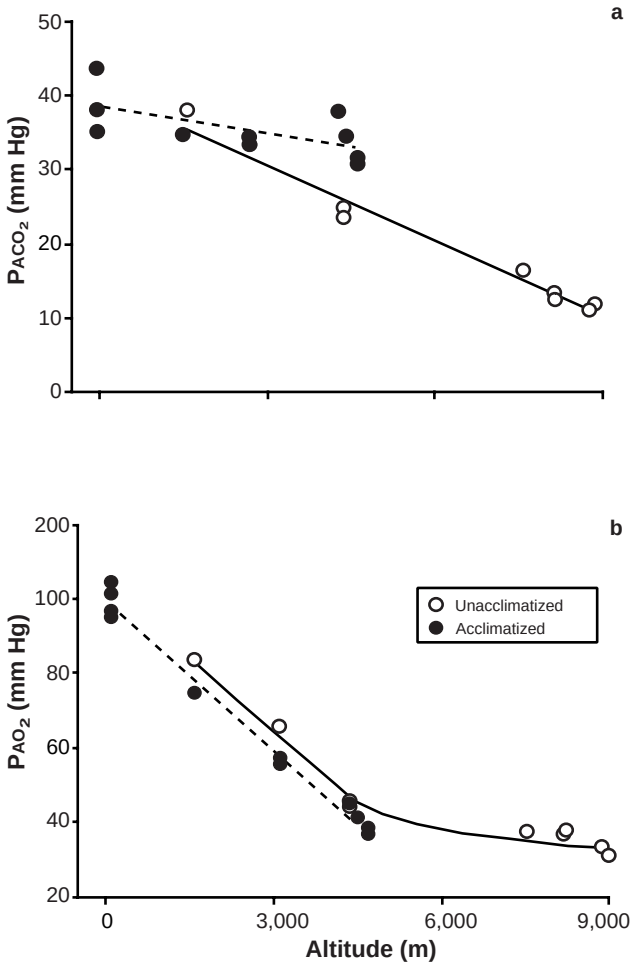

Fig. 21-8. The importance of ventilatory acclimatization becomes greater with increasing altitude. This is demonstrated by extrapolating the relationship between (**a**) the partial pressure of alveolar carbon dioxide (P_{ACO_2}) and (**b**) the partial pressure of alveolar oxygen (P_{AO_2}) in subjects unacclimatized to the high elevations (open circles, dotted lines[1–5]) and then comparing the extrapolated values with those observed in acclimatized subjects (closed circles, solid lines[6–12]).
Data sources for a: (1) Sutton JR, Reeves JT, Wagner PD, et al. Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol.* 1988;64:1309–1321. (2) Wagner PD, Gale GE, Moon R.E, Torre-Bueno JR, Stolp BW, Saltzman HA. Pulmonary gas exchange in humans exercising at sea level and simulated altitude. *J Appl Physiol*. 1986;61:260–270. (3) Bender PR, Groves BM, McCullough RE, et al. Oxygen transport to exercising leg in chronic hypoxia. *J Appl Physiol*. 1988;65:2592–2597. (4) Bender PR, McCullough RE, McCullough RG, et al. Increased exercise Sa_{O_2} independent of ventilatory acclimatization at 4300 m. *J Appl Physiol*. 1989;66:2733–2738. (5) Dempsey JA, Reddan WG, Birnbaum ML, et al. Effects of acute through life-long hypoxic exposure on exercise, pulmonary gas exchange. *Resp Physiol*. 1971;13:62–89.
Data sources for b: (6) Huang SY, Alexander JK, Grover RF, et al. Hypocapnia and sustained hypoxia blunt ventilation on arrival at high altitude. *J Appl Physiol*. 1984;56:602–606. (7) Malconian MK, Rock PB, Reeves JT, Cymerman A, Houston CS. Operation Everest II: Gas tensions in expired air and arterial blood at extreme altitude. *Aviat Space and Environ Med*. 1993;64:37–42. (8) Sutton JR, Reeves JT, Wagner PD, et al. Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol.* 1988;64:1309–1321. (9) West JB, Hackett PH, Maret KH, et al. Pulmonary gas exchange on the summit of Mount Everest. *J Appl Physiol*. 1983;55:678–687. (10) Bender PR, Groves BM, McCullough RE, et al. Oxygen transport to exercising leg in chronic hypoxia. *J Appl Physiol*. 1988;65:2592–2597. (11) Dempsey JA, Reddan WG, Birnbaum ML, et al. Effects of acute through life-long hypoxic exposure on exercise, pulmonary gas exchange. *Resp Physiol*. 1971;13:62–89. (12) Authors' unpublished observations.

and Operation Everest II,[30] which are shown for comparison. Despite being obtained at higher altitudes, the more-recent data show good agreement with the earlier findings from lower elevations.

The crucial importance of ventilatory acclimatization for ascent to extreme altitudes is demonstrated in Figure 21-9. Without an increase in ventilation at altitude, human beings breathing air might not be able to climb Mont Blanc, and certainly could not scale Mount Everest. At the summit of Mount Everest, the inspired P_{O_2} is only 43 mm Hg. If there were no increase in ventilation, then the P_{IO_2}-to-P_{AO_2} gradient would remain the same as at sea level, at 40 mm Hg. In that case, the P_{AO_2} would fall to 3 mm Hg, and life would not be possible. However, the increased ventilation with acclimatization enables the resting alveolar P_{AO_2} to be maintained at 33 to 35 mm Hg on the summit of Mount Everest, only 8 to 10 mm Hg less than that in the inspired air, values that are compatible with life.[30] Thus the ventilation-mediated reduction in P_{ACO_2} reduces the P_{O_2} gradient from the inspired to the alveolar air, resulting in an alveolar oxygen concentration higher than would otherwise be possible.

Acclimatization to Altitude: Exercise

Exercise and hypoxia act synergistically to increase ventilation.[31] The synergism may be seen by comparing ventilatory changes during progressive hypoxia at rest (ie, the standard hypoxic ventilatory response) with the analogous ventilatory response to progressive hypoxia measured in exercising subjects. At rest, the increase in ventilation

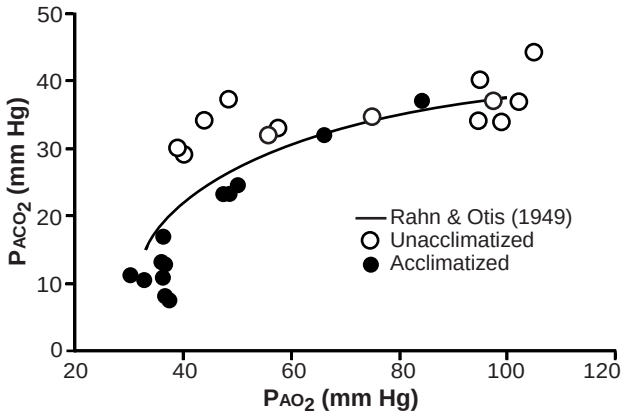

Fig. 21-9. The relationship between the partial pressure of alveolar carbon dioxide (P_{ACO_2}) and oxygen (P_{AO_2}) shifts with ventilatory acclimatization, as indicated by the diagram, which is drawn from data from unacclimatized subjects[1–5] (open symbols) and acclimatized subjects[6–12] (closed symbols). Also shown (solid line) for comparison is the curve redrawn from older data reported by Rahn and Otis.[13]
Data sources for unacclimatized subjects: (1) Sutton JR, Reeves JT, Wagner PD, et al. Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol.* 1988;64:1309–1321. (2) Wagner PD, Gale GE, Moon R.E, Torre-Bueno JR, Stolp BW, Saltzman HA. Pulmonary gas exchange in humans exercising at sea level and simulated altitude. *J Appl Physiol*. 1986;61:260–270. (3) Bender PR, Groves BM, McCullough RE, et al. Oxygen transport to exercising leg in chronic hypoxia. *J Appl Physiol*. 1988;65:2592–2597. (4) Bender RR, McCullough RE, McCullough RG, et al. Increased exercise Sa_{O_2} independent of ventilatory acclimatization at 4300 m. *J Appl Physiol*. 1989;66:2733–2738. (5) Torre-Bueno JR, Wagner PD, Saltzman HA, Gale GE, Moon RE. Diffusion limitation in normal humans during exercise at sea level and simulated altitude. *J Appl Physiol*. 1985;58:989–995.
Data sources for acclimatized subjects: (6) Huang SY, Alexander JK, Grover RF, et al. Hypocapnia and sustained hypoxia blunt ventilation on arrival at high altitude. *J Appl Physiol*. 1984;56:602–606. (7) Malconian MK, Rock PB, Reeves JT, Cymerman A, Houston CS. Operation Everest II: Gas tensions in expired air and arterial blood at extreme altitude. *Aviat Space and Environ Med*. 1993;64:37–42. (8) Sutton JR, Reeves JT, Wagner PD, et al. Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol*. 1988;64:1309–1321. (9) West JB, Hackett PH, Maret KH, et al. Pulmonary gas exchange on the summit of Mount Everest. *J Appl Physiol*. 1983;55:678–687. (10) Bender PR, Groves BM, McCullough RE, et al. Oxygen transport to exercising leg in chronic hypoxia. *J Appl Physiol*. 1988;65:2592–2597. (11) Dempsey JA, Reddan WG, Birnbaum ML, et al. Effects of acute through life-long hypoxic exposure on exercise, pulmonary gas exchange. *Resp Physiol*. 1971;13:62–89. (12) Authors' unpublished observations
Data source for comparison curve: (13) Rahn H, Otis AB. Man's respiratory response during and after acclimatization to high altitude. *Am J Physiol*. 1949;157:445–462.

with a falling P_{O_2} is curvilinear, being greater the more severe the hypoxia (Figure 21-10). During exercise, however, the whole curve is shifted to higher values of ventilation for any value of P_{O_2}. The shift to higher ventilation values is more pronounced at low than at high P_{O_2}, and the hypoxic ventilatory response curves at low P_{O_2} values become very much steeper during exercise than at rest. The synergistic effects of exercise and hypoxia on ventilation, which are more than a simple additive effect, are likely to be of great importance at altitude but not at sea level, where, in normal persons, other mechanisms of ventilatory control predominate.[32] The locus of the synergism remains unclear, but exercise may in some way increase the "gain" of the carotid chemoreceptor. For example, as depicted in Figure 21-10a, during exercise, ventilation increases in response to even small decrements in P_{O_2} within what is generally considered the normoxic range. Thus, while the hypoxic ventilatory response curve appears relatively flat in the range of 100 mm Hg in resting subjects, a pronounced slope is apparent in this range in exercising subjects. Figure 21-10b shows that a similar exercise-associated increase in chemoreceptor gain is apparent in the ventilatory response to increasing P_{CO_2}.

At issue is the application of these effects on the exercise ventilation of persons ascending to and remaining at high altitude. The report of Dempsey and colleagues[33] provides insight regarding the time course and magnitude for acclimatization of exercise ventilation during sojourns at high altitude. In that study,[33] ventilation of normal sea-level residents was measured both at rest and during exercise at sea level, before and after they were switched from breathing normoxic gas to a P_{IO_2} of 100 mm Hg, simulating ambient air at Leadville, Colorado (3,100 m). Ventilation was measured again during rest and exercise and while breathing ambient air on days 4, 21, and 45 of residence at Leadville. Figure 21-10c shows that, as panel (a) predicts, resting ventilation remained little changed (8.6–8.7 L/min) with acute hypoxia, even though Pa_{O_2} in these subjects fell to 56 mm Hg. In contrast, Figure 21-10d shows that ventilation during exercise increased dramatically when the breathing mixture was acutely switched from normoxic to a P_{IO_2} of 100 mm Hg, even though Pa_{O_2} fell similarly (to 55 mm Hg)

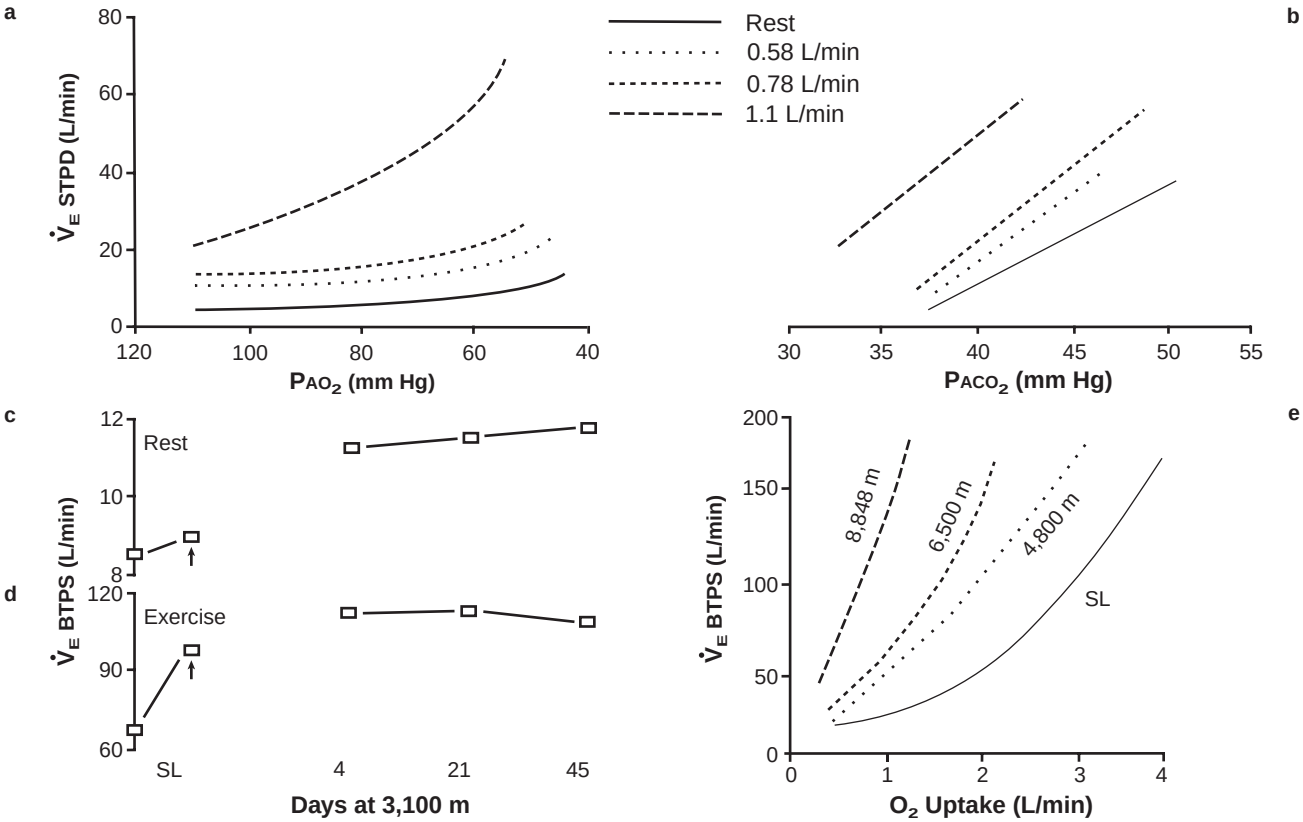

Fig. 21-10. The effect of exercise on ventilation is synergistic with those of hypoxia and hypercapnia. (**a**) Ventilation at standard temperature, pressure, and dry ($P_{H_2O} = 0$) ($\dot{V}_{E\ STPD}$), is measured during acute progressive hypoxia in subjects resting (solid line) or exercising at three different intensities (broken lines) on a supine cycle ergometer. As indicated, increasing metabolism results in increasing ventilation at all partial pressures of alveolar oxygen (P_{AO_2}), but the increments in ventilation with increasing metabolism are greatest at the lowest P_{AO_2}. (**b**) A similar synergism on ventilation of the effects of increasing metabolism is seen with increasing partial pressure of alveolar carbon dioxide (P_{ACO_2}).

The duration of exposure to altitude affects the ventilatory response to exercise. (**c**) Resting ventilation and (**d**) exercise ($\dot{V}O_2 = 2.29$ L/min) ventilation at body temperature, pressure, and saturated ($\dot{V}_{E\ BTPS}$) are shown in subjects at sea level breathing normoxic air and hypoxic air (indicated by the arrow) simulating 3,100 m, and breathing ambient air at Leadville, Colorado (3,100 m), on days 4, 21, and 45. The stimulating effect of acute hypoxia on ventilation at sea level is more pronounced during exercise (seen in **d**) than at rest (seen in **c**), whereas the effect of ventilatory acclimatization appears more pronounced when measured during rest than during exercise. The relation between oxygen uptake ($\dot{V}O_2$) and ventilatory response ($\dot{V}_{E\ BTPS}$) at different altitudes is shown in (**e**). As elevation increases, so does the increment in ventilation for a given $\dot{V}O_2$, but ventilation during maximal effort is only slightly increased at altitude.

Graphs a and b: Adapted with permission from Weil JV, Bryne-Quinn E, Sodal IE, Kline JS, McCullough RE, Filley GF. Augmentation of chemosensitivity during mild exercise in normal man. *J Appl Physiol*. 1972;33:813–819. Graphs c and d: Adapted with permission from Dempsey JA, Forster HV, Birnbaum ML, et al. Control of exercise hyperpnea under varying durations of exposure to moderate hypoxia. *Respir Physiol*. 1972;16:213–231. Graph e: Adapted with permission from Sutton JR, Reeves JT, Wagner PD, et al. Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol.* 1988;64:1309–1321.

during hypoxic exercise and during hypoxic rest. The exercise increased $\dot{V}O_2$ 8-fold above the resting rate, to 2.3 L/min. Ventilation during normoxic exercise was 70 L/min, also 8-fold higher than the resting level; however, during hypoxic exercise, ventilation was almost 12-fold greater than the resting level. After 4 days' residence at Leadville, the effects of ventilatory acclimatization increased resting ventilation by 38% (to 3.7 L/min), whereas exercise ventilation increased only an additional 9% (6 L/min). There were no further changes in resting or exercise ventilation over the remainder of the 45-day stay at Leadville, indicating that, at least for altitudes around 3,100 m, ventilatory acclimatiza-

tion was complete in 4 days.

Why ventilatory acclimatization appears to have a lesser effect on exercise ventilation than on resting ventilation remains unclear, because mechanisms linking ventilation to metabolism are not fully understood. One possibility is that during exercise when the metabolic rate is high, chemoreceptor sensitivity is augmented so that stimulation of ventilation is very near the maximal levels in response acute hypoxia, with little further potential increase possible following acclimatization. Further, during rest, ventilation rates are low and respiratory muscle fatigue would not be expected to develop or limit ventilatory increases with acclimatization; but during exercise at high altitude, high ventilation rates may well lead to respiratory muscle fatigue, precluding manifestation of ventilatory acclimatization during exercise. Another potential modulating mechanism involves (*a*) the accumulation of metabolic acid (primarily lactic) during exercise and (*b*) the buffering capacity of blood plasma (ie, plasma [HCO_3^-]), both of which change with acute hypoxic exposure and altitude acclimatization. Thus during ventilatory acclimatization, ventilatory stimulation due to changes in blood pH and acid concentration during exercise will be varying. Clearly, mechanisms regulating exercise ventilation during ventilatory acclimatization require further study.

