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CHAPTER 12

HUMAN PERFORMANCE AND ACUTE HYPOXIA

Charles S. Fulco, M.A.T. and Allen Cymerman, Ph.D.



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INTRODUCTION

Men have ventured into high mountainous regions from the beginning of recorded history for many reasons, not the least of which was to escape from the ravages of their fellow man. Religious reasons and natural resource exploitation have also had a large influence on early travels to remote high environments. The first recorded description of the possible ill effects due to oxygen deficiency was described in Alexander's troops crossing into India in 328 B.C. (62). But it was not until the Renaissance that man's increasing curiosity about himself and his surroundings resulted in new knowledge of the properties and chemistry of his natural environment. It has now been about 300 years since the importance of "oxygen" in mammalian respiration was dramatically shown by John Mayow in mouse-bell jar experiments (41). Significant steps in our knowledge of oxygen and its effects were slowly made over the next 200 years, but a giant step was made in 1878 with the studies of Paul Bert. Bert, the father of modern high-altitude physiology, demonstrated in the mid to late nineteenth century that oxygen deficiency resulted in specific symptoms which were due to the decrease in the partial pressure of oxygen and that this decrease could be caused by a reduction of the total barometric pressure from either chamber decompression or mountain ascension.

Man is the only animal who purposefully subjects himself to the rigors of hypoxic environments such as those found in the mountainous regions of the world for reasons other than pure survival. In recent times, ascent by sea-

level residents using modern conveyances to high altitude regions of the world for trekking, tourism, mountaineering, business, and scientific and military reasons has increased many fold. It is estimated that 4000 tourists ascend daily via cable car from Chamonix, France (1000 m) to Arguille du Midi (3800 m) in 20 minutes, remain for several hours, and then descend. Similar numbers are found in the Western Hemisphere but to an even higher altitude. In the 1987 season, approximately 500,000 tourists ascended Pikes Peak, Colorado (1830 m to 4300 m) in about one hour by car, bus, or railway. The number of skiing and mountain enthusiasts that enjoy their hobbies after rapid translocation from sea-level originations is inestimable. Because of the large numbers of individuals, the elevations to which they are ascending, the rapidity, and the relatively high level of associated physical exertion, there is no question that increased numbers of people are being affected by the relative hypoxia.

This chapter considers the acute human physiological responses to hypoxia from both the temporal (< 4 hours) and severity domains (inspired oxygen pressure from approximately 110 torr or 2440 m elevation to 70 torr or 5500 m). The following two chapters discuss longer hypoxic exposures and the potential medical problems, respectively. A number of recent reviews, in part or in their entirety, expertly discuss various aspects of the acute responses to reduced partial pressures of oxygen (17,34,69,87). The present chapter will be limited to a discussion of the effects of acute exposure to hypoxia on human performance.

In the present context, "acute" will be defined as four hours or less. It should be understood that the designation of four hours is quite

arbitrary. It is certainly not an objective point in time denoting a significant physiological change. Rather, the four-hour designation allows this chapter to include much of the information gathered during early periods of hypobaric chamber exposures as well as the information gathered during hypoxic gas breathing. The information presented from field studies will be limited since altitude field studies imply longer exposures, possible staging effects, and uncontrollable factors such as exertion, nutrition, dehydration, etc.

The term "acute" is also often used to mean "of short duration". But does short duration mean seconds, minutes, hours, days or weeks? Scientific investigations studying hypoxia have been as short as seconds or as long as months. In many of these, "acute" has been useful as a relative term to describe the earlier period of study in contrast to a later period in the same experiment, usually described as "chronic" or "long-term". While this time-period classification system may be adequate for intra-experimental comparisons, it is not appropriate for comparing "acute" phases of different experiments. For example, in a study lasting several months, acute may be defined for descriptive purposes as any time period up to weeks, whereas in a study lasting an hour acute may be defined as minutes.