Therefore, subjects acclimatized to high altitude have higher ventilations for a given $\dot{V}O_2$ at altitude than sea level, although maximal ventilation is similar for all altitudes. Further, as the elevation increases, so does the increment in ventilation for a given $\dot{V}O_2$, as depicted in Figure 21-10e. This increase in exercise ventilation at high altitude should be viewed in perspective, however. For many years it has been recognized that when ventilation is expressed under standard (STPD) rather than body (BTPS) conditions, the ventilation during rest and exercise at different intensities is relatively independent of altitude.[34] This suggests that for a given $\dot{V}O_2$, the same number of oxygen molecules is respired at all altitudes, including sea level. The respiratory system seems to function in a remarkably well-regulated manner, regardless of the individual's elevation, acclimatization status, or severity of effort, such that ventilation brings to the lung approximately $1.7 \bullet 10^{23}$ molecules of oxygen for each liter of oxygen consumed.[3]

Blood Acid–Base Balance Following Ventilatory Acclimatization

The bicarbonate buffer system is the body's most important regulator of body fluid pH because of the

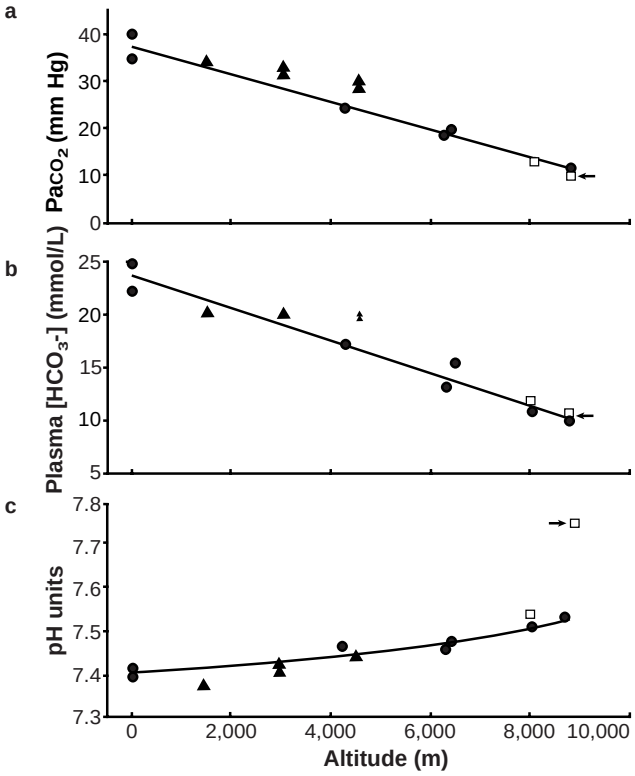

Fig. 21-11. The bicarbonate buffer system minimizes pH changes in persons ascending to high altitudes. (**a**) The closed circles indicate resting partial pressure of arterial carbon dioxide ($Paco_2$), (**b**) plasma bicarbonate concentration ([HCO_3^-]),and (**c**) arterial pH (pHa) of acclimatized subjects during a simulated ascent to the summit of Mount Everest.[1] The open squares indicate values reported[2] from an actual climb of Mount Everest, where pHa and [HCO_3^-] at the summit were estimated from alveolar air samples collected at the summit (arrow), and from a venous blood sample taken the next day at a lower altitude. The closed triangles indicate measurements from arterial blood samples obtained during acute altitude exposure.[3,4]
Data sources: (1) Sutton JR, Reeves JT, Wagner PD, et al. Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol.* 1988;64:1309–1321. (2) Sorensen SC, Severinghaus JW. Irreversible respiratory insensitvity to acute hypoxia in man born at high altitude. *J Appl Physiol*. 1968;25:217–220. (3) Gale GE, Torre-Bueno JR, Moon RE, Saltzman HA, Wagner PD. Ventilation perfusion inequality in normal humans during exercise at sea level and simulated altitude. *J Appl Physiol*. 1985;58:978–988. (4) Wagner PD, Gale GE, Moon R.E, Torre-Bueno JR, Stolp BW, Saltzman HA. Pulmonary gas exchange in humans exercising at sea level and simulated altitude. *J Appl Physiol*. 1986;61:260–270.

large body stores of bicarbonate and the link between ventilation and $Paco_2$. Changes in blood pH, $Paco_2$, and bicarbonate concentration $[HCO_3^-]$ influence each other, as described by Equation 11, also known as the Henderson-Hasslebach Equation:

$$(11) \qquad pH = pK + \log ([HCO_3^-] \div 0.03 \bullet Pco_2)$$

where $[HCO_3^-]$ represents plasma bicarbonate concentration (in mmol/L), Pco_2 is expressed in mm Hg, and *pK* represents the equilibrium constant for the formation of carbonic acid from CO_2 and H_2O, which is about 6.1 at body temperature. The equation shows that if a fall in $Paco_2$ is not accompanied by an offsetting fall in plasma $[HCO_3^-]$, then blood pH will rise. The decline in $Paco_2$ that occurs with ventilatory acclimatization during ascent to moderate elevations (< 5,000 m) is accompanied by a fall in plasma $[HCO_3^-]$, which maintains higher blood pH values in acclimatized[2,35] compared with unacclimatized[36,37] subjects (Figure 21-11). Over time, HCO_3^- is eliminated from the body in the urine; however, the body stores of HCO_3^- are quite large. For example, a 70-kg person living at sea level with plasma $[HCO_3^-]$ of 25 mEq/L, has approximately 90 mEq $[HCO_3^-]$ in the blood, 260 mEq in the interstitial fluid, and 700 mEq in the intracellular fluid. Elimination of approximately 400 mEq of HCO_3^- to allow blood concentration to fall to 15 mEq/L, the value normally seen after acclimatization at 4,300 m, requires 10 to 14 days.

In well-acclimatized subjects, the $Paco_2$ and plasma $[HCO_3^-]$ continue to decrease with ascent to higher altitudes, but not sufficiently to prevent a rise in pH. In fact, findings reported from AMREE suggest that pH may rise extraordinarily high in persons ascending to the summit of Mount Everest.[2] During AMREE, a pH of 7.78 was calculated indirectly from $Paco_2$, which was determined by measuring (*a*) Pco_2 in a subject's alveolar air sample, obtained shortly after he reached the summit (8,848 m), and (*b*) plasma $[HCO_3^-]$, which was determined from a blood sample obtained at a lower altitude the following day.[38] In contrast, direct measurements of resting arterial pH in subjects participating in the Operation Everest II altitude chamber study[35] averaged 7.56 at the barometric pressure equivalent of the summit of Mount Everest (P_B = 253 mm Hg). The extreme exertion required to actually reach the summit of Everest, the nonsimultaneous sampling of blood and alveolar air, and the substantially lower pH values in Operation Everest II subjects at the simulated summit raise questions about the validity of extreme alkalotic arterial pH estimated from the AMREE measurements. Figure 21-11 shows that the calculated pH values reported from AMREE at the slightly lower elevation of 8,050 m, where the blood and alveolar air were sampled at the same altitude and time, fell close to the arterial pH values measured directly at the equivalent pressure during the Operation Everest II study. However, a chamber study does not reproduce all the conditions of a climb, so the issue of how high arterial pH can rise at high altitude remains open, pending direct measurements of arterial pH in subjects actually ascending Everest.

Exercise alters the acid–base balance. The interactions between (*a*) effects of altitude and exercise on acid–base balance and (*b*) the three variables of interest ($[HCO_3^-]$, pH, and Pco_2) may be examined in Figure 21-12. At sea level, release of fixed acids (primarily lactic acid) during exercise of increasing

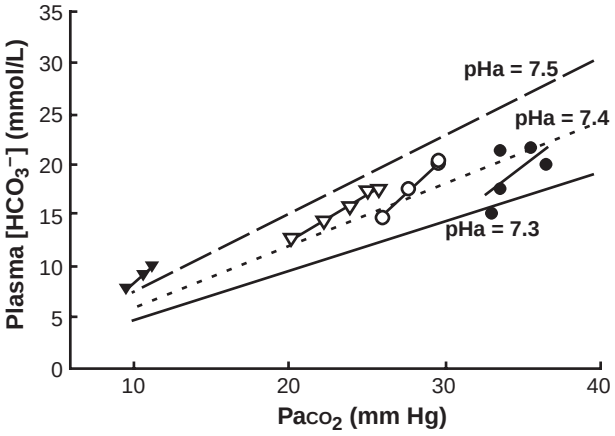

Fig. 21-12. Acute exposure to high altitude and altitude acclimatization affect the components of the Henderson-Hasslebach Equation such that acid–base balance during exercise is altered. At sea level (closed circles), the partial pressure of arterial carbon dioxide ($Paco_2$), plasma bicarbonate concentration ($[HCO_3^-]$) and arterial ph (pHa) progressively decrease from resting levels (on the right of the graph) as intensity increases to maximal (toward the left). The decrease also occurs at high altitude, but the relationship among $Paco_2$, plasma $[HCO_3^-]$, and pHa is shifted with acute (unacclimatized at 4,570 m, open circles) and chronic (acclimatized at 4,500 m, open triangles) exposure to altitude, and at the pressure equivalent of the summit of Mount Everest (closed triangles).
Data sources: (1) Sutton JR, Reeves JT, Wagner PD, et al. Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol*. 1988;64:1309–1321. (2) Wagner PD, Gale GE, Moon R.E, Torre-Bueno JR, Stolp BW, Saltzman HA. Pulmonary gas exchange in humans exercising at sea level and simulated altitude. *J Appl Physiol*. 1986;61:260–270.

intensity up to maximal effort causes pH to fall progressively below the resting value with an accompanying slight decrease in Pa_{CO_2} and plasma [HCO_3^-]. At altitude, the release of fixed acids during exercise also results in acidosis. However, the changes in pH during exercise at altitude are modulated by the respiratory hypocapnic alkalosis, lactate production and disposal, and the buffering capacity of the blood, all of which begin changing on arrival at high altitude. With acute altitude exposure, the exercise-related metabolic acidosis is superimposed over the initial altitude-related respiratory alkalosis that slightly elevates resting pH. For acclimatized subjects at altitude, the hypocapnic alkalosis is fully developed, as evidenced by the more marked fall in resting Pa_{CO_2} and plasma [HCO_3^-], and the rise in resting pH. As at sea level, pH falls with progressively increasing exercise intensity up to maximal, accompanied by slight decreases in P_{CO_2} and [HCO_3^-]. The important point is that the lactic acid concentration in arterial blood correlates closely with developing acidosis during progressively increasing exercise intensity to maximal both at sea level and at high altitude (Figure 21-13).

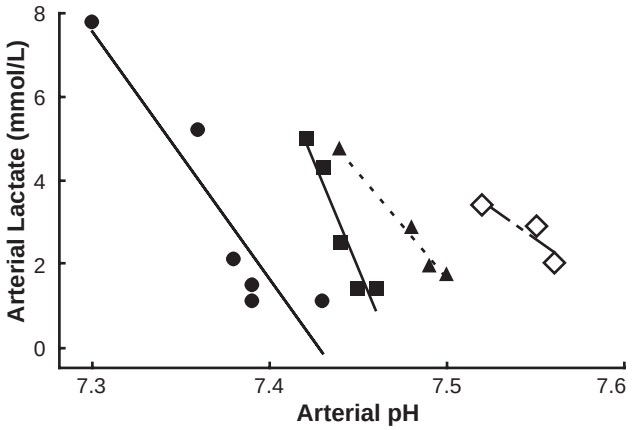

Fig. 21-13. Changes in arterial lactate concentration and arterial pH are closely related during progressive intensity exercise from rest to maximal, both at sea level and at high altitudes, even in acclimatized lowlanders exercising at extreme altitudes, when lactate concentrations do not increase much. The circles, squares, triangles, and diamonds represent measurements that were made at sea level and at simulated altitudes of 4,900, 6,100, and 7,620 m. Data source: Sutton JR, Reeves JT, Wagner PD, et al. Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol.* 1988;64:Tables 2–5.

Summary of Ventilation at High Altitude

The ventilatory changes experienced by lowlanders who ascend to high altitudes and remain can be summarized as follows. As barometric pressure falls, ventilation (the first step in the oxygen cascade) increases, raising alveolar oxygen tension and limiting the fall in the P_{O_2} pressure gradient from the inspired air to the alveolus. The increased ventilation at altitude is driven primarily by the increased carotid chemoreceptor activity. The increased ventilation also increases the removal of carbon dioxide from the blood. The resulting hypocapnic alkalosis, which accompanies the increased ventilation, may be partially responsible for delaying the full increase in ventilation (ie, ventilatory acclimatization), which can require a week or more to develop at moderately high altitudes. Ventilation ($\dot{V}_{E\ BTPS}$) during maximal exercise appears to be similar at all altitudes, but the number of oxygen molecules that can be transported $\dot{V}_{E\ STPD}$ decreases with altitude. Given the close relationship of the number of oxygen molecules ventilated and those taken up, then at low barometric pressure, ventilation is particularly important in limiting the fall in maximum exercise capacity.

ALVEOLAR–ARTERIAL OXYGEN PRESSURE GRADIENT

The P_{O_2} gradient from alveolus (P_{AO_2}) to artery (Pa_{O_2}) has two components: (1) venous admixture of arterial blood and (2) the oxygen diffusion gradient from alveolus to the lung capillary blood. Although under normal circumstances, systemic arterial P_{O_2} is only slightly less than the P_{O_2} of blood leaving a pulmonary capillary, certain physiological states create a rapid capillary transfer that may not allow for anywhere near normal diffusion time. This effect becomes increasingly apparent during exercise at altitude and can be quantitated by measuring the difference between alveolar P_{O_2} and systemic artery P_{O_2} ($P_{AO_2} - Pa_{O_2}$), by convention this being taken as pressure that drives diffusion. Systemic Pa_{O_2}, which can easily be measured, is taken as a surrogate for P_{O_2} at the end of a capillary, which cannot be measured. One characteristic of the $P_{AO_2} - Pa_{O_2}$ shown in Figure 21-14 is that it increases with increasing oxygen uptake at all altitudes. However, the relative contribution to the $P_{AO_2} - Pa_{O_2}$ by venous admixture versus diffusion changes with increasing altitude.

The ODC is not, strictly speaking, a component of the $P_{AO_2} - Pa_{O_2}$ gradient. However, the ODC defines the relationship between changes in Pa_{O_2}, Sa_{O_2}, and Ca_{O_2}. The ODC is determined by the af-

finity of hemoglobin for oxygen, which varies with Pa_{O_2} as shown in Figure 21-15. The Ca_{O_2} is determined by Equation 12:

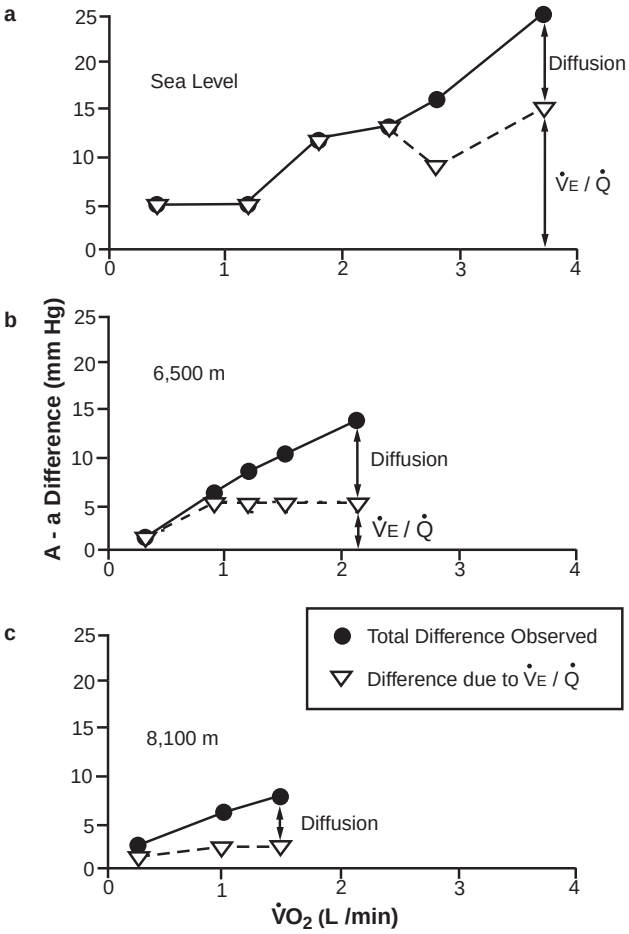

Fig. 21-14. The alveolar – arterial difference in the partial pressure of oxygen ($P_{AO_2} - Pa_{O_2}$) widens with increasing exercise intensity and oxygen consumption per unit time ($\dot{V}_{O_2}$), both at (**a**) sea level and (**b** and **c**) high altitude (6,100 m and 8,100 m, respectively). The $P_{AO_2} - Pa_{O_2}$ can be partitioned into components of diffusion and venous admixture. Venous admixture results from shunting and ventilation–perfusion mismatch ($\dot{V}_E/\dot{Q}$), with the latter predominating during exercise or at high altitude. When the $\dot{V}_E/\dot{Q}$ component (open symbols) of the $P_{AO_2} - Pa_{O_2}$ accounts for less than the total $P_{AO_2} - Pa_{O_2}$ measured (closed symbols), the difference represents the diffusion component. As exercise intensity increases, the diffusion accounts for increasingly more of the total $P_{AO_2} - Pa_{O_2}$. As elevation increases, the diffusion component becomes significant at lower exercise intensities than at sea level. Adapted with permission from Wagner PD, Sutton JR, Reeves JT, Cymerman A, Groves BM, Malconian MK. Operation Everest II: Pulmonary gas exchange during a simulated ascent of Mt Everest. *J Appl Physiol*. 1987;63:2354.

(12) $$Ca_{O_2} = Sa_{O_2} \bullet [Hb] \bullet A$$

where Ca_{O_2} represents arterial oxygen content, Sa_{O_2} represents the oxygen saturation of arterial blood, *[Hb]* represents arterial hemoglobin concentration, and the constant *A* defines the maximal amount of oxygen that can bind to a unit of hemoglobin (the value of which varies among individuals from 1.34 to 1.36 mL of oxygen per gram of hemoglobin). The shape of the ODC allows Sa_{O_2} and Ca_{O_2} to fall minimally with the changes in Pa_{O_2} that occur during the initial ascent from sea level to altitudes around 1,000 m. The changes in Pa_{O_2} that occur when ascending higher, however, occur on the steeper portion of the ODC, and thus cause a disproportionately greater decline in Sa_{O_2} and Ca_{O_2}. Thus, as we discuss next, the shape of the ODC causes more pronounced pulmonary diffusion limitations and ventilation–perfusion inequities during exercise at altitude than at sea level.