The problem of defining acute hypoxia is more than an exercise in semantics. Many hypoxic responses are initiated almost immediately and are continually readjusting for the entire duration of the exposure. To compare an acute period of exposure lasting minutes to one lasting days would surely lead to inconsistent and contradictory conclusions. Unfortunately, there does not exist an operational definition of acute as it relates to hypoxia

research, although attempts have been made (19). But as pointed out by Welch (87), the idea was never widely accepted. It may be appropriate to mention the concepts discussed by Bouverot (6) who used the term "accommodation" to refer to hypoxic exposures resulting from simulated or real exposures lasting from seconds to hours depending on the severity. We will use the term "acute" since, medically speaking, "accommodation" connotes a relatively rapid return toward a normal state as occurs with the visual, olfactory, and subthreshold nerve stimulation. "Acclimation" and "acclimatization" can be accurately associated with simulated and real exposures lasting from days to months, respectively.

The study of the effects of hypoxia requires a reduction in the partial pressure of ambient oxygen by decreasing either the oxygen concentration of the inspired gas or the ambient barometric pressure. While each procedure is thought to elicit the same responses (29,70), it is often desirable to use one method in preference to another. In experiments where immediate responses to hypoxia are being studied, breathing a hypoxic gas mixture may be warranted. If acclimatization to hypoxia is of primary interest, experiments conducted in a high-altitude field laboratory for a number of weeks would be appropriate. Hypobaric chambers, capable of housing a limited number of subjects, are ideal for: (a) experiments lasting from several hours to several days; (b) experiments where the level of hypoxia will be varied; or (c) for use of experimental procedures too risky to perform in a field laboratory.

Basic Concepts

An uninterrupted supply of oxygen must be made available to man for him to function for more than a few minutes. Each cell of the body receives oxygen and rids itself of carbon dioxide. However, because of the distance between most cells and the ambient air, the cells cannot exchange these gases directly. They must rely on a delivery and exchange system that includes: movement of gases between the ambient air and the lungs; matching of ventilation with blood flow; diffusion between alveolar air and capillary blood; vascular transportation from the lungs to the tissues; and finally, diffusion between capillary blood and the tissues.

At each level of gas exchange, oxygen and carbon dioxide readily diffuse "down" their pressure gradients. At sea level, the partial pressure of oxygen (P_{O_2}) in the ambient air is 159 torr ($760 \text{ torr} \times 20.95\% O_2$). As the inspired air passes through the respiratory passages where it becomes totally humidified, the P_{O_2} will have been reduced by the partial pressure of water vapor (47 torr at a body temperature of $37^\circ C$) to a value of 149 torr ($(760 - 47 \text{ torr}) \times 20.95\%$), and is designated as $P_{I}O_2$. $P_{I}O_2$ is further reduced to approximately 104 torr in the alveolar air because of incomplete replacement of oxygen in the alveolar air as well as the fact that oxygen is constantly diffusing out of the alveoli into pulmonary capillaries. Since the P_{O_2} of venous blood entering the pulmonary capillary is 40 torr, the 64 torr pressure gradient ($104 - 40 \text{ torr}$) causes oxygen to rapidly diffuse into the capillary. In approximately 0.25 sec, pulmonary arterial blood will become almost completely saturated, and the P_{O_2} on the arterial side of the capillary will be almost equal to the P_{O_2} of the alveolar air under sea-level

conditions, even with mild to moderate exercise. Because of the presence of veno-arterial shunts, unequal matching of ventilation with perfusion, and to a lesser extent, the actual physical diffusion barrier of the pulmonary and circulatory membranes, not all of the blood becomes totally oxygenated. The P_{O_2} of the blood that is actually pumped by the left heart into the aorta and the peripheral arteries is reduced to approximately 95-97 torr. Oxygen then diffuses rapidly from the blood into the interstitial fluid where the P_{O_2} is 38-40 torr and continues into the cells where the average intracellular P_{O_2} is 20-25 torr.

Carbon dioxide diffuses in the opposite direction at each level of gas exchange. But because carbon dioxide diffuses 20 times as rapidly as oxygen, the pressure differences are much less than are required for oxygen to effect adequate transfer. Thus, the intracellular partial pressure of carbon dioxide (PCO_2) of about 46 torr provides a sufficient pressure gradient for diffusion of CO_2 into the interstitial spaces (45 torr) and subsequently into the tissue capillaries where the PCO_2 of the arterial blood is 40 torr. The PCO_2 of the venous blood leaving the tissue capillaries and entering the pulmonary capillaries is about 45 torr. The CO_2 then diffuses into the alveolar air (40 torr) and is subsequently released into the atmosphere. CO_2 is transported in a physically dissolved state (7%), by the bicarbonate ion after conversion from carbonic acid (70%), and by its combination with hemoglobin and plasma proteins (23%).

As man ascends from sea level to altitude, the $P_{I}O_2$ is diminished in direct proportion to the reduction in atmospheric barometric pressure. At 448 torr or 4300 m, the P_{O_2} of the tracheal air is 84 torr $((448-47 \text{ torr}) \times$

20.95%) and the arterial PO_2 (P_{aO_2}) is approximately 40-45 torr. Thus, the oxygen pressure gradient for diffusion into the pulmonary capillary is 39-44 torr, considerably less than the sea-level value. The PO_2 gradient at each level of gas exchange is also reduced. The result is an impaired ability to transport oxygen from the atmosphere to the cell. Table 1 lists the partial pressures of oxygen at several stages of the oxygen cascade for five different altitudes. Figure 1 graphically illustrates the reduction in the pressure gradient at each step of the oxygen transport chain for an altitude of 4300 m.

TABLE 1 HERE

FIGURE 1 HERE

RESTING VENTILATION

Man's initial response to hypoxia ($PIO_2 < 110$ torr) during rest is an increase in minute pulmonary ventilation. The increase can be measured within minutes of exposure and is inversely related to the reduction in ambient barometric pressure (22,47,65). Resting ventilation increases linearly as the barometric pressure is reduced to about 400 torr and exponentially below this level of hypobaria (47). If minute ventilation is

recorded within 5 minutes of a rapid exposure to an ambient P_{O_2} of less than 100 torr ($P_{O_2} < 55$ torr) and the values compared to those measured within an hour later while at the same level of hypoxia, then the latter values will be lower but still be increased over sea-level (22,47,65). This reduction in ventilation is thought to be caused by hyperventilation-induced hypocapnia decreasing both the central and peripheral hypoxic drives (43,47,86). Evidence obtained from animals which have had their peripheral chemoreceptors denervated suggests the presence of central (suprapontine) inhibition of ventilation during acute hypoxia (79). To add to the complexity of the inhibitory response, Moore *et al.* (50) have suggested that individuals with higher CO_2 sensitivities may have greater hypocapnia-induced inhibition of the ventilatory response to hypoxia. Furthermore, a recent study by Easton *et al.* (22) indicated that the relative reduction in ventilation still occurs even when hypocapnia is prevented. Thus, although the exact mechanisms and interactions responsible for the relative reduction in ventilation are still to be determined, there appears to be a balance between peripheral mechanisms increasing ventilation and central mechanisms inhibiting ventilation. Excellent reviews of the acute modulation of ventilation by hypoxia in humans and animals are given by Lahiri (49), Lahiri and Gelfand (48), and Dempsey and Forester (17).

The initial increase in pulmonary ventilation during hypoxic exposure is associated primarily with an increase in tidal volume. If the exposure is extended or the level of hypoxia more severe, the frequency of breathing will also increase (29,65). Enhancement of the volume and depth of breathing causes a more complete turnover of alveolar gases with atmospheric air, effectively limiting the drop in the alveolar P_{O_2} ($P_{A_{O_2}}$).