Pulmonary Venous Admixture

Venous admixture (the mixing of non-reoxygenated venous blood with oxygenated blood) reduces the Ca_{O_2} and increases the $P_{AO_2} - Pa_{O_2}$ by two primary mechanisms. First, oxygen-depleted blood draining

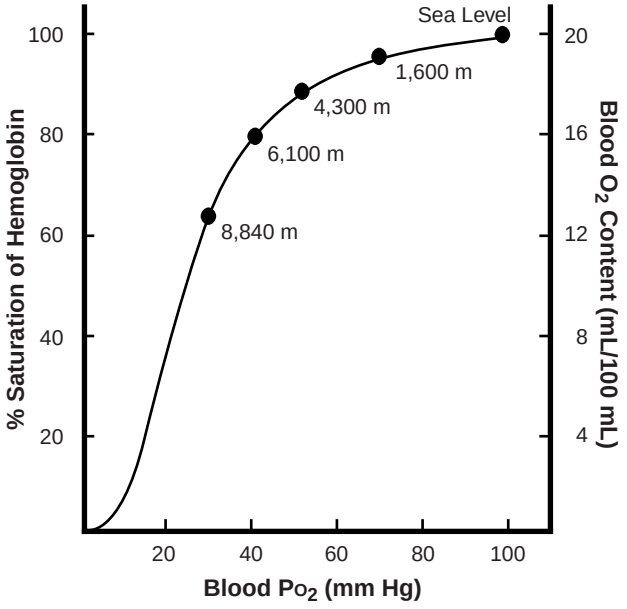

Fig. 21-15. The percentage of hemoglobin that is bound and combined with oxygen, and thus the amount of oxygen in the blood, is not linear over the physiological range of oxygen tension in the blood (blood P_{O_2}), as depicted in the classic oxygen–hemoglobin dissociation curve.

from the intrapulmonary bronchi veins into the pulmonary veins, a process referred to as *shunt*, mixes with the oxygenated blood draining the pulmonary capillaries. Second, blood flow and ventilation are not uniformly distributed over even the normal lung at sea level, nor is the distribution of flow perfectly matched to the distribution of ventilation. The ratio of the rates of ventilation and perfusion ($\dot{V}_E/\dot{Q}$) quantifies this inequality. Capillary blood perfusing poorly ventilated lung (ie, lung units having a low $\dot{V}_E/\dot{Q}$) is inadequately oxygenated, which lowers Pa_{O_2} and contributes to the $P_{AO_2} - Pa_{O_2}$ at all altitudes.

At sea level, bronchial venous flow is normally less than 1% of resting pulmonary capillary flow. Nevertheless, this small flow of poorly oxygenated blood entering the pulmonary veins measurably decreases the P_{O_2} before the blood reaches the systemic arteries and is the major component of the approximately 10-mm Hg $P_{AO_2} - Pa_{O_2}$ gradient at sea level. This is because pulmonary capillary blood P_{O_2} is on the flat part of the ODC, where small reductions in arterial content correspond to relatively large changes in P_{O_2}. In contrast, the lung capillary P_{O_2} at high altitude is on the steep part of the ODC, so while shunt from intrapulmonary bronchi may reduce oxygen content similarly to the reduction at sea level, the corresponding reduction in P_{O_2} is smaller, and it contributes relatively less to the $P_{AO_2} - Pa_{O_2}$.[37,39] Furthermore, during exercise, the increase in pulmonary capillary blood flow is much greater than the increase in shunt, so the relative contribution of shunt to the venous admixture component of the $P_{AO_2} - Pa_{O_2}$ declines with exercise, both at sea level and at altitude.[37,39] Thus, shunt contributes to the $P_{AO_2} - Pa_{O_2}$ during rest at sea level, but during exercise or at high altitude, the venous admixture component of the $P_{AO_2} - Pa_{O_2}$ is predominately due to $\dot{V}_E/\dot{Q}$ mismatch.

It is possible to estimate the contribution of $\dot{V}_E/\dot{Q}$ mismatch to the $P_{AO_2} - Pa_{O_2}$ using a complex method, the multiple inert gas elimination technique, which involves inhalation of a mixture of gases having different solubilities and measuring these gases in exhaled air and arterial blood.[40] The $\dot{V}_E/\dot{Q}$ mismatch and the resulting $P_{AO_2} - Pa_{O_2}$ increase during exercise (see Figure 21-14). Even in normal healthy subjects at sea level, the contribution of low $\dot{V}_E/\dot{Q}$ areas to the $P_{AO_2} - Pa_{O_2}$ increased with increasing exertion, and at high altitude, the low $\dot{V}_E/\dot{Q}$ areas still contribute to the $P_{AO_2} - Pa_{O_2}$ with exercise. Note in Figure 21-14 that with increasing $\dot{V}_{O_2}$, the observed $P_{AO_2} - Pa_{O_2}$ exceeds that which is accounted for by $\dot{V}_E/\dot{Q}$ mismatch, and that the exercise intensity $\dot{V}_{O_2}$ at which this becomes apparent decreases with increasing altitude. The difference between the observed $P_{AO_2} - Pa_{O_2}$ and that which can be accounted for by $\dot{V}_E/\dot{Q}$ mismatch is assumed to represent a component of the $P_{AO_2} - Pa_{O_2}$ due to the diffusion limitation.[39]

Diffusing Capacity

Having reached the alveolus, the oxygen molecule must diffuse across the alveolar–capillary membrane and into the red blood cells in the pulmonary capillary blood. This diffusion occurs along the oxygen pressure gradient from alveolus to blood. Moving from upright to a supine posture, increasing ventilation, initiating exercise, and exposure to hypoxia all increase distension and recruitment of pulmonary microcirculation (arterioles, capillaries, and venules), increasing the lung surface area for gas exchange, as does an exercise-induced increased microvascular pressure. During maximal effort, lung diffusion capacity for oxygen is maximal ($D_{LO_2}max$). The $D_{LO_2}max$ is proportional to the maximal oxygen uptake ($\dot{V}_{O_2}max$) divided by the oxygen pressure gradient from alveolus (P_{AO_2}) to pulmonary capillary blood ($P_{C'O_2}$), as shown in Equation 13:

$$(13) \quad D_{LO_2}max = k \bullet [\dot{V}_{O_2}max \div (P_{AO_2} - P_{C'O_2})]$$

where the constant *k* represents the oxygen conductivity of the alveolar capillary and the red blood cell membrane. However, membrane thickness, membrane surface area, and reaction of oxygen in the red blood cell are unlikely to be changed by moving to high altitude. Therefore, during maximal exercise in health, microvascular surface area and diffusing membrane thickness are likely to be similar at sea level and at altitude.

In humans, $P_{C'O_2}$ cannot be measured directly. However, if we assume that during exercise at sea level and during rest and exercise at high altitude, the reduction in arterial content resulting from venous admixture causes but little fall in the Pa_{O_2}, then the $P_{C'O_2}$ can be taken to be approximately equal to Pa_{O_2} under those conditions. Therefore, subtracting the contribution of $\dot{V}_E/\dot{Q}$ from the total $P_{AO_2} - Pa_{O_2}$ allows us to estimate the contribution of diffusion, as described above and shown in Figure 21-14. As altitude increases, the relative contributions of shunt and $\dot{V}_E/\dot{Q}$ to the $P_{AO_2} - Pa_{O_2}$ decrease, while the contribution of diffusion increases. Further, Figure 21-14 shows that at sea level the diffusion limitation of the lung for oxygen transfer does not become apparent until oxygen uptakes exceeds 2.5 L/min, whereas at altitude,

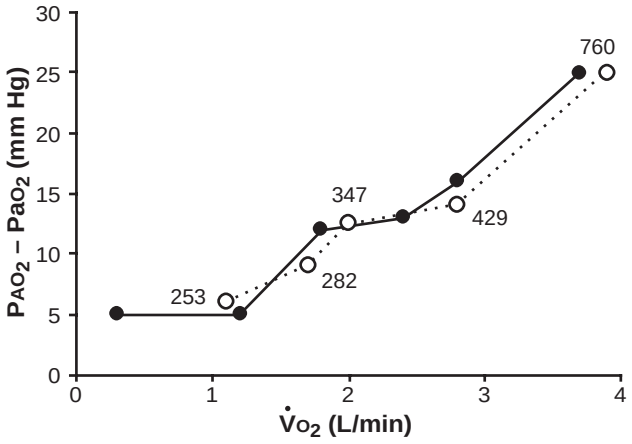

Fig. 21-16. The alveolar – arterial difference in partial pressure of oxygen ($P_{AO_2} - Pa_{O_2}$) widens with increasing oxygen uptake ($\dot{V}_{O_2}$) during exercise. The closed circles show the gradient at sea level during rest and at different incremental stages during progressive intensity exercise up to maximal oxygen uptake. The open circles represent the gradient measured during exercise at maximal oxygen uptake at each barometric pressure shown. Adapted with permission from Sutton JR, Reeves JT, Wagner PD, et al. Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol.* 1988;64:1317.

diffusion limitation becomes apparent at oxygen uptakes of less than 1 L/min.

At sea level, the $P_{AO_2} - Pa_{O_2}$ during exercise widens as exercise intensity increases. Although the $P_{AO_2} - Pa_{O_2}$ results from complex interactions among pulmonary shunting, $\dot{V}_E/\dot{Q}$ mismatch, and pulmonary diffusion (Figure 21-16), the size of the gradient increases in a nearly linear fashion, with increasing oxygen uptakes between 1 and 4 L/min. Even during maximal exercise, Pa_{O_2} is maintained at 80 mm or higher in most normal healthy persons, because arterial oxygenation is occurring on the flat portion of the ODC. Elite, highly conditioned athletes might be an exception to this, in that their cardiovascular systems have the capacity to transport such large amounts of oxygen that the membrane diffusion capacity of the lung may be insufficient to allow arterial oxygen levels to be maintained constant during maximal exercise, even at sea level.

At altitude, however, Pa_{O_2} is reduced to the range where the limitations inherent in the diffusing capacity of lung membrane become significant relative to the total oxygen pressure gradient, and Pa_{O_2} and saturation fall below resting levels during exercise. As depicted in Figure 21-14, the $P_{AO_2} - Pa_{O_2}$ during maximal exercise at high altitude is largely the result of limitations in pulmonary diffusion. At the summit of Mount Everest, where the inspired P_{O_2} is only 43 mm Hg, the resting P_{AO_2} is severely hypoxic. Exercise, by increasing the oxygen uptake, also increases the alveolar-to-arterial P_{O_2} gradient. Because the P_{AO_2} is little changed, the P_{O_2} must fall. Even at rest, the arterial oxygen saturation is on the steep part of the ODC (resting $Sa_{O_2} = 58\%$), and increasing oxygen uptake required for maximal exercise causes the arterial oxygen saturation to fall to approximately 50%.

The fall in arterial saturation, $P_{AO_2} - Pa_{O_2}$, and the diffusion component of the $P_{AO_2} - Pa_{O_2}$ during rest and near maximal exercise with increasing terrestrial elevation are shown in Figure 21-17a. The exercise saturations are less than those at rest largely because pulmonary diffusing capacity for oxygen is more limiting with increasing altitude.[39] As shown in Figure 21-16 and discussed above, the decrease in total $P_{AO_2} - Pa_{O_2}$ with increasing altitude is linked to the decline in $\dot{V}_{O_2}$max. However, the diffusion component of that difference during maximal exercise remains nearly unchanged (Figure 21-17b). As a result, the diffusion component becomes progressively more significant with increasing altitude (Figure 21-17c).

It is clear that the low environmental oxygen at altitude is associated with reduced P_{AO_2} at rest. With exercise, diffusion limitation inherent in the normal lung reduces Pa_{O_2} even further. At modest altitudes, diffusion limitation is only apparent during heavy exercise and high oxygen uptake, but with increasing altitude and decreasing P_{AO_2}, the diffusion limitation becomes apparent at progressively lower exercise intensities and oxygen uptakes. In the extreme circumstance, namely, at the summit of Mount Everest, diffusion limitation is apparent, with oxygen uptakes of less than 1 L/min.

SYSTEMIC OXYGEN TRANSPORT AT HIGH ALTITUDE

Unacclimatized Lowlanders on Arrival at High Altitude

The decline in Sa_{O_2} and Ca_{O_2} that lowlanders experience with ascent to high altitude necessitates adjustments in systemic oxygen transport to maintain sufficient oxygen delivery to meet the metabolic needs of the body. Equation 14, the Fick Equation, defines the relationship between systemic oxygen transport and oxygen uptake:

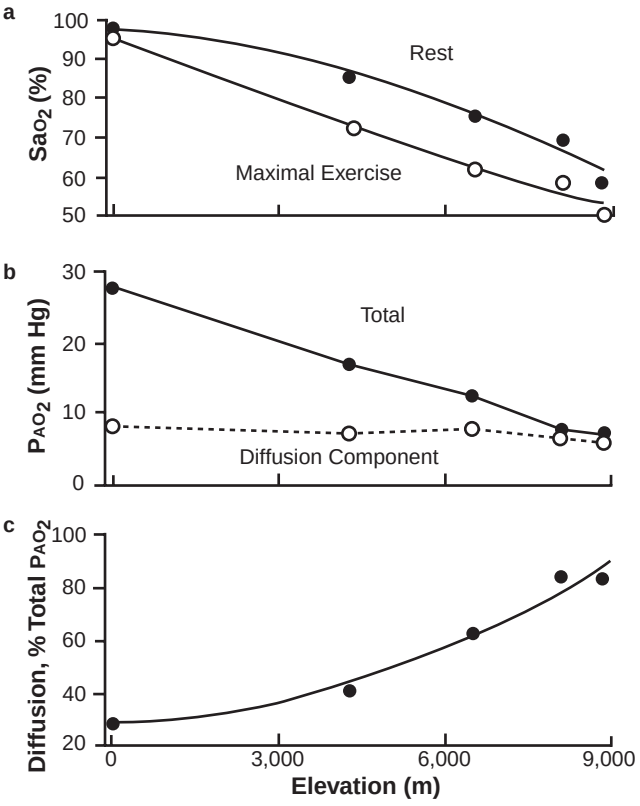

Fig. 21-17. The reduction in ambient and alveolar oxygen pressure with increasing altitude causes (**a**) the decrease in arterial oxgyen saturation (Sa_{O_2}) during rest (closed circles), and the development of pulmonary diffusing limitations causes the additional decrease during maximal exercise (open circles). (**b**) The total alveolar – arterial difference in partial pressure of oxygen ($P_{AO_2} - Pa_{O_2}$, closed circles) decreases with increasing altitude because maximal oxygen uptake declines, but the diffusion component (open circles) remains unchanged in magnitude. Thus, diffusion accounts for (**c**) an increasing proportion of the total $P_{AO_2} - Pa_{O_2}$ as altitude increases (closed circles).
Data source: Wagner PD, Sutton JR, Reeves JT, Cymerman A, Groves BM, Malconian MK. Operation Everest II: Pulmonary gas exchange during a simulated ascent of Mt Everest. *J Appl Physiol*. 1987;63:2348–2359.

$$\dot{V}O_2 = Q_C \bullet (Ca_{O_2} - C\bar{v}_{O_2}), \quad (14)$$

where $\dot{V}O_2$ represents oxygen uptake, Q_C represents cardiac output, Ca_{O_2} represents arterial oxygen content, and $C\bar{v}_{O_2}$ represents mixed venous oxygen content. The steady state $\dot{V}O_2$ elicited during submaximal exercise at a given absolute exercise intensity or power output is the same at high altitude as at sea level.[41–44] The Fick Equation shows that to sustain a given $\dot{V}O_2$, the reduction in Ca_{O_2} at high altitude could be compensated for by a higher Q_C, a lower $C\bar{v}_{O_2}$, or both.

Increased Cardiac Output

Experimental observations indicate that both adjustments are invoked. Oxygen tensions in venous blood that drains contracting muscle fall lower during submaximal exercise at high altitude than at sea level—not low enough, however, to fully compensate for the decrease in Ca_{O_2}; thus, the arteriovenous oxygen difference narrows (Figure 21-18).[45] Many studies have confirmed that unacclimatized lowlanders exhibit a higher cardiac output for any given $\dot{V}O_2$ during steady state submaximal exercise at high altitude than at sea level.[43,46,47] This increased cardiac output is achieved by an increased heart rate, while stroke volume during exercise tends to be lower on arrival at altitude than at sea level.[43] However, maximal cardiac output remains unchanged from sea-level values in unacclimatized lowlanders, as does the $C\bar{v}_{O_2}$ during maximal exercise.[43] Hence these physiological limits are achieved at lower absolute exercise intensities at high altitude than sea level, and $\dot{V}O_2$max is reduced.

Decrement in Maximal Oxygen Uptake

The decline in $\dot{V}O_2$max at high altitude varies. The primary factor that modulates the decline is the actual elevation ascended above sea level. Lowlanders

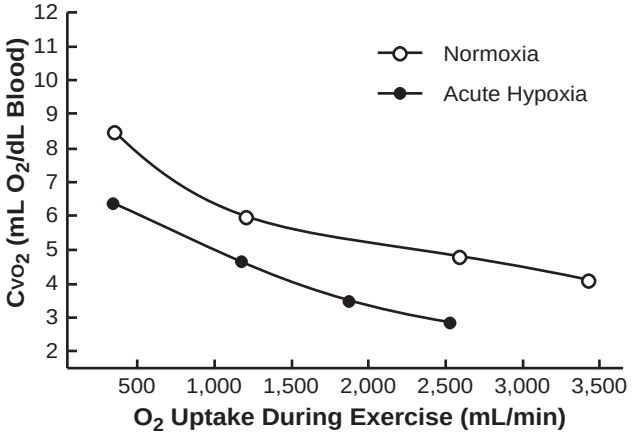

Fig. 21-18. During both rest (left of graph) and exercise (right of graph), venous oxygen content (Cv_{O_2}) falls lower under hypoxic than normoxic conditions.
Data source: Bender PR, Groves BM, McCullough RE, et al. Oxygen transport to exercising leg in chronic hypoxia. *J Appl Physiol*. 1988;65:2592–2597.

experience no measurable decline in $\dot{V}O_2$max until they ascend above about 900 to 1,000 m, and only a small decrement between 1,000 and 2,000 m above sea level.[48] Above 2,000 m elevation, the decrement averages about 10% for every 1,000 meters ascended.[49,50] Although the average decrement in $\dot{V}O_2$max at any given altitude is predictable for a group of subjects, the decrement varies considerably between individuals.[51] For example, in a group of 51 male sea-level residents, the decrement in $\dot{V}O_2$max at 4,300 m altitude compared with the decrement at sea level was normally distributed in a range from 9% to 54%, and averaged 27%.[51]

The physiological factors that account for the variability in the decrement in $\dot{V}O_2$max experienced at a given altitude are not fully understood. Intraindividual variability in hypoxic ventilatory responsiveness, hemoglobin affinity for oxygen, and body fluid movements are a few factors that might play a role. However, one factor in particular, the individual's level of aerobic physical fitness, has received considerable attention.[50–53] As Fulco and Cymerman point out in Chapter 22, Physical Performance at Varying Terrestrial Altitudes, the decrement in $\dot{V}O_2$max with ascent to high altitude is more pronounced in aerobically fit, compared with less fit, persons. In fact, variability in aerobic fitness may account for as much as one third of the variability in the altitude-induced decrement in $\dot{V}O_2$max.[51] One explanation that has been postulated for this, although it is unproven, is that highly aerobically fit persons exhibit relative hypoventilation during maximal exercise,[54] and their maximal cardiac outputs, hence maximal pulmonary capillary blood flows, are higher and pulmonary capillary transit times shorter than in less fit persons.[55] Both factors could exaggerate pulmonary diffusion limitations and ventilation perfusion inequalities at high altitude in fit compared with less-fit persons.