Chemoreceptor Control

A myriad of both direct and indirect experimental evidence indicates that the chemoreceptors within the carotid and aortic bodies mediate the increase in ventilation during acute exposure to hypoxia. No other known mechanism is involved in the initial phase of exposure. The most compelling evidence, perhaps, is that total denervation of these structures significantly attenuates or completely abolishes the ventilatory response to acute hypoxia (49). Chemoreceptors are stimulated when the P_{aO_2} and not the arterial oxygen content (C_{aO_2}) is reduced. Blood flow through the chemoreceptors is extremely high, allowing any reduction in P_{aO_2} to be sensed immediately with a resultant increase in chemoreceptor afferent firing activity that is proportional to the decrease in P_{aO_2} . The transmission rate to the central respiratory center is greatly increased when the P_{aO_2} is reduced below 60-65 torr. This is approximately the P_{O_2} level marking the beginning of the "steep" portion of the oxygen dissociation curve.

The exact mechanism by which a low P_{aO_2} stimulates the chemoreceptors is not known. Direct stimulation of the respiratory center with hypoxic arterial blood has no effect. Neural output from the chemoreceptors to the medulla for a given reduction in P_{aO_2} is not diminished with prolonged periods of hypoxia (49). There is also a large inter-individual range of ventilatory responses to hypoxia suggesting that differing sensitivities of chemoreceptors exist from individual to individual (51).

GAS EXCHANGE AND TRANSPORT

Once oxygen has entered the alveolar sacs, the next step is diffusion across the alveolar-capillary membrane to oxygenate the arterial blood. There are two important factors that can affect how complete the gas exchange will be and thus how well the arterial blood will be oxygenated. One is the actual process of diffusion occurring between functional alveoli and their immediately adjacent capillaries. The other is an optimal matching of ventilation with blood flow within various regions of the lung.

Diffusion and Ventilation/Perfusion at Rest

The pressure gradient between $P_{A}O_2$ and the $P_{a}O_2$ plays an important role in the rate of diffusion of oxygen through the alveolar-capillary membrane. During rest at sea level, the $P_{A}O_2$ is approximately 100-104 torr and that of the venous capillary PO_2 , 40 torr. Within about 0.25 sec, before the blood exits the capillary, the PO_2 of the arterial side of the capillary will be in equilibrium with the $P_{A}O_2$. During rest and acute exposure to altitude, the partial pressure gradient across the alveolar-capillary membrane is lessened. At 448 torr or 4300 m, the $P_{A}O_2$ is reduced to 53 torr. The venous capillary PO_2 is correspondingly decreased to about 20-30 torr, reducing the pressure gradient to the capillary to 23-33 torr. Since the volume of oxygen that diffuses across the membrane is directly related to the PO_2 gradient, the rate with which oxygen diffuses through is lessened. Thus, the potential for pulmonary arterial blood to become equilibrated while still in proximity to the functional alveoli is also lessened. However, in the normal lung during

acute exposure to a moderate altitude, the ability to reach equilibrium does not seem to be a problem, making it unlikely that a diffusion limitation to the transport of oxygen exists at rest (80). At extreme altitudes (>7600 m) however, a diffusion limitation at rest is detectable in some individuals (85). Figure 2 illustrates the difference in equilibrium times at rest between sea level (A) and 4300 m (B).

FIGURE 2 HERE

An increase in the thickness of the respiratory membrane due to fluid edema would also slow down the rate of diffusion and increase the time necessary for pulmonary arterial blood to become as fully oxygenated as possible. There is some evidence which suggests that subclinical pulmonary edema may occur after as little as two hours of decompression to 447 torr (9). However, the chance of pulmonary edema occurring during acute exposure to hypoxia to the degree necessary to cause a significant impairment of gas exchange at rest has to be considered unlikely.

The efficiency with which gas exchange occurs is also dependent upon the distribution of the ratios of alveolar ventilation to blood perfusion ($\dot{V}_A/Q$) throughout the lung (51). At rest, not all alveoli are ventilated equally nor is blood flow through the alveolar capillaries the same for each alveolus. Therefore, alveolar ventilation and alveolar capillary blood flow are usually not distributed uniformly. The upper lobes of the lung are ventilated more than the lower lobes but are perfused less. The $\dot{V}_A/Q$ ratio

thus ranges from a high value in the upper lobes to a lower value in the lower lobes. It should be obvious then that the overall total $\dot{V}_A/\dot{Q}$ actually represents a mean value of $\dot{V}_A/\dot{Q}$ relationships throughout the lung.