Acclimatization Effects on Systemic Oxygen Transport

The initial physiological adjustments in the components of systemic oxygen transport (increased cardiac output, tachycardia, etc) elicited when lowlanders first ascend to high altitude occur at the expense of increases in cardiac work, myocardial oxygen uptake, and coronary blood flow.[56–58] These responses increase cardiovascular strain and probably contribute to the decreased endurance that most lowlanders experience when they arrive at high altitude. However, in lowlanders who remain at high altitude and acclimatize, the acute responses are progressively replaced by physiological adjustments that alleviate the increased demand on the heart while still allowing systemic oxygen transport requirements of activity to be sustained.

Cardiac Output Declines

One of the more pronounced effects of altitude acclimatization at moderate altitudes is a reduction in cardiac output. The acclimatization-induced reduction in cardiac output is observable during rest[59–61] as well as during both submaximal[59,61] and maximal[41,59,62] exercise. Most studies indicate that this reduction in cardiac output is more pronounced than the initial increase observed on arrival at high altitude. Thus, for any given $\dot{V}O_2$, cardiac output is not only lower after acclimatization than on arrival at altitude but it is also lower than it was at sea level before ascent (Figure 21-19). At altitudes between 3,000 and 5,000 m, this adjustment first becomes observable in as few as 2 days of acclimatization[61,62] and continues to develop over the following 8 to 10 days.[41,59,61,62] Staging (ie, gradual ascent with stops at intermediate altitudes) appears to blunt both the initial increase in cardiac output and the subsequent decline,[47] and persons who continue ascending to very extreme altitudes (> 6,000 m) do not appear to exhibit a decline in cardiac output below sea-level values.[63]

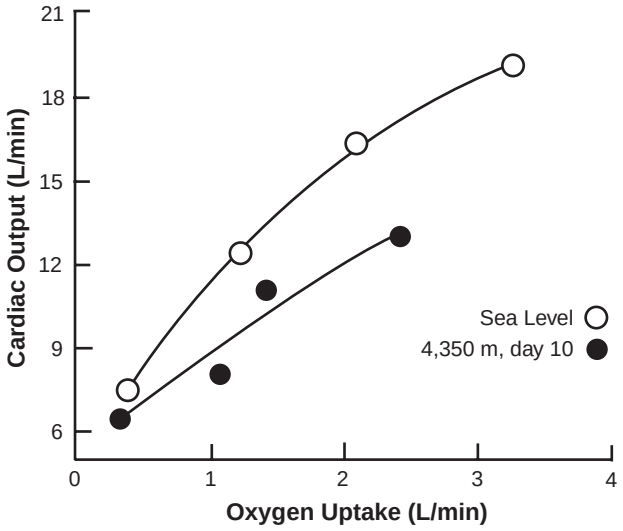

Fig. 21-19. Following altitude acclimatization (closed symbols), cardiac output during exercise is lower than it is at sea level (open symbols).
Data source: Vogel JA, Hartley LH, Cruz JC, Hogan RP. Cardiac output during exercise in sea-level residents at sea level and high altitude. *J Appl Physiol.* 1974;36:169–172.

The reduction in cardiac output with altitude acclimatization results primarily from reduced stroke volume and, to a lesser extent, alleviation of the exercise tachycardia exhibited on arrival at high altitude.[64] Stroke volume, both at rest and during submaximal and maximal exercise, clearly declines with altitude acclimatization, and the time course for this adjustment parallels the decline in cardiac output.[59,61,62] On the other hand, as a comprehensive review[64] details, some reports indicate no effect of acclimatization on heart rate responses, while others indicate that the initial altitude-induced tachycardia abates. Differences in altitude, exposure duration, ascent profile, and individual variability contribute to the disparate observations.[64] Acclimatization effects on heart rate may also vary with exercise intensity. Altitude-induced tachycardia has been reported[65] to be attenuated at high, near-maximal intensities, but not at low intensities.

Conceivably, a depression in myocardial contractility, decreased cardiac filling, or both could cause the decline in stroke volume. The possibility that a hypoxia-related decline in myocardial contractility and function contributed to the decline in stroke volume that was postulated earlier by some investigators[60,61] is not consistent with the most recent experimental observations. Lowlanders who are chronically exposed to very high altitudes exhibit no change in the cardiac filling pressure–stroke volume relationship,[63] and their ejection fraction increases despite reduced ventricular volumes[66] when breathing either hypoxic or normoxic air. Thus, a reduction in cardiac filling is probably the principal mechanism mediating the decrease in stroke volume with altitude acclimatization. The hematological and hemodynamic adjustments experienced as the lowlander acclimatizes to high altitude may act to limit cardiac filling.

Development of Hemoconcentration

The lowlanders' hematocrit and hemoglobin concentration increase during the first 7 to 14 days of altitude acclimatization, concomitant with the decline in stroke volume. The increases in the hematocrit and the hemoglobin concentration during the first 2 to 3 weeks at high altitude are sometimes mistakenly attributed to an increase in circulating red blood cells, but that response does not develop until later in the acclimatization process. The early rise in hematocrit and hemoglobin, in fact, results from a hemoconcentration in which plasma volume is lost[61,67–69] while erythrocyte volume remains unchanged[69]; thus blood volume decreases.[61,67–69] At moderate elevations (3,000–4,300 m), the magnitude of this effect is modest, with plasma volume losses reported averaging 250 to 500 mL[61,67,69]; but at higher altitudes the loss of plasma volume is more pronounced.[70] At face value, this hemoconcentration appears to be the mechanism responsible for the decline in stroke volume that is experienced as lowlanders acclimatize at altitude, because experimental manipulations that prevent the altitude-induced hemoconcentration also prevent the reduction in stroke volume.[71]

Exactly how hemoconcentration exerts this effect remains unresolved, but several mechanisms could be acting to limit cardiac output and stroke volume in acclimatized lowlanders. A reduction in blood volume might reduce stroke volume, according to the Frank-Starling curve, in which cardiac output or stroke volume can be plotted in relation to end diastolic volume. However, infusing 500 mL of dextran into two lowlanders acclimatized 10 days at 3,100 m expanded blood and plasma volume to preacclimatization levels without restoring stroke volume during exercise.[61] In contrast, when 450 mL of whole blood was removed from five lowlanders acclimatized at 4,300 m and replaced with Ringers lactate, hematocrit and viscosity returned to preacclimation levels without a change in blood volume, and stroke volume during exercise increased back to preacclimatization levels.[72] Horstman, Weiskopf, and Jackson suggested that the findings they reported were consistent with the development of a viscosity-related limitation to cardiac filling and stroke volume.[72] However, erythrocyte infusion (also known as blood doping) experiments at sea level demonstrate that hematocrit and viscosity increases that are comparable to changes that occur during acclimatization at moderate altitude do not produce a viscosity impairment of stroke volume and cardiac output.[73] The most plausible explanation for the changes in cardiac output and stroke volume during the first 2 weeks of altitude acclimatization is that the reduced Ca_{O_2} and partial pressure of venous oxygen (Pv_{O_2}) on arrival at high altitude cause a dilation of peripheral vasculature with concomitant elevation in cardiac output (metaboreflex), which is then reversed when the acclimatization-induced hemoconcentration raises Ca_{O_2} and Pv_{O_2}.

Arterial Oxygen Content Increases

Regardless of the precise mechanism for the reduction in stroke volume and cardiac output in lowlanders remaining at altitude, the lower cardiac

output for a given oxygen uptake necessitates compensatory adjustments in systemic oxygen transport and delivery. The Fick Equation (see Equation 14 above) indicates that an increased tissue oxygen extraction must accompany the reduction in cardiac output at a given oxygen uptake. This has been experimentally demonstrated.[45,60,74] Figure 21-20 shows that during rest and submaximal exercise, the difference between arterial and venous oxygen contents, which narrowed with ascent to altitude, widens after about 10 days of acclimatization. Following acclimatization, the oxygen content of venous blood draining active muscle during exercise at altitude is the same[45] or only slightly lower[74,75] than it was before. Therefore, the key factor that enables systemic oxygen transport requirements to be achieved with lower cardiac output than before, for a given oxygen uptake after altitude acclimatization, is an increased oxygen extraction that is primarily due to an increased Ca_{O_2}.

After 7 to 10 days of acclimatization, lowlanders sojourning at high altitude exhibit higher Ca_{O_2} during both rest and exercise. For example, Hannon and Vogel[76] observed that the average resting Ca_{O_2} of six lowlanders sojourning at 4,300 m increased by 2.6 milliliters of oxygen per 100 milliliters of blood between the 2nd and 14th day of altitude acclimatization. Several physiological adjustments contribute to this increase in Ca_{O_2} with acclimatization. As described before and illustrated in Figure 21-21, a hemoconcentration develops over this same time, increasing hematocrit and owing to a decrease in plasma volume, while erythrocyte volume remains unchanged.[61,69] This hemoconcentration increased hemoglobin concentration by 0.7 grams per 100 milliliters of blood, accounting for about 25% of the increase in Ca_{O_2} over that same time. The remainder of the increase in Ca_{O_2} observed in Hannon and Vogel's study[76] was attributable to an increase in Sa_{O_2}.

During the first week or so of acclimatization, lowlanders sojourning at high altitude experience an increase in Sa_{O_2} measured during both rest and exercise. For example, in lowlanders ascending from sea level to the summit of Pikes Peak (4,300 m), resting Sa_{O_2} generally falls to 78% to 80% on arrival, after which it rises, reaching about 84% after 3 to 4 days and 87% after 9 to 10 days.[16,77,78] It has been generally accepted that the increase in saturation reflects the effects of the increase in ventilation that develops progressively over the first few days after arriving at high altitude (ventilatory acclimatization). However, while resting Sa_{O_2}

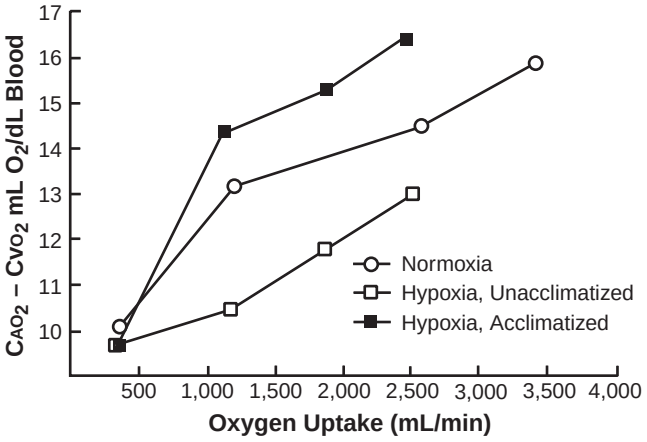

Fig. 21-20. For a given intensity of exercise and oxgyen uptake, extraction of oxgyen (the alveolar – venous oxygen contents, as measured in milliliters of oxygen per deciliters of blood, or Ca_{O_2} – Cv_{O_2}) decreases on arrival at high altitude compared with at sea level, but with acclimatization extraction increases above sea level values.
Data source: Bender PR, Groves BM, McCullough RE, et al. Oxygen transport to exercising leg in chronic hypoxia. *J Appl Physiol*. 1988;65:2592–2597.

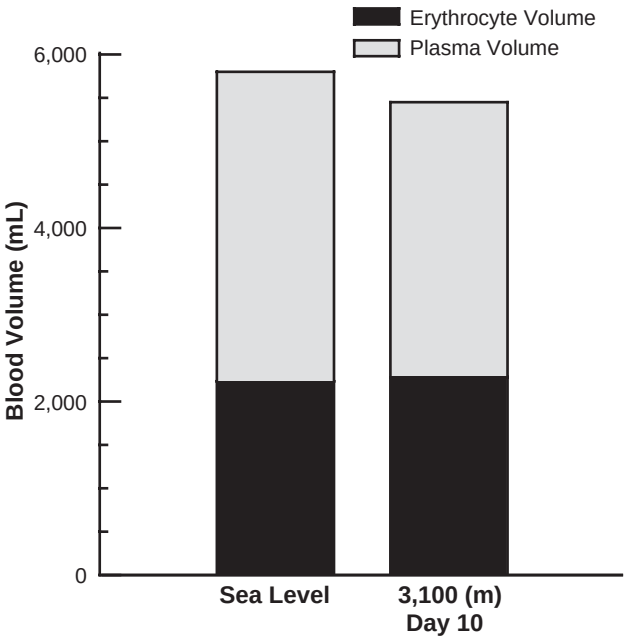

Fig. 21-21. During the first 2 weeks of high-altitude acclimatization, the mass of red blood cells does not change, but a modest decrease in the volume of plasma increases the hematocrit.
Data source: Alexander JK, Hartley LH, Modelski M, Grover RF. Reduction of stroke volume during exercise in man following ascent to 3,100 m altitude. *J Appl Physiol*. 1967;23:849–858.

reaches a plateau after about 8 days of acclimatization, Sa_{O_2} maintained during exercise continues to rise between the 8th and 22nd day of acclimatization, despite the fact ventilation during exercise remains the same over this period.[77] Thus, the rise in Sa_{O_2} that lowlanders experience as they acclimatize to high altitude is only partially explained by the effects of ventilatory acclimatization. A decreased pulmonary capillary transit time secondary to the decline in cardiac output with acclimatization (discussed above) also contributes to an increase in Sa_{O_2} in the acclimatizing lowlander, along with other adjustments that may develop, such as a decreased pulmonary diffusion limitation (increased diffusing capacity), improved $\dot{V}_E/\dot{Q}$, and, as will be discussed below, a left shift in the ODC.

While increased erythrocyte volume does not account for the initial rise in hematocrit, hemoglobin concentration, and Ca_{O_2} that lowlanders experience during their first 2 weeks at high altitude,[69] an increased erythrocyte volume is manifested later during acclimatization.[70,79] The time course for the increase in erythrocyte volume has not been adequately investigated and remains unclear, although this appears to be one of the slower adjustments elicited during altitude acclimatization.[70,79] No changes in erythrocyte volume are apparent in lowlanders after 8 days' residence at 1,600 m,[80] 10 days at 3,100 m,[61] or 13 days at 4,300 m.[69] However, Pugh[81] observed a 33% increase in erythrocyte volume in two lowlanders who had remained above 5,800 m for at about 8 weeks and about a 17% increase in three other lowlanders who had resided between 4,650 and 5,800 m for 14 weeks. Pugh's data also indicate that after 3 to 4 months at high altitude, some of the plasma volume lost during the initial phase of acclimatization has been recovered.[81] This blunts further increases in blood hemoglobin concentration despite the expanding erythrocyte volume, and lowlanders who become well acclimatized to altitude (4–6 mo, 4,000–5,800 m elevation) exhibit hemoglobin concentrations (17–20 mg/100 mL blood) that are similar to those of healthy, native-born, high-altitude residents.[70] Thus, while short-term acclimatization brings about a relatively rapid increase in arterial oxygen content by hemoconcentration, in long-term acclimatization, increased arterial oxygen content is sustained by expansion of erythrocyte volume.

Oxyhemoglobin Dissociation Curve Shifts

In lowlanders who ascend to altitudes between 1,800 and 4,500 m and remain, blood samples obtained during rest demonstrate a decrease in hemoglobin's affinity for oxygen. Blood P_{50} (the P_{O_2} when Sa_{O_2} is 50%) increases due to a rightward shift in the ODC.[82–84] This adjustment occurs within hours after arriving at high altitude[83,84] and persists even in lifelong high-altitude residents.[82,83] The rightward shift in the ODC at these moderately high altitudes represents the net effect of opposing factors. A rise in the erythrocyte concentration of the glycolytic intermediate 2,3 diphosphoglycerate (2,3 DPG) mediates a rightward shift[84] in the ODC. This effect more than compensates for the tendency of blood alkalosis and decreased P_{CO_2} to shift the curve leftward (the Bohr effect). Interestingly, it is the blood alkalosis associated with increased ventilation that appears to be the factor that stimulates 2,3 DPG to increase at high altitude. Pharmacological intervention to maintain experimental subjects at an acidotic pH during altitude sojourns prevents the rise in 2,3 DPG and the right shift in the ODC.[84] Above about 4,500 m, the Bohr effect becomes sufficient to overcome the 2,3 DPG effect on hemoglobin affinity for oxygen, and the ODC is shifted to the left.

Right shifts in the ODC facilitate oxygen unloading in capillaries of active tissue, because decreased hemoglobin–oxygen affinity allows greater desaturation at a given blood P_{O_2}; whereas left shifts facilitate oxygen loading in the pulmonary capillaries, because increased hemoglobin–oxygen affinity allows higher saturation to be attained at given blood P_{O_2}. Whether a left or a right shift in the ODC confers an advantage or disadvantage to lowlanders sojourning at high altitude appears to depend on the elevation ascended and the intensity of activity. A theoretical analysis of optimal P_{50} suggests that up to moderate altitudes ($Pa_{O_2} > \sim 75$ mm Hg), a high P_{50} (ie, right-shifted ODC) allows a higher partial pressure of venous oxygen (Pv_{O_2}) to be sustained, which facilitates oxygen unloading in the tissues without compromising oxygen loading in the pulmonary capillaries, as the ODC at Pa_{O_2} higher than 75 mm Hg is relatively flat.[83,85] As altitude increases and Pa_{O_2} decreases, the advantage of a high P_{50} for maintaining high Pv_{O_2} diminishes, and at altitudes where Pa_{O_2} is lower than 40 mm Hg, a lower P_{50} (left-shifted ODC) maintains the Pv_{O_2} at a higher level. Thus, the right shift in the ODC that is experienced when lowlanders sojourn at low altitudes, followed by the left shift as they ascend higher, both serve to optimize oxygen transport under the conditions in which the shifts occur.

Exercise-induced acidosis would increase the P_{50} and shift the ODC rightward. During exercise, which increases oxygen extraction, the advantage of a left-shifted ODC becomes apparent at either

higher Pa_{O_2} or lower elevations, rather than during rest.[85] As is discussed below, exercise-induced shifts due to acidosis are exacerbated in unacclimatized lowlanders on arrival at high altitude compared with sea level, and this effect abates after a few weeks of acclimatization. Thus, the rightward shifts in the ODC may be pronounced when unacclimatized persons exercise at altitude, but the shifts will be less pronounced after acclimatization.

Net Effects of Systemic Oxygen Transport Adjustments

During the first month or so at high altitude, the decline in cardiac output and the increase in Ca_{O_2} with acclimatization appear to offset each other with respect to the net effects on systemic oxygen transport during exercise. Whole-body $\dot{V}_{O_2}$ during steady state submaximal exercise at a given absolute intensity or power output at altitude is unchanged with acclimatization.[78,86–88] The lowlander's $\dot{V}_{O_2}$max remains reduced to the same degree after up to 3 weeks of acclimatization as it was on arrival at altitude,[65,78,86,88,89] perhaps because the hypovolemia and elevated viscosity that result from hemoconcentration limit maximal cardiac output.