At altitudes above 2500 m, the increase in alveolar ventilation is matched by an increase in pulmonary perfusion to poorly perfused areas of the lung (e.g., apices), secondary to an increase in pulmonary artery pressure (51). The end result is an enlarged surface area. While the subsequent improvement in perfusion would seem to lead to an enhancement of the $\dot{V}_A/\dot{Q}$ distribution, such is not always the case, suggesting that the functional, intraregional $\dot{V}_A/\dot{Q}$ relationships worsen (29,35). In other words, the more uniform, overall topographical distribution of perfusion is offset by the individuality of a number of intraregional $\dot{V}_A/\dot{Q}$ mismatches so that the overall $\dot{V}_A/\dot{Q}$ relationship at rest does not change with altitude exposure (29,84).

FIGURE 3 HERE

Diffusion and Ventilation/Perfusion during Exercise

During heavy exercise at sea level, arterial oxygen saturation (S_{aO_2}) is slightly reduced from resting values (1). Similarly, heavy exercise causes a more marked desaturation at high altitude than at sea level (29,38,78,84). The magnitude of the desaturation during exercise under

hypoxic conditions is directly proportional to the level of hypoxia (see Figure 3). Desaturation due to an increase in alveolar-arterial P_{O_2} difference $[(A-a)DO_2]$ during heavy exercise at altitude can be attributed to either a diffusion limitation, a worsening $\dot{V}_A/Q$ relationship, or an increased amount of shunted blood bypassing the oxygenation process. While it is theoretically possible that each of these factors plays a role in the observed increase in $(A-a)DO_2$, it has been difficult to distinguish their relative contribution.

In recent years, the expanded use of the multiple inert gas elimination technique has allowed such discrimination (29,36,80,84). Gale et al. (29) investigated the effects of acute exposure to three levels of hypobaria (632, 523 and 429 torr) on $\dot{V}_A/Q$ relationships during light, moderate and heavy exercise. They reported increases in $\dot{V}_A/Q$ mismatching at 523 and 429 torr but not at 632 torr. At 429 torr, during exercise, one third of the $(A-a)DO_2$ was attributed to a $\dot{V}_A/Q$ mismatch and the remainder to alveolar-end-capillary diffusion disequilibrium. They also reported that the $\dot{V}_A/Q$ mismatch was completely reversed by breathing 100% O_2 . This finding suggested that the degree of $\dot{V}_A/Q$ inequality is related to the degree of pulmonary hypertension, possibly due to nonuniform hypoxic pulmonary vasoconstriction. Torre-Bueno et al. (80) showed that when oxygen uptake ($\dot{V}O_2$) exceeded $1.0 \text{ l}\cdot\text{min}^{-1}$ at 523 torr and $0.5 \text{ l}\cdot\text{min}^{-1}$ at 429 torr, the $(A-a)DO_2$ widened. The contribution of a diffusion limitation was found to be slightly higher than the $\dot{V}_A/Q$ mismatch to the increase in $(A-a)DO_2$. Post-pulmonary shunt was excluded as a contributing factor to the increase in $(A-a)DO_2$. In further support of the increasing importance of a diffusion limitation, Wagner et al. (84) showed

that the contribution of the diffusion limitation to the total $(A-a)DO_2$ increases progressively with exercise at 523 and 429 torr, while the contribution of the V_A/Q mismatch to $(A-a)DO_2$ became proportionally less. They were also able to show that V_A/Q was related to mean pulmonary arterial pressure and to confirm previous work (80) showing that the contribution of post-pulmonary shunt towards the $(A-a)DO_2$ is minimal at altitude. The data from all of these studies suggest that during exercise at altitude, the primary pulmonary factor interfering with gas exchange and increasing the $(A-a)DO_2$ is an alveolar-end-capillary diffusion limitation.