However, the hemoconcentration that rapidly increases Ca_{O_2} at the expense of decreased blood volume and increased viscosity during short-term acclimatization is eventually replaced by expansion of erythrocyte volume, which sustains the increased Ca_{O_2} with long-term acclimatization. The expanded erythrocyte volume, in combination with a partial recovery of lost plasma volume, restores normovolemia or may even expand blood volume, and the increase in blood viscosity is to some degree alleviated. If the hypovolemia and elevated viscosity associated with hemoconcentration are indeed the factors limiting stroke volume and cardiac output during maximal exercise for the first month or so that lowlanders live at altitude, as some have suggested,[72,73] then this secondary adaptation with long-term (> 4 mo) sustaining of Ca_{O_2} with a more normal blood volume and viscosity could ameliorate that limitation, perhaps ultimately leading to some recovery of $\dot{V}_{O_2}$max. The reductions in $\dot{V}_{O_2}$max and maximal cardiac output at 4,350 m compared with sea level are smaller for high-altitude natives,[90] who are presumably fully acclimatized, than they are for lowlanders acclimatized for 10 days at 4,350 m,[59] tending to support this suggestion, but confirmatory studies of maximal exercise responses in persons acclimatizing for sufficient time (ie, > 4 mo) to fully develop the expansion of erythrocyte volume are required.

METABOLISM AT HIGH ALTITUDE

High-Altitude Weight Loss

Lowlanders who ascend to high altitude and remain for more than a few days typically lose weight. The magnitude of weight loss observed varies considerably, with values reported in different investigations ranging from 80 to nearly 500 g/d.[91] The large range of weight losses observed undoubtedly relates to discrepancies among the studies with respect to such factors as hydration and dietary control, rate of ascent, altitude attained, duration of exposure, and the activity level of subjects under investigation. Both hypohydration and negative energy balance contribute to the body weight loss experienced by lowlanders sojourning at high altitude.[91–94]

Body Water Changes

Lowlanders usually experience an apparent progressive reduction in total body water when they ascend to high altitude and remain.[67,92,95] At moderate altitudes (eg, 3,500–5,000 m), the reduction in body water is measurable after as few as 3 days and persists for at least 12 days.[67,92,95] Some[92,95] have suggested that this hypohydration causes the decrease in plasma volume described above, as well as decreases in intracellular and extracellular fluid volumes. However, in other studies, lowlanders sojourning at altitude reportedly experienced a decrease in plasma volume or extracellular fluid volume[69,80,96] without a change in total body water. These observations have been interpreted as suggesting that acclimatization causes a redistribution of fluid from extracellular to intracellular compartments, rather than just dehydration. Longitudinal studies have not documented how intracellular and extracellular fluid volumes and total body water respond during altitude sojourns longer than 2 weeks, but cross-sectional studies suggest that total body water is not reduced in either lowlanders who have been acclimatized at altitude for at least 10 weeks[97] or native-born, high-altitude residents.[98]

Both decreased water intake and increased water loss can affect water balance in lowlanders acclimatizing to high altitude. The primary mechanisms for water loss include respiratory and cutaneous evaporation and urine formation. It is widely believed that increased pulmonary ventilation ex-

acerbates respiratory water loss in lowlanders sojourning at high altitude. However, Hoyt and Honig[92] reported that respiratory water losses in soldiers working hard outdoors in winter were similar at moderate altitudes (eg, 2,200–3,100 m) and at sea level, ranging from 400 to 800 mL/d, depending on energy expenditure. This suggests that with the increased ventilation during exertion at moderate elevations in cold weather, inspired air may not become fully saturated. The decreased expired air temperature and lower water vapor pressure at altitude (compared with sea level) reduces maximum water content of saturated expired air, apparently counterbalancing the tendency of elevated ventilation to facilitate respiratory water loss, at least at moderate altitude. On the other hand, prediction modeling indicates that ventilation increases sufficiently at higher altitudes (4,300 m) to outweigh the decreased water content, such that respiratory water loss increases by 200 mL/d or more.[92]

Cutaneous evaporative water loss may be greater at altitude than at sea level. Lowlanders usually engage in more vigorous physical activity at high altitude than they do at sea level, which could increase the requirement for sweating. Unacclimatized lowlanders exposed to hypoxia exhibit suppressed sweating during the onset of exercise. A given change in core temperature produces a smaller rise in sweating rate under hypoxic than under normoxic conditions (Figure 21-22).[99,100] This leads to greater heat storage during the transition from rest to steady state exercise in hypoxic conditions. Thus, core temperature rises higher during prolonged submaximal exercise of a given absolute intensity and duration under hypoxic than it does under normoxic conditions, with a correspondingly higher sweat loss.[101]

Unacclimatized lowlanders also experience diuresis when they breathe moderately hypoxic gas mixtures,[102,103] or during the first few days following arrival at moderate (< 5,000 m) altitudes.[91,92,95,104] As will be discussed later in this chapter, this diuresis is at least partially mediated by hormonal mechanisms. To some degree, diuresis at altitude is probably beneficial because (*a*) individuals who do not exhibit diuresis are more likely to experience the signs and symptoms of altitude illnesses, and (*b*) diuresis may not occur at extreme altitudes, where most persons experience some altitude illness.[104] Some diuresis during altitude sojourn can be attributable to the release of water during catabolism of fat and lean body mass secondary to negative energy balance.[91] However, even when

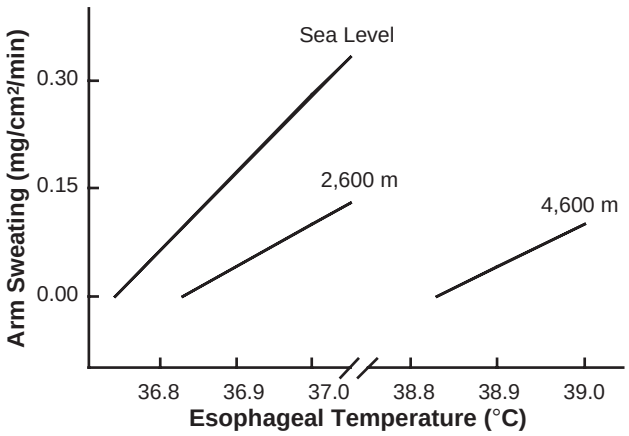

Fig. 21-22. Sweating responses appear to be suppressed in unacclimatized lowlanders exercising at high altitude, compared with acclimatized people, although sweating responses in the latter have not been well characterized. A given change in core temperature causes a smaller increase in sweat rate under hypoxic (altitude: 4,600 m) than normoxic (altitude: 2,600 m) conditions.
Data source: Kolka MA, Stephenson LA, Gonzalez RR. Depressed sweating during exercise at altitude. *J Therm Biol*. 1989;14:167–170.

nutrition is adequate to maintain energy balance and prevent cachexia at altitude, some diuresis still occurs.[91]

Thirst and appetite are diminished at altitude,[91,92,104] which could contribute to negative water balance when drinking is ad libitum. However, water intake can be controlled and standardized such that total body water remains unchanged during altitude sojourns.[69] Thus, while an increase in the rate that body water is lost may be inevitable and perhaps beneficial at altitude, aggressive steps to encouraging drinking can sustain proper hydration in lowlanders ascending to high altitude.

Energy Balance at Altitude

Obviously, individuals who maintain a negative energy balance (caloric intake less than caloric expenditure) will experience cachexia and weight loss over time during altitude sojourns, just as would be expected at sea level.[91,94] Under experimental conditions, a controlled nutritional regimen accurately matching energy intake with energy expenditure can prevent cachexia in lowlanders sojourning at altitudes up to 4,300 m.[91] However, this degree of control over energy balance is not usually maintained by lowlanders trekking and climbing in mountainous

regions under expedition conditions.

Several factors may disrupt energy balance in lowlanders sojourning at altitude. Anorexia is common among newcomers at altitude, especially those experiencing symptoms of acute mountain sickness (AMS).[91] Furthermore, appetite suppression can persist even after acclimatization alleviates AMS symptoms.[94] Anecdotal observations[105] and one limited experimental study[106] suggest that in lowlanders sojourning at altitudes above 6,000 m, gastrointestinal fat absorption may deteriorate, which could limit effective energy intake. However, extensive controlled evaluations failed to confirm this observation or demonstrate any evidence that gastrointestinal fat, protein, or carbohydrate absorption is impaired in lowlanders sojourning at more-moderate altitudes up to 5,500 m.[91]

An increase in energy expenditure may shift overall energy balance to negative in lowlanders sojourning at altitude. Energy expenditure required to sustain a given activity (at a given absolute intensity or power output) for a given duration is the same at both altitude and sea level.[107] However, lowlanders typically engage in strenuous activities when they ascend to high altitudes, which increases their energy expenditure. Furthermore, the basal metabolic rate (BMR) increases 7% to 17% over the first 2 to 3 days after arrival at high altitude, declining thereafter.[4,91,106,108,109] Some investigators report that the BMR returns to sea-level values by 7 to 20 days,[106,108] while others report a sustained elevation.[109] Butterfield[91,109] reviewed these discrepant observations and suggested that in those studies in which the BMR fell completely back to sea-level values, negative energy balance and loss of metabolically active tissue had suppressed the subjects' BMRs, whereas when positive energy balance was maintained, the subjects' BMRs remained somewhat elevated throughout the duration of the altitude sojourn.

Thus, a decrease in fluid and energy intake, an increase in energy expenditure, or both can contribute to the inability of lowlanders sojourning at high altitude to maintain proper hydration and energy balance in situations where diet is ad libitum and uncontrolled. The magnitude and composition (ie, water, fat, lean tissue) of the weight loss at altitude will depend on the severity and duration of periods of negative water and energy balance. It is, however, possible to institute countermeasures (eg, nutritional supplementation, enforced eating and drinking regimens) that can ameliorate these effects, minimize dehydration and cachexia, and sustain body mass during altitude sojourns, at least at moderate elevations below 5,000 m.

Energy Metabolism During Exercise at High Altitude: The Lactate Paradox

The energy demands of contracting skeletal muscle are supplied by the breakdown of biochemical compounds containing high-energy phosphate bonds. The metabolic processes involved in the breakdown and regeneration of these high-energy phosphate compounds during exercise under normoxic conditions are reviewed in detail elsewhere.[110–117] This section of the chapter will consider (1) the pronounced effects that hypoxia and altitude acclimatization have on energy metabolism during exercise, and (2) how these effects contribute to changes in physical work capacity and performance of lowlanders sojourning at high altitude.

The collective manifestation of the effects of hypoxia and subsequent altitude acclimatization on energy metabolism during exercise is a phenomenon referred to as the "lactate paradox." This phenomenon, first reported by Dill[118] and subsequently confirmed by Edwards,[119] is characterized by higher blood lactate concentrations during exercise at altitude than at sea level in unacclimatized persons, but lower blood lactate levels—sometimes even lower than at sea level—in acclimatized persons exercising at altitude. If it is assumed that the hypoxia accelerates blood lactate accumulation in unacclimatized persons exercising at altitude, via Pasteur's effect, then a paradox arises in explaining the decline that acclimatized persons exhibit in lactate accumulation during exercise at high altitude since hypoxia continues unrelieved.

Accelerated Glycolytic Metabolism Before Acclimatization

In one of the earliest studies of altitude effects on blood lactate, Edwards[119] observed that resting concentrations of unacclimatized lowlanders were the same on their first day at high altitude (2,810 m) as at sea level, whereas postexercise concentrations were higher at altitude, despite the fact that the metabolic rate during exercise was the same as at sea level for a given power output. Many subsequent studies have repeated these observations. Hypoxia (rather than hypobaria or other stresses associated with the mountainous environment) causes the higher blood lactate accumulation at altitude, because the same effects can be produced in

hypobaric decompression chambers[120–123] or by breathing hypoxic gas mixtures under normobaric conditions.[124,125]

The elevation ascended (ie, the magnitude of hypoxia) and the metabolic rate modulate the altitude effect on blood lactate responses to exercise. In general, the increment in lactate accumulation during exercise becomes greater at a given altitude with increasing exercise intensity,[122,126] and the altitude-induced increment in lactate accumulation at any particular exercise intensity becomes greater as the elevation increases and P_{IO_2} falls.[123,125–127] Thus, elevations in resting lactate concentrations are not observed unless unacclimatized persons are acutely exposed to altitudes above 4,600 m,[120,121] which is fairly rare outside of experimental circumstances. At moderate elevations (2,000 to 4,500 m), blood lactates of unacclimatized lowlanders are similar to sea-level values during rest or low intensity exercise, but when $\dot{V}O_2$ exceeds about 1.5 L/min, an elevation in lactate concentration becomes apparent.[122,126,127] Lactate concentration in unacclimatized persons following maximal exercise is the same at high altitude as at sea level, but because of the reduction in maximal work capacity at altitude, maximal lactate concentrations are achieved at lower power outputs.[78,124,126,128–131]

Interestingly, the altitude effect just described is not observed when lactate concentrations are compared at the same relative intensity (ie, at the same percentage of $\dot{V}O_2$max) (Figure 21-23). Hermansen and Saltin[126] first observed this phenomenon, but others[78,122] have subsequently confirmed that although blood lactate concentrations in unacclimatized lowlanders exercising on arrival at high altitude or during acute hypoxic exposure were higher than during normoxic exercise for a given absolute intensity, lactate concentrations are similar when exercise of the same relative intensity is compared. A similar relationship has been observed for the effect of hypoxia on muscle lactate concentrations during short exercise bouts[122] and during longer (10–30 min) steady state exercise.[89,132] Further, the so-called "lactate threshold" during progressive-intensity exercise occurs at a lower power output and $\dot{V}O_2$ in unacclimatized lowlanders at 4,200 m simulated altitude than in normoxia; however, this threshold, expressed as relative exercise intensity, occurred at about 50% $\dot{V}O_2$max at both simulated high altitude and sea level.[131]

The increased blood lactate accumulation during hypoxic exercise reflects increased lactate release

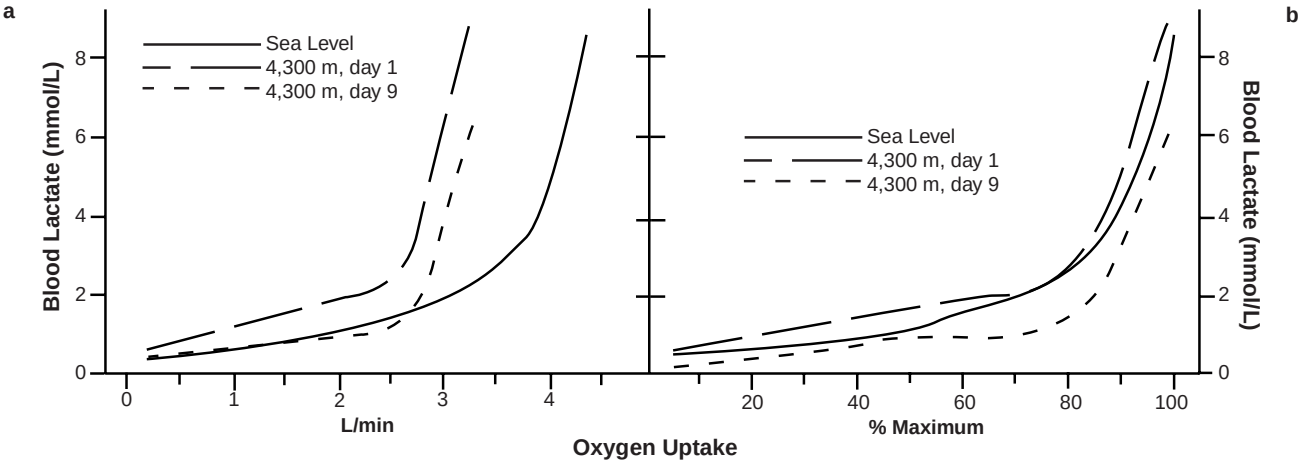

Fig. 21-23. The effects of high altitude on blood lactate accumulation during exercise differ, depending on whether comparisons are made at a given absolute or at a relative exercise intensity. (**a**) For a given absolute exercise intensity, lactate accumulation is accelerated in lowlanders on arrival at high altitude, as compared with sea level. (**b**) In contrast, lactate accumulation in unacclimatized lowlanders exercising at a given percentage of maximum oxygen uptake ($\dot{V}O_2$max) is the same at sea level and on arrival at high altitude. Regardless of whether comparisons are made of similar absolute or relative intensities, following 1 to 3 weeks of altitude acclimatization, a reduction in lactate accumulation during exercise is apparent. Because the lactate accumulation is blunted with altitude acclimatization while the hypoxia persists, this adaptation is referred to as the "lactate paradox" by many altitude researchers.
Data source: Young AJ, Sawka MN, Boushel R, et al. Erythrocyte reinfusion alters systemic O_2 transport during exercise at high altitude. *Med Sci Sports Exerc*. 1995;27:S109.

from active muscle rather than a decrease in lactate clearance. Rowell and colleagues[133] showed that hepatic blood flow increased approximately 10% and hepatic lactate extraction (ie, arterial–hepatic venous lactate difference) increased 5-fold when subjects performing steady state submaximal exercise were switched from a normoxic to a hypoxic (F_{IO_2} ~ 0.11) breathing mixture. Thus, lactate uptake by the liver (and probably also by inactive skeletal muscle) is greater during exercise under acute hypoxic conditions than during normoxia. Bender and colleagues[134] observed, on the other hand, an 80% increase in leg muscle lactate release (femoral arterial–femoral venous difference multiplied by femoral blood flow) during steady state exercise while breathing hypoxic (P_{IO_2} = 83 mm Hg), as compared with normoxic, air mixtures. More recently, Brooks and colleagues[135] measured simultaneous rates of appearance and removal of blood lactate during exercise at sea level and high altitude, and concluded that both were exaggerated on arrival at high altitude.

Muscle lactate efflux during exercise is increased by acute hypoxia.[134] Muscle lactate efflux increases during exercise because the rate that lactate appears in muscle exceeds the capacity of the muscle to oxidize the lactate. The accelerated muscle lactate efflux in unacclimatized lowlanders exercising under hypoxic conditions could reflect an increase in muscle lactate production, a decrease in lactate oxidation within the muscle, or both. The effects of acute hypoxic exposure on muscle lactate production and oxidation have not been directly measured independent of one another. However, lactic acid formation during exercise is probably accelerated under conditions of acute hypoxia. Lactate dehydrogenase activity is stimulated by increasing cytosolic nicotinamide adenine dinucleotide (reduced form, NADH) availability, and total muscle NADH concentration increases more during exercise with respiratory hypoxia than with normoxia.[136] Whether mitochondrial hypoxia per se is directly responsible for the accelerated muscle NADH accumulation remains controversial.[137] Further, the rate of lactate formation is closely linked to the overall rate of glycolysis due to the mass-action effect of pyruvate accumulation, and there is evidence that muscle glycolysis is accelerated during exercise with acute hypoxic exposure compared with normoxic exercise.