Transportation of Oxygen in the Blood

Oxygen diffuses into the pulmonary capillary where it is carried by the blood to the tissues. The oxygen is carried both in a dissolved state in the aqueous phase and in a loose, reversible chemical combination with hemoglobin. Transportation of oxygen to the tissues in physical solution accounts for less than one percent of the total blood content at sea level and is even less of a factor with increasing levels of hypoxia. The amount of oxygen in the dissolved state is insufficient to supply tissue needs even at rest. It is therefore evident that most (>99%) of the oxygen is transported in combination with hemoglobin.

The hemoglobin complex is remarkable in that it has the ability to combine extremely rapidly with oxygen in the lungs (less than 0.01 sec) and transport the oxygen to the tissues where the oxygen is unloaded. A sigmoidal-shaped oxyhemoglobin dissociation curve describes the relationship

between the P_{aO_2} and the completeness with which the hemoglobin is saturated with oxygen. Blood temperature, blood pH, P_{aCO_2} , and 2,3 diphosphoglycerate (2,3 DPG) can all affect the position of the curve and thereby alter the relationship between the P_{aO_2} and saturation.

Acute exposure to hypoxia causes a shift of the standard oxygen dissociation curve to the right. The amount of displacement is proportional to the level of hypoxia (50). The shift seems to be due to a net effect of a number of interrelated factors. The increase in ventilation occurring during exposure reduces the arterial PCO_2 and increases arterial pH. Also occurring within hours of exposure to altitude is an increase in 2,3 DPG. This increase is thought to be the main cause of the shift because without it, the shift doesn't occur (50). However, it should also be noted that without an increase in pH, an increase in 2,3 DPG will not occur (49).

It appears that a rightward shift would be advantageous since oxygen delivery to the tissues would be enhanced. For any given P_{aO_2} , a rightward shift would present to the tissues a greater PO_2 . However, an increase in 2,3 DPG also makes it more difficult for oxygen to combine with the hemoglobin in the lungs. Thus, the advantage at the tissues is lessened by the disadvantage in the lungs. At levels of hypoxia less than that found at altitudes of 3500 m, there is a net advantage (51). At very high altitudes, the inability to pick up oxygen at the lungs may outweigh the advantage provided to the tissues.

Blood to Tissue Oxygen Transport

Oxygen travels from the peripheral capillaries, through the interstitial and intracellular fluids, and finally into the mitochondria. In the mitochondria, the P_{O_2} is nearly zero even at sea level (8). To adequately support oxidative reactions, a minimum of one to three torr oxygen pressure gradient is required between the cytoplasm and the mitochondria while a 10 torr P_{O_2} difference may be needed between the plasma and the cytoplasm (8,69). Apparently, only during heavy exercise in extreme hypobaria (240 torr) are these values approached and to be considered as possibly limiting (67).

EXERCISE

FIGURE 4 HERE

Maximal Cardiorespiratory Responses

The maximal oxygen uptake ($\dot{V}O_{2max}$) of sea-level residents is reduced immediately during acute exposure to altitudes greater than 1500 m (720 torr) or during breathing of hypoxic gas mixtures with less than 17.5% O_2 (73,87). The reduction in sea-level $\dot{V}O_{2max}$ is about 10% for every 1000 m of elevation after 1500 m (7) (Figure 4). While there seems to be a wide variation in the

magnitude of $\dot{V}O_{2\max}$ reduction among males at a given level of hypoxia, the variation seems to be weakly related to an individual's fitness level at sea level (89).