Uptake and clearance of blood glucose by active muscle were observed to increase more on the day of arrival at high altitude than during the same exercise at sea level[138]; however, the investigators questioned whether the increase was sufficient to entirely account for the concomitant increase in blood lactate.[135] Other studies have investigated the effects of hypoxia or acute high-altitude exposure on muscle glycogenolysis during exercise in unacclimatized lowlanders. Young and colleagues[89] observed no difference in muscle glycogen utilization when unacclimatized lowlanders exercised at the same relative intensity (85% $\dot{V}O_2$max) for 30 minutes at sea level and at 4,300 m simulated altitude. In those experiments, however, absolute power output was lower in the hypoxic than in the normoxic experiment to offset the reduction in $\dot{V}O_2$max and to maintain relative intensity constant for both trials.[89] This led to the suggestion that muscle glycogenolysis would have been greater under acute hypoxic conditions than normoxia if the exercise had been done at the same absolute power output,[49] but in subsequent experiments, muscle glycogenolysis was found to be the same or even slightly less during 45 minutes of exercise at given absolute exercise intensity on the first day at high altitude as at sea level.[139] Thus, the accelerated lactate accumulation exhibited by unacclimatized lowlanders exercising at high altitude may reflect an accelerated muscle glycolytic rate fueled by enhanced uptake of glucose by active muscle.

The accelerated muscle glycolysis and lactate accumulation in unacclimatized lowlanders exercising on arrival at high altitude is usually attributed to Pasteur's effect. That is, the decreased Ca_{O_2} at high altitude is thought to cause muscle hypoxia, which, in turn, limits oxidative energy production and necessitates an increase in glycolytic metabolism to satisfy the adenosine 5'-triphosphate (ATP) requirements of muscle contraction.[140] However, experimental findings suggest that this may not be the actual mechanism for the increased lactate accumulation. For one thing, compensatory mechanisms increase blood flow to active muscle when Ca_{O_2} is reduced, allowing the same oxygen delivery and uptake by the muscle to be maintained during exercise at a given absolute intensity under both acute hypoxic conditions and at sea level.[45,127,141] Furthermore, if oxygen availability limited aerobic muscle metabolism during exercise in hypoxic environments, then $\dot{V}O_2$ during steady state submaximal exercise at a given power output should be reduced at high altitude compared with sea level, which it is not. Lastly, as depicted in Figure 21-24, net lactate release by the muscle at a given level of oxygen delivery was greater under acute hypoxic than normoxic conditions.[134]

Muscle glycogen breakdown and lactate accumulation during exercise could be accelerated during

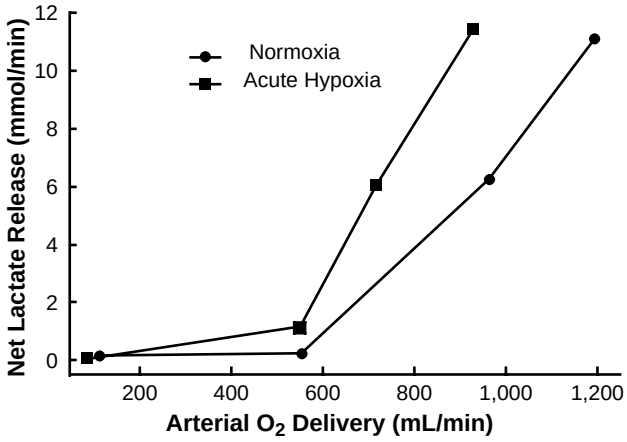

Fig. 21-24. Net lactate release from muscle during exercise (ie, the product of the muscle blood flow rate and the arterial – venous lactate concentration difference) is greater during hypoxia (squares) than normoxia (circles) for any given rate of arterial oxygen delivery to the muscle. This indicates that the mechanism for the accleration in lactate accumulation during exercise at high altitude is not a simple Pasteur effect.
Data sources: (1) Bender PR, Groves BM, McCullough RE, et al. Oxygen transport to exercising leg in chronic hypoxia. *J Appl Physiol*. 1988;65:2592–2597. (2) Bender PR, Groves BM, McCullough RE, et al. Decreased exercise muscle lactate release after high altitude acclimatization. *J Appl Physiol*. 1989;67:1556–1462.

acute hypoxic exposure by mechanisms other than tissue oxygen lack. Experiments with animals indicate that epinephrine stimulates glycolysis in contracting fast-twitch muscle fibers, even at exercise intensities that are otherwise too low to elicit glycogenolysis in the absence of epinephrine.[142] Circulating epinephrine levels of unacclimatized lowlanders exercising under acute hypoxic conditions are elevated, compared with the levels in normoxic conditions, and the elevation in epinephrine concentrations is correlated with the elevation in lactate accumulation.[143] Thus, elevated epinephrine levels in unacclimatized lowlanders exercising at altitude may stimulate muscle glycogenolysis, particularly in fast-twitch (type II) fibers, which have a greater capacity for glycolysis and lactic acid production than slow-twitch (type I) fibers.

Glycogen Sparing With Altitude Acclimatization

Changes in blood lactate responses to exercise were the first reported indication that altitude acclimatization affected muscle metabolism. As mentioned, Edwards[119] reported that acclimatized (6 wk) subjects exercising at 2,810 m exhibited the same or smaller increments in blood lactate as during sea-level exercise at the same power output. Shortly thereafter, Dill and colleagues[118] reported similar observations, and many subsequent investigators have confirmed and extended these findings.

The observation that blood lactate concentrations are lower at altitude than at sea level when acclimatized lowlanders exercise maximally[78,128,144–146] has generated some controversy. Because the reduction in $\dot{V}O_2$max at altitude persists even after acclimatization, those lower blood lactate values may simply reflect the lower maximal power outputs achieved and reduced exercise durations rather than a metabolic adaptation.[49] This explanation is consistent with observations that the reduction in lactate accumulation during maximal exercise at altitude after acclimatization is associated with a reduced glycolytic flux unrelated to any metabolic impairment due to substrate (ie, glycogen, glucose) availability[146] or inhibition of maximal glycolytic or glycogenolytic enzyme activity.[147] That acclimatized subjects achieve the same maximal lactate concentrations 48 hours after returning to sea level as before ascent is thought to confirm the absence of any metabolic adaptation.[147] One suggestion[146] is that the contractile apparatus does not become as fully activated during maximal exercise at altitude after acclimatization as during maximal exercise at sea level. However, Grassi and colleagues[145] found that in acclimatized lowlanders performing maximal exercise at 5,050 m, acute restoration of normoxia enabled the subjects to attain higher power outputs than while breathing ambient air, but maximal lactate levels did not increase. Collectively, these findings suggest that in acclimatized persons exercising at high altitude, a central fatigue mechanism may limit maximal muscle contractile activity, while another mechanism may limit maximal rates of glycogenolytic/glycolytic metabolism.

The lactate responses to steady state submaximal exercise also change with acclimatization. Maher, Jones, and Hartley[132] observed that plasma lactate concentrations of sea-level residents did not increase as much during 20 minutes of exercise at 75% $\dot{V}O_2$max on day 12 of residence at 4,300 m as on the second day at high altitude, or at sea level. That blood lactate accumulation during prolonged steady state submaximal exercise decreases with altitude acclimation has been confirmed in many subsequent studies.[89,131,134,135,148,149]

The effect of altitude acclimatization on lactate accumulation during exercise probably reflects a decrease in lactate production and release into the

blood rather than an increase in metabolic clearance. Studies involving infusion of radioactively labeled metabolites demonstrate decreases in both lactate removal from the blood and metabolic clearance following altitude acclimatization, secondary to a decrease in the rate of lactate appearance in the blood. This observation (combined with earlier findings that net lactate release from muscle,[134] muscle lactate accumulation,[148] and the decrease in muscle pH[139,149] during submaximal exercise at altitude are all less pronounced after acclimatization, whereas pyruvate oxidation appears unchanged[139]) indicates that the lower lactate concentrations reflect a decreased glycolytic production of lactate in contracting muscle.

Indeed, experimental evidence confirms that altitude acclimatization enables a decreased muscle glycogenolysis during exercise. Young and colleagues[89] measured muscle glycogen utilization of sea-level residents during 30 minutes of exercise at 85% $\dot{V}O_2$max at sea level, during the first 2 hours at a simulated altitude of 4,300 m, and again after 18 days of acclimatization at 4,300 m; the two altitude trials were at the same absolute intensity. Muscle glycogen utilization and blood lactate accumulation during exercise at high altitude before acclimatization were the same as at sea level, but were both reduced after 18 days of altitude acclimatization.[89] Green and colleagues[139] confirmed and extended those findings using a similar altitude protocol but employing the same absolute exercise intensity for all three trials.

The mechanism enabling the glycogen-sparing effect of altitude acclimatization is not fully understood. Young and colleagues[89] originally suggested that an increase in fat oxidation during exercise might provide the energy to enable a decreased muscle glycogenolysis. This speculation was based on differences observed in blood–free fatty acid and -glycerol concentrations during exercise at sea level and at altitude. However, while subsequent studies employing strict dietary control and more-precise approaches to measuring fat metabolism have confirmed the glycogen-sparing effect of altitude acclimatization,[139] the most current findings demonstrate that muscles, in fact, decrease utilization of fat as an energy substrate following altitude acclimatization.[150] On the other hand, uptake and clearance of blood glucose by muscle during exercise at altitude is greater following acclimatization, indicating that increased availability of glucose may permit sparing of glycogen stores within the muscle.[131]

The glycogen-sparing adaptation appears to be due to different mechanisms than the metabolic adaptation resulting from chronic aerobic endurance-type training. In the case of endurance training, increased oxidative enzyme activity in skeletal muscle appears to account, at least in part, for metabolic adaptations to physical training at sea level. However, humans acclimatized for 3 weeks at 4,300 m exhibited no change in hexokinase, glycogen phosphorylase, lactate dehydrogenase, malate dehydrogenase,[149] or citrate synthetase (unpublished observations from this laboratory—AJY) activities in the vastus lateralis muscle. Similarly, during a 40-day altitude exposure simulating a progressive ascent to the summit of Mount Everest (282 mm Hg), eight male subjects exhibited no change in vastus lateralis enzyme activities of 3-hydroxyacyl CoA dehydrogenase, pyruvate kinase, or alpha-glycerophosphate dehydrogenase, decreases in succinic dehydrogenase, and citrate synthetase.[147] Thus, the changes in metabolic responses to exercise observed after 2 to 3 weeks of altitude acclimatization do not appear to be due to changes in muscle glycolytic or oxidative enzyme activities.

A progressive rise in resting plasma norepinephrine with unchanged epinephrine occurs during the same time frame that the aforementioned metabolic adaptations to high altitude take place.[148,151] This prompted Young and colleagues[89] to speculate that increased sympathetic nervous activity mediated those adaptations, based on their conclusion that the glycogen-sparing effect of altitude acclimatization had resulted from increased fatty acid mobilization and subsequent oxidation by muscle, because at sea level, increased sympathetic activity stimulates lipolysis. More-recent observations, however, demonstrate that an increased utilization of fatty acids does not necessarily accompany the reduction in glycogen utilization and lactate accumulation that occur with altitude acclimatization.[148,150] Another possibility is that chronically elevated circulating norepinephrine levels during altitude acclimatization induces a decrease in the number or sensitivity, or both, of muscle β_2-adrenergic receptors. Cardiac β_2-adrenergic receptor density and sensitivity in lowlanders declines during altitude acclimatization.[152,153] Stimulation of β_2-adrenergic receptors in muscle activates glycogenolysis, so down-regulation of these receptors could blunt glycogenolysis and lactate accumulation during exercise. However, β_2-adrenergic blockade with propranolol during altitude acclimatization does not prevent the glycogen-sparing adaptation.[148]

These findings suggest that chronic β_2-adrenergic stimulation during altitude acclimatization may not cause the reduction in glycogen utilization and

lactate accumulation during exercise. However, this is not to say that changes in β_2-adrenergic stimulation play no role in the changes in muscle energy metabolism induced by altitude acclimatization. Epinephrine release into the blood during exercise, which is greatly exaggerated on arrival at high altitude compared with that at sea level, is blunted following 2 to 3 weeks of acclimatization.[143,148] As described above, the increase in lactate accumulation during exercise that unacclimatized lowlanders exhibit on arrival at high altitude is closely correlated with the more pronounced increment in epinephrine levels. Thus, a blunting of epinephrine release into the blood appears to be the most likely mechanism by which muscle glycogenolysis and lactate accumulation during exercise at high altitude could be diminished following acclimatization, but this requires experimental verification.

Endocrine Responses at High Altitude

The preceding section described how epinephrine, and perhaps norepinephrine, appeared to mediate the effects of altitude acclimatization on glycogenolysis and lactate accumulation during exercise. While the catecholamines appear to play a principal role in the mechanism by which adjustments in energy metabolism occur during altitude acclimatization, other hormones involved in metabolic regulation may also be affected by sojourn to high altitude. In addition, other hormonal responses to ascent to high altitude and subsequent acclimatization may also modulate the body water adjustments discussed at the beginning of this section.

Insulin and glucagon act to regulate the relative contribution of carbohydrate and fat metabolism to the overall metabolic energy requirements. Glucagon levels appear unchanged in lowlanders sojourning at high altitude, during either rest or exercise.[154] However, changes in the insulin response to exercise, or in the insulin sensitivity of muscle tissue, may contribute to the changes in muscle energy metabolism during exercise at high altitude. Acute hypoxic exposure does not affect resting insulin concentrations in unacclimatized lowlanders up to about 3,000 m.[155] In unacclimatized lowlanders ascending to 4,300 m and higher, resting insulin levels at altitude appear to be elevated, compared with those at sea level.[131,156,157] During exercise at altitude, insulin remains constant at these elevated levels[131,154,156] or increases if the exercise intensity is maximal.[155] Insulin levels, both at rest and during exercise, decrease back to sea-level values with 2 or more weeks of acclimatization,[131,156] unless the sojourner continues ascending to more extreme altitudes.[154]

Thus, on arrival at high altitude, an increase in insulin levels may facilitate glucose uptake by muscle to sustain the accelerated glycolysis and increased lactate accumulation that are apparently stimulated by an exaggerated epinephrine release during exercise. This is consistent with the apparent increase in the uptake and utilization of blood glucose by muscle when unacclimatized lowlanders exercise at high altitude. However, the subsequent decline in insulin levels back to sea-level values that occurs during altitude acclimatization is not consistent with the finding that glucose uptake and utilization by muscle remain elevated. Insulin sensitivity of muscle tissue might increase during acclimatization, but this possibility remains to be investigated. Alternatively, the increased uptake of blood glucose during exercise in acclimatized lowlanders may reflect the actions of growth hormone. Acutely, changes in growth hormone concentrations exert effects on glucose uptake that are similar to those of insulin. Although circulating growth hormone levels during rest are unaffected by sojourn at altitude, growth hormone levels increase more rapidly during exercise at altitude after acclimatization.[87]

The transient elevation in BMR during the first few days after lowlanders arrive at high altitude, which was discussed earlier in this section, appears to be mediated by the thyroid hormones. Within 24 hours after lowlanders arrive at high altitude, plasma thyroxine (T_4) and triiodothyronine (T_3) concentrations both begin to increase.[158] The T_4 and T_3 levels appear to peak between the third and eighth day at altitude,[106,159] and thereafter levels decline.[158,159] This time course parallels that of changes in the BMR.[5,91,106,108,109] When the elevation ascended is extreme (> 5,400 m), thyroid stimulating hormone (TSH) increases along with T_4 and T_3.[160] However, it is interesting to note that at lower altitudes, an increase in TSH has not always been observed to accompany the increase in T_4 and T_3.[158,159] This might suggest that the elevated T_4 and T_3 levels may not be mediated by altitude effects on the hypothalamic-pituitary-thyroid axis activity. Because T_4 and T_3 are transported bound to plasma proteins, changes in these hormone levels may simply reflect the reduction in volume of distribution for the plasma proteins, owing to hemoconcentration during the first week at altitude.

Hormonal responses are thought to be involved in mediating adjustments on body fluid homeostasis experienced by lowlanders during sojourns at high altitude; however, the exact mechanisms are unclear. Arginine vasopressin (AVP), or antidiuretic

hormone, regulates water loss in urine by increasing the permeability of the collecting duct to water, thus promoting water resorption. Unacclimatized lowlanders exposed to moderate hypoxia (at elevations of about 11,000 ft [3,385 m]) exhibit a decrease in AVP over the first 2 hours.[161] Exposure to more extreme elevations appears to have no effect or cause no increase in AVP levels.[161] Furthermore, after 24 hours of hypoxic exposure, and thereafter at altitude, AVP levels are similar to those at sea level.[161] Thus, AVP might play a role in initiating the decrease in body water and plasma volume that lowlanders experience during altitude sojourns, but other mechanisms are involved in sustaining that response.

It is generally agreed that on arrival at high altitude, aldosterone levels in lowlanders are decreased, both at rest and during exercise.[161,162] Aldosterone normally functions to defend normal fluid volume. Aldosterone acts on the kidney to increase sodium and water resorption; thus, a decrease in aldosterone levels would contribute to the increased urine formation and decrease in plasma volume that unacclimatized lowlanders experience on arrival at altitude. With several weeks of altitude acclimatization, aldosterone returns to preascent levels, although the reduction in plasma volume appears to persist longer.[162]

At sea level, aldosterone secretion is controlled by the renin–angiotensin mechanism, in which reduced blood volume or pressure stimulates the kidney to secrete renin, which catalyzes conversion of blood angiotensinogin to angiotensin I, which in turn is converted to angiotensin II by the action of angiotensin-converting enzyme (ACE) in the vascular endothelium. Angiotensin II stimulates release of aldosterone, and exerts a vasoconstrictor effect as well. One frequently cited investigation reported that the acute altitude exposure disrupted the control mechanism at the conversion from angiotensin I to II, based on observations that plasma ACE levels decreased in unacclimatized lowlanders newly arrived at high altitude.[38,163] However, the authors repeatedly failed to confirm their observations, either in subsequent follow-up studies or even when archived blood samples from the original study were reanalyzed, which ultimately led them to retract their conclusion. Thus, Maher and colleagues'[162] observations that renin, both at rest and during exercise, decreases along with aldosterone after 14 hours at 4,300 m, and that resting levels of angiotensin II were also decreased (although exercise levels were not), indicate that the fall in aldosterone secretion on arrival at altitude is appropriate and normally regulated by the renin–angiotensin system.

The decrease in aldosterone synthesis may be a response to what is sensed as, but is not, a progressive increase in blood volume. Within several hours after arrival at high altitude, lowlanders exhibit a sustained peripheral venoconstriction, which progressively increases over the first week of acclimatization.[164,165] Peripheral venoconstriction decreases venous vascular capacity, translocating blood to the central circulation (possibly signaling an increase in blood volume to the kidney, which then decreases renin secretion), and ultimately effecting a decrease in aldosterone levels. Alternatively, the decline in aldosterone levels may reflect a decrease in aldosterone synthesis mediated by a hypoxia-induced decrease in expression of genes for enzymes required in the metabolic synthesis of aldosterone.[166]

Another hormonally mediated process altered in lowlanders sojourning at altitude is erythropoieses, which at sea level is stimulated by an increase in circulating erythropoietin levels. Erythropoietin is released mainly by the kidney (and to a lesser degree by the liver and other extrarenal sites) in response to hypoxemia or blood loss. The expansion of erythrocyte volume that lowlanders experience after several months' acclimatization at high altitude is usually attributed to this hormonal mechanism.[70,167] However, the time course for the changes in erythropoietin in lowlanders sojourning at high altitude is difficult to reconcile with the time course of the expansion of erythrocyte volume.

In contrast to the expansion of erythrocyte volume, which is not manifested until the lowlander has spent several months at high altitude, erythropoietin begins increasing within several hours after ascent.[69,70,167] In one study,[69] erythropoietin levels were elevated 3-fold over sea-level values within 10 to 14 hours after rapid ascent from sea level to 4,300 m. Yet, this increase is short lived. Peak erythropoietin levels are achieved between 24 and 48 hours after arrival at 4,300 m,[168] but decline thereafter, reaching preascent values by the ninth day at this altitude.[69,168] A similar response pattern and time course have been reported at lower[169, 170] and higher[171] elevations, but a more pronounced increase in circulating erythropoietin is observed[171] with ascent above 5,000 m. Given that the acclimatizing lowlander's hormone levels return to sea-level values well before the expansion of erythrocytes is manifested and without alleviation of hypoxemia, the role of this response in the mechanism of erythrocyte volume expansion is unclear and remains to be fully investigated.

CONCLUDING THOUGHTS

At sea level, circulation is thought to be the dominant factor limiting maximal exercise performance.[172] Indeed, maximum oxygen uptake at sea level varies markedly among subjects, and that variability is closely linked to the variability in maximum cardiac output.[173] However, this variability among subjects in their maximum oxygen uptake is markedly reduced as elevation is increased.[174] Considering the limitation imposed on the number of oxygen molecules that can be ventilated at high altitude, and the limitation of lung diffusing capacity at altitude, one might conclude that the respiratory rather than circulatory system limits maximal oxygen uptake at high altitude. If oxygen does not reach the arterial blood, then increasing cardiac output might not greatly facilitate oxygen transport to the tissues. Wagner's analysis[172] indicates that at the summit of Mount Everest, a doubling of maximal cardiac output will increase maximum oxygen uptake by less than 10%. The altitude limitations in total body oxygen transport begin to appear above 2,000 m, where these respiratory limitations might be expected. Thus, the respiratory system imposes greater limitations on overall exercise performance at altitude than at sea level.

Even if respiratory factors limit maximal oxygen uptake at high altitude more than circulatory factors, this is not to say that the systemic oxygen transport and muscle energy metabolism adjustments that occur at high altitude do not affect physical performance. Most physical activities elicit oxygen uptakes well below the maximal, and thus are not limited by $\dot{V}O_2max$, either at sea level or at high altitude. While ascent to high altitude does causes $\dot{V}O_2max$ to decrease, it is not until extreme altitudes are reached that the reduction is sufficient that the oxygen uptake required for activities such as walking approaches maximal. In unacclimatized lowlanders arriving at high altitude, steady state submaximal exercise is sustained by an increase in cardiac output and an accelerated glycolysis and lactate accumulation. Both factors could limit endurance for a given activity at high altitude more than at sea level, the first by increased cardiac work and the second by an increased rate of energy substrate depletion.

With as few as 12 to 16 days of acclimatization, submaximal exercise endurance increases 40% to 60% compared with exercise endurance on arrival at altitude, even though maximal oxygen uptake remains lower.[132,175] After altitude acclimatization, systemic oxygen transport requirements during exercise at altitude can be satisfied with a lower cardiac output, and thus reduced cardiac work, than on arrival.[56] In large part, this adaptation is enabled by the higher Sa_{O_2} resulting from ventilatory acclimatization, which, along with hemoconcentration due to high-altitude diuresis during the initial weeks at altitude and expanded erythrocyte volume after several months, raises Ca_{O_2}.

The development of a glycogen-sparing adaptation further contributes to the improvement in exercise performance. Thus, in lowlanders ascending to high altitude, maximal performance appears to be limited by respiratory factors and submaximal performance by nonrespiratory factors, but both respiratory and nonrespiratory factors appear to contribute importantly to performance improvements with acclimatization.

REFERENCES

1. Ward MP, Milledge JS, West JB. *High Altitude Medicine and Physiology*. New York, NY: Oxford University Press; 2000.

2. West JB, Hackett PH, Maret KH, et al. Pulmonary gas exchange on the summit of Mount Everest. *J Appl Physiol*. 1983;55:678–687.

3. Reeves JT, Groves BM, Sutton JR, et al. Adaptations to hypoxia: Lessons from Operation Everest II. In: Simmons DH, ed. *Current Pulmonology*. St. Louis, Mo: Mosby–Year Book; 1991: 23–50.

4. Howard LSGE, Robbins PA. Ventilatory response to 8 h of isocapnic and poikilocapnic hypoxia in humans. *J Appl Physiol*. 1995;78:1092–1097.

5. Moore JM, Cymerman A, Huang SY, et al. Propranolol blocks metabolic rate increase but not ventilatory acclimatization to 4300 m. *Respir Physiol*. 1987;70:195–204.

6. Hornbein TF. The relation between stimulus to chemoreceptors and their response. In: Torrance RW, ed. *Arterial Chemoreceptors*. Edinburgh, Scotland: Blackwell Scientific Publications; 1968: 65–78.

7. von Euler US, Liljestrand G, Zotterman Y. The excitation mechanism of the chemoreceptor in the carotid body. *Scand Arch Physiol*. 1939;83:132–152.

8. Weil JV, Byrne-Quinn E, Sodal IE, Filley GF, Grover RF. Hypoxic ventilatory drive in normal man. *J Clin Invest*. 1971;50:186–195.

9. Bisgard GE. The role of arterial chemoreceptors in ventilatory acclimatization to hypoxia. *Adv Exp Med Biol.* 1994;360:109–122.

10. Lopez-Barneo J, Lopez-Lopez JR, Urena J, Gonzales C. Chemotransduction in the carotid body: K+ modulated by P_{O_2} in type 1 chemoreceptor cells. *Science*. 1988;242:580–582.

11. Benot AR, Ganfornia MD, Lopez-Barneo J. Potassium channel modulated by hypoxia and the redox status in glomus cells of the carotid body. In: Weir EK, Hume JR, Reeves JT, eds. *Ion Flux in Pulmonary Vascular Control*. New York, NY: Plenum Press; 1992: 177–188.

12. Weil JV. Ventilatory control at high altitude. In: Fishman AP, Cherniak NS, Widdicombe JG, Geiger SR, eds. *Handbook of Physiology: The Respiratory System. Control of Breathing, Vol 2* Bethesda, Md: American Physiological Society; 1986: 703–728.

13. Stea A, Jackson L, Macintyre L, Nurse CA. Long-term modulation of inward currents in O_2 chemoreceptors in chronic hypoxia and cyclic AMP in vitro. *J Neurosci*. 1995;15:2192–2202.

14. Hirschman CA, McCullough RE, Weil JV. Normal values for hypoxic and hypercapnic ventilatory drives in man. *J Appl Physiol*. 1975;38:1095–1098.

15. Collins DD, Scoggin CH, Zwillich CW, Weil JV. Hereditary aspects of decreased hypoxic response. *J Clin Invest*. 1978;62(1):105–110.

16. Huang SY, Alexander JK, Grover RF, et al. Hypocapnia and sustained hypoxia blunt ventilation on arrival at high altitude. *J Appl Physiol*. 1984;56:602–606.

17. Reeves JT, McCullough RE, Moore LG, Cymerman A, Weil JV. Sea-level P_{CO_2} relates to ventilatory acclimatization at 4300 m. *J Appl Physiol*. 1993;75:1117–1122.

18. Van Beek JHGM, Berkenbosch A, Degoode J, Olievier CN. Effects of brainstem hypoxemia on the regulation of breathing. *Respir Physiol*. 1984;57:171–188.

19. Nilsson GE, Lutz PL. Role of GABA in hypoxia tolerance, metabolic depression, and hibernation: Possible links to neurotransmitter evolution. *Comp Biochem Physiol Comp Pharmacol*. 1993;105:329–336.

20. Kazemi H, Hoop B. Glutamic acid and gamma-aminobutyric acid neurotransmitters in central control of breathing. *J Appl Physiol*. 1991;70:1–7.

21. Weil JV. Ventilatory responses to CO_2 and hypoxia after sustained hypoxia in awake cats. *J Appl Physiol*. 1994;76:2251–2252.

22. Robbins PA. Commentary: Hypoxic ventilatory decline. *J Appl Physiol*. 1995;79:373–374.

23. Butterfield GE, Gates J, Fleming S, Brooks GA, Sutton JR, Reeves JT. Increased energy intake minimizes weight loss in men at high altitude. *J Appl Physiol*. 1992;72:1741–1748.

24. Howard LSGE, Robbins PA. Alterations in respiratory control during 8 h of isocapnic and poikilocapnic hypoxia in humans. *J Appl Physiol*. 1995;78:1098–1107.

25. Dempsey JA, Forster HV. Mediation of ventilatory adaptations. *Physiol Rev*. 1982;62:262–331.

26. Visek M, Pickett CK, Weil JV. Increased carotid body sensitivity during acclimatization to hypobaric hypoxia. *J Appl Physiol*. 1987;63:2403–2410.

27. Cruz JC, Reeves JT, Grover RF, et al. Ventilatory acclimatization to high altitude is prevented by CO_2 breathing. *Respiration*. 1980;39(3):121–130.

28. Fitzgerald MP. Further observations on the changes in the breathing and the blood at various high altitudes. *Proc Royal Soc*. 1914;88:248–258.

29. Rahn H, Otis AB. Man's respiratory response during and after acclimatization to high altitude. *Am J Physiol*. 1949;157:445–462.

30. Malconian MK, Rock PB, Reeves JT, Cymerman A, Houston CS. Operation Everest II: Gas tensions in expired air and arterial blood at extreme altitude. *Aviat Space and Environ Med*. 1993;64:37–42.

31. Weil JV, Bryne-Quinn E, Sodal IE, Kline JS, McCullough RE, Filley GF. Augmentation of chemosensitivity during mild exercise in normal man. *J Appl Physiol*. 1972;33:813–819.

32. Waldrop TG, Eldrige FL, Iwamoto GA, Mitchell JH. Central neural control of respiration and circulation during exercise. In: Rowell LB, Sheperd JT, eds. *Handbook of Physiology.* Section 12: *Exercise: Regulation and Integration of Multiple Systems*. New York, NY: Oxford University Press; 1996: 333–380.

33. Dempsey JA, Forster HV, Birnbaum ML, et al. Control of exercise hyperpnea under varying durations of exposure to moderate hypoxia. *Resp. Physiol*. 1972;16:213–231.

34. Christensen EH. Sauerstoff aufnahme and repiratorische functionen in gross hohen [in German]. *Skand Arch Physiol*. 1937;76:88–100.

35. Sutton JR, Reeves JT, Wagner PD, et al. Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol*. 1988;64:1309–1321.

36. Gale GE, Torre-Bueno JR, Moon RE, Saltzman HA, Wagner PD. Ventilation perfusion inequality in normal humans during exercise at sea level and simulated altitude. *J Appl Physiol*. 1985;58:978–988.

37. Wagner PD, Gale GE, Moon RE, Torre-Bueno JR, Stolp BW, Saltzman HA. Pulmonary gas exchange in humans exercising at sea level and simulated altitude. *J Appl Physiol*. 1986;61:260–270.

38. Milledge JS, Catley DM, Ward MP, Williams ES, Clarke CRA. Renin-aldosterone and angiotensin–converting enzyme during prolonged altitude exposure. *J Appl Physiol*. 1983;55:699–702.

39. Wagner PD, Sutton JR, Reeves JT, Cymerman A, Groves BM, Malconian MK. Operation Everest II: Pulmonary gas exchange during a simulated ascent of Mt Everest. *J Appl Physiol*. 1987;63:2348–2359.

40. Evans JW, Wagner PD. $\dot{V}/\dot{Q}$ distributions from analysis of experimental inert gas elimination. *J Appl Physiol*. 1977;42:889–898.

41. Saltin B, Grover RF, Blomqvist CG, Hartley LH, Johnson RL. Maximal oxygen uptake and cardiac output after 2 weeks at 4300 m. *J Appl Physiol*. 1968;25:400–409.

42. Valeri CR, Pivacek LE, Gray AD, et al. The safety and therapeutic effectiveness of human red cells stored at –80°C for as long as 21 years. *Transfusion*. 1989;29:429–437.

43. Stenberg J, Ekblom B, Messin R. Hemodynamic response to work at simulated altitude, 4000 m. *J Appl Physiol*. 1966;21:1589–1594.

44. Pugh LGCE, Gill MB, Lahiri S, Milledge JS, Ward MP, West JB. Muscular exercise at great altitudes. *J Appl Physiol*. 1964;19:431–440.

45. Bender PR, Groves BM, McCullough RE, et al. Oxygen transport to exercising leg in chronic hypoxia. *J Appl Physiol*. 1988;65:2592–2597.

46. Hartley LH, Vogel JA, Landowne M. Central, femoral, and brachial circulation during exercise in hypoxia. *J Appl Physiol*. 1973;34:87–90.

47. Vogel JA, Hansen JE, Harris CW. Cardiovascular responses in man during exhaustive work at sea level and high altitude. *J Appl Physiol*. 1967;23:531–539.

48. Squires RW, Buskirk ER. Aerobic capacity during acute exposure to simulated altitude, 914 to 2286 meters. *Med Sci Sports Exerc*. 1986;14:36–40.

49. Young AJ. Energy substrate utilization during exercise in extreme environments. In: Pandolf KB, Holloszy JO, eds. *Exercise and Sport Sciences Reviews*. Baltimore, Md: Williams & Wilkins; 1990: 65–117.

50. Buskirk ER. Decrease in physical working capacity at high altitude. In: Hegnaurer AH, ed. *Biomedicine Problems of High Terrestrial Elevations*. Natick, Mass: US Army Research Institute of Environmental Medicine; 1969: 204–222.

51. Young AJ, Cymerman A, Burse RL. The influence of cardiorespiratory fitness on the decrement in maximal aerobic power at high altitude. *Eur J Appl Physiol*. 1985;54:12–15.

52. Grover RF, Reeves JT, Grover EB, Leathers JE. Muscular exercise in young men native to 3100 m altitude. *J Appl Physiol*. 1967;22:555–564.

53. Saltin B. Aerobic and anaerobic work capacity at an altitude of 2250 meters. In: Goddard RF, ed. *The Effects of Altitude on Physical Performance*. Albuquerque, NM: The Athletic Institute; 1967: 97–102.

54. Powers SK, Lawler J, Dempsey JA, Dodd S, Landry G. Effects of incomplete pulmonary gas exchange on $\dot{V}O_2$max. *J Appl Physiol*. 1989;66:2491–2495.

55. Astrand PO, Cuddy TE, Saltin B, Stenberg J. Cardiac output during submaximal and maximal work. *J Appl Physiol*. 1964;19:268–274.

56. Grover RF, Lufschanowski R, Alexander JK. Alterations in the coronary circulation of man following ascent to 3100 m altitude. *J Appl Physiol*. 1976;41:832–838.

57. Hultgren HN. Coronary heart disease and trekking. *J Wild Med*. 1990;1:154–161.

58. Grover RF, Tucker CE, McGroaty SR, Travis RR. The coronary stress of skiing at high altitude. *Arch Intern Med*. 1990;150:1205–1208.

59. Vogel JA, Hartley LH, Cruz JC, Hogan RP. Cardiac output during exercise in sea-level residents at sea level and high altitude. *J Appl Physiol*. 1974;36:169–172.

60. Hartley LH, Alexander JK, Modelski M, Grover RF. Subnormal cardiac output at rest and during exercise in residents at 3,100 m altitude. *J Appl Physiol*. 1967;23:839–848.

61. Alexander JK, Hartley LH, Modelski M, Grover RF. Reduction of stroke volume during exercise in man following ascent to 3,100 m altitude. *J Appl Physiol*. 1967;23:849–858.

62. Klausen K. Cardiac output in man in rest and work during and after acclimatization to 3,800 m. *J Appl Physiol*. 1966;21:609–616.

63. Reeves JT, Groves BM, Sutton JR, et al. Operation Everest II: Preservation of cardiac function at extreme altitude. *J Appl Physiol*. 1987;63:531–539.

64. Grover RF, Weil JV, Reeves JT. Cardiovascular adaptation to exercise and high altitude. In: Pandolf KB, ed. *Exercise and Sport Sciences Reviews*. New York, NY: Macmillan; 1986: 269–302.

65. Moore LG, Cymerman A, Shao-Yung H, et al. Propranolol does not impair exercise oxygen uptake in normal men at high altitude. *J. Appl Physiol*. 1986;61:1935–1941.

66. Suarez J, Alexander JK, Houston CS. Enhanced left ventricular performance at high altitude during Operation Everest II. *Am J Cardiol*. 1987;60:137–142.

67. Jain SC, Bardhan J, Swamy YV, Krishina B, Nayar HS. Body fluid compartments in humans during acute high-altitude exposure. *Aviat Space Environ Med*. 1980;51:234–236.

68. Jung RC, Dill DB, Horton R, Horvath SM. Effects of age on plasma aldosterone levels and hemoconcentration at altitude. *J Appl Physiol*. 1971;31:593–597.

69. Sawka MN, Young AJ, Rock PB, et al. Altitude acclimatization and blood volume: Effects of erythrocyte volume expansion. *J Appl Physiol*. 1996;81:636–642.

70. Ward MP, Milledge JS, West JB. *Haematological Changes and Plasma Volume*. London, England: Chapman & Hall; 1989: Chap 9.

71. Grover RF, Reeves JT, Maher JT, et al. Maintained stroke volume but impaired arterial oxygenation in man at high altitude with supplemental CO_2. *Circ Res*. 1976;38:391–396.

72. Horstman D, Weiskopf R, Jackson RE. Work capacity during 3–wk sojourn at 4,300 m: Effects of relative polycythemia. *J Appl Physiol*. 1980;49(2):311–318.

73. Ekblom B, Wilson G, Astrand PO. Central circulation during exercise after venesection and reinfusion of red blood cells. *J Appl Physiol*. 1976;40:379–383.

74. Young AJ, Sawka MN, Boushel R, et al. Erythrocyte reinfusion alters systemic O_2 transport during exercise at high altitude. *Med Sci Sports Exerc*. 1995;27:S109.

75. Dempsey JA, Thomson JM, Forster HV, Cerny FC, Chosy LW. HbO_2 dissociation in man during prolonged work in chronic hypoxia. *J Appl Physiol*. 1975;38:1022–1029.

76. Hannon JP, Vogel JA. Oxygen transport during early altitude acclimatization: A perspective study. *Eur J Appl Physiol*. 1977;36:285–297.

77. Bender PR, McCullough RE, McCullough RG, et al. Increased exercise Sa_{O_2} independent of ventilatory acclimatization at 4300 m. *J Appl Physiol*. 1989;66:2733–2738.