Recent evidence reported by Paterson *et al.* (61) suggests that females may be better able to limit the reduction in $\dot{V}O_{2\max}$ at altitude than males. While breathing a gas mixture containing 11.81% oxygen (approximating 4500 m), males had a reduction in $\dot{V}O_{2\max}$ of 29.5%, a value close to the 30% that would have been predicted from Figure 4. The $\dot{V}O_{2\max}$ of the females, however, was reduced only 24% (61). However, because of the small number of female subjects in that study ($n=4$), it cannot be stated for certain that a difference in the magnitude of reduction in $\dot{V}O_{2\max}$ during acute hypoxia represents a true gender difference. The difference in decrement between genders in this study could also be a reflection of a normal intersubject variation among males and females. For example, in two studies (21,24) which were performed in approximately the same level of hypoxia (12.6-12.8%; 3962-4100 meter equivalents), the difference in reported findings for $\dot{V}O_{2\max}$ decrements between the two studies were significant. In one study (21), the mean reduction in $\dot{V}O_{2\max}$ was 26.7%. In the other study (24), the mean reduction in $\dot{V}O_{2\max}$ was only 18% for both the 17 males and 20 females tested.

While there is no disagreement that $\dot{V}O_{2\max}$ is reduced immediately in response to hypoxia and that the reduction in $\dot{V}O_{2\max}$ can be fairly well predicted at a given altitude, there is less agreement as to the exact cause of the reduction. Maximal oxygen uptake is the product of the maximal values of heart rate, stroke volume, and arterial oxygen content. During acute exposure to altitudes up to about 4600 m, maximal values for heart rate have

been reported to decrease (28,37,38,61) or not change (26,30,75) from sea-level values. A reduction in maximal heart rate at altitude is hard to reconcile given that the sympathetic nervous system becomes more active under hypoxic conditions (68).

The reason for the difference in reported findings for maximal heart rate is not readily apparent. However, one possibility may be related to the difference in the definition of "maximal" heart rate. For example, some studies may be reporting the "average" heart rate over some period of time (i.e. last 30 sec at an exercise intensity) while other studies may report a "peak" heart rate. Furthermore, it is not always apparent that the reported maximal heart rate was obtained at the same exercise intensity from which the $\dot{V}O_{2\max}$ value was obtained or from a higher, supramaximal exercise intensity for which only a heart rate, but not a $\dot{V}O_{2\max}$, value was obtained (e.g., due to a lack of a plateau in $\dot{V}O_2$).

Other methodological possibilities for the difference in reported findings in heart rate may include differences in the mode of testing (treadmill vs ergometer) or in the type of $\dot{V}O_{2\max}$ test protocol used (steady-state or progressive; continuous or discontinuous). These points, as well as additional, related comments provided by Welch (87) also apply to the maximal values for stroke volume and cardiac output.

While the bulk of the literature shows that the maximal values for stroke volume or cardiac output do not differ between sea level and acute altitude exposure (34,38,75,82), some report an increase in maximal stroke volume (38) and a reduction in cardiac output (see ref. 87). Given that subjects of similar age and sex (male) were evaluated at comparable altitudes

in all these studies, could the difference in results of the reported maximal values for stroke volume and cardiac output be related to a difference in protocols?

At sea level, the values of $\dot{V}O_{2\max}$ and its determinants are fairly independent of the type of protocol used (55,74). During a hypoxic exposure, however, the selection of the type of protocol employed may be more critical. Knuttgen and Saltin (46) showed that in normoxia, steady state for any given exercise intensity was obtained by the end of the third minute of exercise. During hypobaria (462 torr), the attainment of steady-state $\dot{V}O_2$ for each exercise intensity was delayed. In some subjects, steady-state $\dot{V}O_2$ was not obtained even after four minutes at the same exercise intensity. The implication of these findings is that when comparisons are to be made between sea level and altitude for submaximal as well as maximal responses, a protocol using an exercise period at each stage lasting at least five minutes should be used. Otherwise a steady-state $\dot{V}O_2$ value (sea level) may be compared to a nonsteady-state $\dot{V}O_2$ condition (hypoxia). Obviously, an error of unknown proportions would occur in cardiac output determination if the method used assumes steady-state conditions (e.g., CO_2 rebreathing).