78. Young AJ, Sawka MN, Muza SR, et al. Effects of erythrocyte infusion on $\dot{V}_{O_2}$max at high altitude. *J Appl Physiol*. 1996;81:252–259.

79. Heath D, Williams DR. The blood. In: *Man at High Altitude*. Edinburgh, Scotland: Churchill Livingston; 1977: 39–53.

80. Surks MI, Chinn KSK, Matoush LO. Alterations in body composition in man after acute exposure to high altitude. *J Appl Physiol*. 1966;21:1741–1746.

81. Pugh LGCE. Blood volume and haemoglobin concentration at altitudes above 18,000 ft (5500 m). *J Physiol*. 1964;170:344–354.

82. Torrance JD, Lenfant C, Cruz J, Marticorena E. Oxygen transport mechanisms in residents at high altitude. *Resp Physiol*. 1970;11:1–15.

83. Mairbaurl H. Red blood cell function in hypoxia at altitude and exercise. *Int J Sports Med*. 1994;15:51–63.

84. Goldberg SV, Schoene RB, Haynor D, et al. Brain tissue pH and ventilatory acclimatization to high altitude. *J Appl Physiol*. 1992;72:58–63.

85. Willford DC, Hill EP, Moores WY. Theoretical analysis of optimal P_{50}. *J Appl Physiol*. 1982;52:1043–1048.

86. Reeves JT, Grover RF, Cohn JE. Regulation of ventilation during exercise at 10,200 ft in athletes born at low altitude. *J Appl Physiol*. 1967;22:546–554.

87. Raynaud J, Drouet L, Martineaud JP, Bordacha J, Coudert J, Durand J. Time course of plasma growth hormone during exercise in humans at altitude. *J Appl Physiol*. 1981;50:229–233.

88. Brotherhood J, Brozavic B, Pugh LGC. Haematological status of middle- and long-distance runners. *Clin Sci and Mol Med*. 1975;48:139–145.

89. Young AJ, Evans WJ, Cymerman A, Pandolf KB, Knapik JJ, Maher JT. Sparing effect of chronic high-altitude exposure on muscle glycogen utilization. *J Appl Physiol*. 1982;52:857–862.

90. Vogel JA, Hartley LH, Cruz JC. Cardiac output during exercise in altitude natives at sea level and high altitude. *J Appl Physiol*. 1974;36:173–176.

91. Butterfield GE. Maintenance of body weight at altitude: In search of 500 kcal/day. In: Marriot BM, Carlson SJ, eds. *Nutritional Needs in Cold and in High-Altitude Environments*. Washington, DC: National Academy Press; 1996: 357–378.

92. Hoyt RW, Honig A. Environmental influences on body fluid balance during exercise: Altitude. In: Buskirk, ER, Puhl SM, eds. *Body Fluid Balance: Exercise and Sport*. New York, NY: CRC Press; 1996: 183–196.

93. Fulco CS, Cymerman A, Pimental NA, Young AJ, Maher JT. Anthropometric changes at high altitude. *Aviat Space Environ Med*. 1985;56:220–224.

94. Sutton JR. Effect of acute hypoxia on the hormonal response to exercise. *J Appl Physiol*. 1977;42:587–592.

95. Hoyt RW, Honig A. Body fluid and energy metabolism at high altitude. In: Fregley ML, Blatteis CM, eds. *Handbook of Physiology.* Section 4. *Environmental Physiology, Vol 2*. New York, NY: Oxford University Press; 1995: 1277–1289.

96. Hannon JP, Chinn KSK, Shields JL. Effects of acute high altitude exposure on body fluids. *Fed Proc*. 1969;38:1178–1184.

97. Anand IS, Chandrashekhar Y, Rao SK, et al. Body fluid compartments, renal blood flow and hormones at 6,000 m in normal subjects. *J Appl Physiol*. 1993;74:1234–1239.

98. Picon-Reategui E, Lozano R, Valdivieso J. Body composition at sea level and high altitudes. *J Appl Physiol*. 1961;16:589–592.

99. Kolka MA, Stephenson LA, Rock PB, Gonazlez RR. Local sweating and cutaneous blood flow during exercise in hypobaric environments. *J Appl Physiol*. 1987;62:2224–2229.

100. Kolka MA, Stephenson LA, Gonzalez RR. Depressed sweating during exercise at altitude. *J Therm Biol*. 1989;14:167–170.

101. Greenleaf JE, Greenleaf CJ, Card DH, Saltin B. Exercise-temperature regulation in man during acute exposure to simulated altitude. *J Appl Physiol*. 1969;26:290–296.

102. Tucker A, Reeves JT, Robertshaw D, Grover RF. Cardiopulmonary response to acute altitude exposure: Water loading and denitrogenation. *Respir Physiol*. 1983;54:363–380.

103. Ashack R, Farber MO, Weinberger M, Robertson G, Fineberg N, Manfredi F. Renal and hormonal responses to acute hypoxia in normal individuals. *J Lab Clin Med*. 1985;106:12–16.

104. Anand IS, Chandrashekhar Y. Fluid metabolism at high altitudes. In: Marriott BM, Carlson SJ, eds. *Nutritional Needs in Cold and High-Altitude Environments*. Washington, DC: National Academy Press; 1996: 331–356.

105. Pugh LGCE. Physiological and medical aspects of the Himalayan Scientific and Mountaineering Expedition, 1960–61. *Br Med J*. 1962;2:621–627.

106. Surks MI, Beckwitt HJ, Chidsey CA. Changes in plasma thyroxine concentration and metabolism, catecholamine excretion and basal oxygen consumption in man during acute exposure to high altitude. *J Clin Endocrinol*. 1967;27:789–799.

107. Cymerman A, Pandolf KB, Young AJ, Maher JT. Energy expenditure during load carriage at high altitudes. *J Appl Physiol*. 1981;51:14–18.

108. Grover RF. Basal oxygen uptake in man at high altitude. *J Appl Physiol*. 1963;18:909–912.

109. Butterfield GE, Gates J, Fleming S, Brooks GA, Sutton JR, Reeves JT. Increase energy intake minimizes weight loss in men at high altitude. *J Appl Physiol*. 1992;72:1741–1748.

110. Holloszy JO, Coyle EF. Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. *J Appl Physiol*. 1984;56:831–838.

111. Arner P. Impact of exercise on adipose tissue metabolism in humans. *Int J Obes Relat Metab Disord*. 1995;19:S18–S21.

112. Sherman WM. Metabolism of sugars and physical performance. *Am J Clin Nutr*. 1995;62:228S–241S.

113. Wasserman DH. Regulation of glucose fluxes during exercise in the postabsorptive state. *Annu Rev Physiol*. 1995;57:191–218.

114. Coyle EF. Substrate utilization during exercise in active people. *Am J Clin Nutr*. 1995;61:968S–979S.

115. Brooks GA. Balance of carbohydrate and lipid utilization during exercise: The "crossover" concept. *J Appl Physiol*. 1994;76:2253–2261.

116. Conlee RK. Muscle glycogen and exercise endurance: A twenty-year perspective. In: Pandolf KB, ed. *Exercise and Sport Sciences Reviews*. New York, NY: Macmillan; 1987;15:1–28.

117. Aragon JJ, Lowenstein JM. The purine nucleotide cycle: Comparison of the levels of citric acid cycle intermediates with the operation of the purine nucleotide cycle in rat skeletal muscle during exercise and recovery from exercise. *Eur J Biochem*. 1980;110:371–377.

118. Dill DB, Edwards HT, Folling A, Oberg SA, Pappenheimer AM, Talbot JH. Adaptations of the organism to changes in oxygen pressure. *J Physiol*. 1931;71:47–63.

119. Edwards HT. Lactic acid in rest and work at high altitude. *Am J Physiol*. 1936;116:367–375.

120. Friedemann TE, Haugen GE, Kmieciak TC. The level of pyruvic and lactic acids and lactic pyruvic ratio in the blood of human subjects: The effect of food, light muscular activity, and anoxia at high altitude. *J Biol Chem*. 1945;157:673–689.

121. Harboe M. Lactic acid content in human venous blood during hypoxia at high altitude. *Acta Physiol Scand*. 1957;40:248–253.

122. Knuttgen HG, Saltin B. Oxygen uptake, muscle high-energy phosphates, and lactate in exercise under acute, hypoxic conditions in man. *Acta Physiol Scand*. 1973;87:368–376.

123. Lorentzen FV. Lactic acid in blood after various combinations of exercise and hypoxia. *J Appl Physiol*. 1962;17:661–664.

124. Hogan MC, Cox RH, Welch HG. Lactate accumulation during incremental exercise with varied inspired oxygen fractions. *J Appl Physiol*. 1983;55:1134–1140.

125. Naimark A, Jones NL, Lal S. The effect of hypoxia on gas exchange and arterial lactate and pyruvate concentration during moderate exercise in man. *Clin Sci*. 1965;28:1–13.

126. Hermansen L, Saltin B. Blood lactate concentration during exercise at acute exposure to altitude. In: Margaria R, ed. *Exercise at Altitude*. New York, NY: Excerpta Medica Foundation; 1967: 48–53.

127. Linnarsson D, Karlsson J, Fagraeus L, Saltin B. Muscle metabolites and oxygen deficit with exercise in hypoxia and hyperoxia. *J Appl Physiol*. 1974;36:399–402.

128. Dill DB, Myhre LG, Phillips EE, Brown DK. Work capacity in acute exposures to altitude. *J Appl Physiol*. 1966;21:1168–1176.

129. Boouissou P, Guezennec CY, Defer G, Pesquies P. Oxygen consumption, lactate accumulation, and sympathetic response during prolonged exercise under hypoxia. *Int J Sports Med*. 1987;8:266–269.

130. Fagraeus L, Karlsson J, Linnarsson D, Saltin B. Oxygen uptake during maximal work at lowered and raised ambient air pressures. *Acta Physiol Scand*. 1973;87:411–421.

131. McLellan T, Jacobs I, Lewis W. Acute altitude exposure and altered acid–base states, I: Effects on the exercise ventilation and blood lactate responses. *Eur J Appl Physiol*. 1988;57:435–444.

132. Maher JT, Jones LG, Hartley LH. Effects of high-altitude exposure on submaximal endurance capacity of men. *J Appl Physiol*. 1974;37:895–898.

133. Rowell LB, Blackmon JR, Kenny MA, Escourrou P. Splanchnic vasomotor and metabolic adjustments to hypoxia and exercise in humans. *Am J Physiol*. 1984;247:H251–H258.

134. Bender PR, Groves BM, McCullough RE, et al. Decreased exercise muscle lactate release after high altitude acclimatization. *J Appl Physiol*. 1989;67:1556–1462.

135. Brooks GA, Butterfield GE, Wolfe RR, et al. Decreased reliance on lactate during exercise after acclimatization to 4,300 m. *J Appl Physiol*. 1991;71:333–341.

136. Katz A, Sahlin K. Role of oxygen in regulation of glycolysis and lactate production in human skeletal muscle. In: Pandolf KB, Holloszy JO, eds. *Exercise and Sport Sciences Reviews*. Baltimore, Md: Williams & Wilkins; 1990: 1–28.

137. Stainsby WN, Brooks GA. Control of lactic acid metabolism in contracting muscles and during exercise. In: Pandolf KB, Holloszy JO, eds. *Exercise and Sport Sciences Reviews*. Baltimore, Md: Williams & Wilkins; 1990: 29–63.

138. Brooks GA, Butterfield GE, Wolfe RR, et al. Increased dependence on blood glucose after acclimatization to 4300 m. *J Appl Physiol*. 1991;70:919–927.

139. Green HJ, Sutton JR, Wolfel EE, Reeves JT, Butterfield GE, Brooks GA. Altitude acclimatization and energy metabolic adaptations in skeletal muscle during exercise. *J Appl Physiol*. 1992;73:2701–2708.

140. Hill AV, Lupton H. Muscular exercise, lactic acid and the supply and utilization of oxygen. *Q J Med*. 1923;16:135–171.

141. Horstman DH, Gleser M, Delehunt J. Effects of altering O_2 delivery on $\dot{V}_{O_2}$ of isolated, working muscle. *Am J Physiol*. 1976;230:327–334.

142. Richter EA, Ruderman NB, Gavras H, Belur ER, Galbo H. Muscle glycogenolysis during exercise: Dual control by epinephrine and contractions. *Am J Physiol*. 1982;242:E25–E32.

143. Mazzeo RS, Bender PR, Brooks GA, et al. Arterial catecholamine responses during exercise with acute and chronic high-altitude exposure. *Am J Physiol*. 1991;261:E419–E424.

144. Cerretelli P, di Prampero PE. Aerobic and anaerobic metabolism during exercise at altitude. *Med Sports Sci*. 1985;19:1–19.

145. Grassi B, Marzorati M, Kayser B, et al. Peak blood lactate and blood lactate vs workload during acclimatization to 5050 m and in deacclimatization. *J Appl Physiol*. 1996;80:685–692.

146. Green HJ, Sutton J, Young P, Cymerman A, Houston CS. Operation Everest II: Muscle energetics during maximal exhaustive exercise. *J Appl Physiol*. 1989;66:142–150.

147. Green HJ, Sutton JR, Cymerman A, Young PM, Houston CS. Operation Everest II: Adaptations in human skeletal muscle. *J Appl Physiol*. 1989;66:2454–2461.

148. Young AJ, Young PM, McCullough RE, Moore LG, Cymerman A, Reeves JT. Effect of beta-adrenergic blockade on plasma lactate concentration during exercise at high altitude. *Eur J Appl Physiol*. 1991;63:315–322.

149. Young AJ, Evans WJ, Fisher EC, Sharp RL, Costill DL, Maher JT. Skeletal muscle metabolism of sea level natives following short-term high altitude residence. *Eur J Appl Physiol*. 1984;52:463–466.

150. Roberts AC, Butterfield GE, Cymerman A, Reeves JT, Wolfel EE, Brooks GA. Acclimatization to 4,300-m altitude decreases reliance on fat as a substrate. *J Appl Physiol*. 1996;81:1762–1771.

151. Cunningham WL, Becker EJ, Kreuzer F. Catecholamines in plasma and urine at high altitude. *J Appl Physiol*. 1965;20:607–610.

152. Richalet JP, Le-Trong JL, Rathat C, et al. Reversal of hypoxia-induced decrease in human cardiac response to isoproterenol infusion. *J Appl Physiol*. 1989;67:523–527.

153. Richalet JP, Larmignat P, Rathat C, Keromes A, Baud P, Lhoste F. Decreased cardiac response to isoproterenol infusion in acute and chronic hypoxia. *J Appl Physiol*. 1988;65:1957–1961.

154. Young PM, Sutton JR, Green HJ, et al. Operation Everest II: Metabolic and hormonal responses to incremental exercise to exhaustion. *J Appl Physiol*. 1992;73:2574–2579.

155. Kullmer T, Gabriel H, Jungmann E, et al. Increase of serum insulin and stable c-peptide concentrations with exhaustive incremental graded exercise during acute hypoxia in sedentary subjects. *Exp Clin Endocrinol Diabetes*. 1995;103:156–161.

156. Young PM, Rock PB, Fulco CS, Trad LA, Forte VA, Cymerman A. Altitude acclimatization attenuates plasma ammonia accumulation during submaximal exercise. *J Appl Physiol*. 1987;63:758–764.

157. Young PM, Rose MS, Sutton JR, Green HJ, Cymerman A, Houston CS. Operation Everest II: Plasma lipid and hormonal responses during a simulated ascent of Mt Everest. *J Appl Physiol*. 1989;66:1430–1435.

158. Rastogi GK, Malhotra MS, Srivastava MC, et al. Study of the pituitary-thyroid functions at high altitude in man. *J Clin Endocrinol Metab*. 1977;44:447–452.

159. Stock MJ, Chapman C, Stirling JL, Campbell IT. Effects of exercise, altitude, and food on blood hormone and metabolite levels. *J Appl Physiol*. 1978;45:350–354.

160. Mordes JP, Blume FD, Boyer S, Zheng MR, Braverman LE. High-altitude pituitary-thyroid function on Mount Everest. *N Engl J Med*. 1983;308:1135–1138.

161. Claybaugh JR, Wade CE, Cucinell SA. Fluid and electrolyte balance and hormonal response to the hypoxic environment. In: Claybaugh JR, Wade CE, eds. *Hormonal Regulation of Fluid and Electrolytes*. New York, NY: Plenum; 1989: 187–214.

162. Maher JT, Jones LG, Hartley LH, Williams GH, Rose LI. Aldosterone dynamics during graded exercise at sea level and high altitude. *J Appl Physiol*. 1975;39:18–22.

163. Milledge JS, Catley DM, Williams ES, Withey WR, Minty BD. Effect of prolonged exercise at altitude on the renin–aldosterone system. *J Appl Physiol*. 1983;55:413–418.

164. Weil JV, Byrne-Quinn E, Battock DJ, Grover RF, Chidsey CA. Forearm circulation in man at high altitude. *Clin Sci*. 1971;40:235–246.

165. Wiel JV, Battock DJ, Grover RF, Chidsey CA. Venoconstriction in man upon ascent to high altitude: Studies on potential mechanisms. *Fed Proc*. 1969;28:1160–1162.

166. Raff H, Janowski BM, Engeland WC, Oaks MK. Hypoxia in vivo inhibits aldosterone synthesis and aldosterone synthase mRNA in rats. *J Appl Physiol*. 1996;81:604–610.

167. Winslow RM. High-altitude polycythemia. In: West JB, Lahiri S, eds. *High Altitude and Man*. Bethesda, Md: American Physiological Society; 1984: 163–172.

168. Abbrecht PH, Littell JK. Plasma erythropoietin in men and mice during acclimatization to different altitudes. *J Appl Physiol*. 1972;32:54–58.

169. Gunga HC, Kirsch K, Rocker L, Schobersberger W. Time course of erythropoietin, triiodothyronine, thyroxine and thyroid-stimulating hormone at 2,315 m. *J Appl Physiol*. 1994;76:1068–1072.

170. Gunga HC, Rocker L, Behn C, et al. Shift working in the Chilean Andes (> 3,600 m) and its influence on erythropoietin and the low-pressure system. *J Appl Physiol*. 1996;81:846–852.

171. Richalet JP, Souberbielle JC, Antezana AM, et al. Control of erythropoiesis in humans during prolonged exposure to the altitude of 6,542 m. *Am J Physiol*. 1994;266:R756–R764.

172. Wagner PD. An integrated view of the determinants of maximum oxygen uptake. In: Gonzales NC, Fedde MR, eds. *Oxygen Transfer From Atmosphere to Tissues*. New York, NY: Plenum Press; 1988: 245–256.

173. Reeves JT, Groves BM, Cymerman A, et al. Cardiac filling pressures during cycle exercise at sea level. *Respir Physiol*. 1990;80:147–154.

174. Cymerman A, Reeves JT, Sutton JR, et al. Operation Everest II: Maximal oxygen uptake at extreme altitude. *J Appl Physiol*. 1989;66:2446–2453.

175. Khanna PK, Dham SK, Hoon RS. Exercise in an hypoxic environment as a screening test for ischaemic heart disease. *Aviat Space Environ Med*. 1976;47:1114–1117.