To our knowledge, no one has compared different $\dot{V}O_{2\max}$ protocols within the same study under hypoxic conditions and established that each protocol elicits the same maximal values for heart rate, stroke volume, cardiac output or $\dot{V}O_{2\max}$. Until such a definitive study can be performed, support must be given to the results found in the majority of the studies. That is, during acute exposure to hypoxia, the maximal values for heart rate, stroke volume and cardiac output do not differ from normoxia. However, each of these values are reached at a lower maximal exercise intensity.

If maximal cardiac output is not reduced during acute exposure to hypoxia, then the reduction in $\dot{V}O_{2\max}$ must be primarily related to the amount of oxygen in the arterial blood available to the working muscles (28). This is indeed the case. Stenberg *et al.* (75) showed that subjects exposed to 4000 m had a 28% reduction in $\dot{V}O_{2\max}$ and a 26% reduction in C_aO_2 . Similar results have been observed repeatedly (30,83). C_aO_2 is determined by the hemoglobin concentration and the saturation of hemoglobin. Since the hemoglobin concentration is not altered during acute exposure to hypoxia, then C_aO_2 is directly related to the saturation of hemoglobin which is a function of the characteristics of the oxygen dissociation curve and the P_aO_2 .

When the P_aO_2 is greater than about 60 torr (on the flat portion of the curve), hemoglobin will be greater than 90% saturated with oxygen. At this saturation level and above, C_aO_2 (and thus, $\dot{V}O_{2\max}$) is affected slightly. Once the P_aO_2 drops below 60 torr (steep portion of the curve), a small decrease in P_aO_2 will cause a large reduction in hemoglobin saturation resulting in a relatively large drop in C_aO_2 .

Exercise, as well as a hypoxic exposure, causes a rightward shift of the oxygen dissociation curve. The shift is especially pronounced in blood at the site of the working muscle owing to a local increase in temperature, a reduction in pH, and a release of phosphate ions. This local shift obviously enhances the release of oxygen to the working muscles and is especially important during exercise at altitude.

Maximal pulmonary ventilation during acute exposure to hypoxia is similar to sea-level values (21,24,26,28,61,75) even at extreme altitudes

(16). Since $\dot{V}O_{2\max}$ is reduced at altitude, the maximal ventilatory equivalent ($\dot{V}_E/\dot{V}O_2$) will be higher. Although inefficient from a metabolic point of view, such hyperventilation is thought to be essential in defending P_{AO_2} and thus facilitating the diffusion of oxygen (16).

Submaximal Cardiorespiratory Responses

During rest and submaximal exercise in acute hypoxia, the reduced C_aO_2 is compensated for by an increase in cardiac output such that oxygen uptake at rest or for any given exercise intensity up to heavy levels does not differ from sea level (38,75,84). The increase in submaximal cardiac output is due primarily to an increase in heart rate since stroke volume during acute exposure is only slightly affected (5,38,47,75,84). The increase in heart rate above sea-level values both at rest and during submaximal exercise is evident within the first hour of hypobaria (27,75). The initial increase in heart rate seems to result from stimulation of the cardiac beta-adrenergic receptors by the cardiac sympathetic nerves (34,68).

An increase in ventilation at any given exercise intensity is also observable during hypoxic exposures as illustrated in Figure 5. It should also be observed that at any given submaximal oxygen uptake, pulmonary ventilation increases with an increase in hypoxia. Because of the large rise in pulmonary ventilation, P_{AO_2} is much higher than it would be without the increase (1).

Endurance time for performing submaximal exercise at a fixed exercise intensity is reduced immediately in proportion to the level of hypoxia (23). When the exercise intensity is lowered so that it elicits a $\dot{V}O_2$ that is the same percentage of $\dot{V}O_{2\max}$ in hypoxia as in normoxia, endurance time does not change significantly (52).

FIGURE 5 HERE

NEUROENDOCRINE RESPONSES TO HYPOXIA

Rest

Exposure to acute hypoxia causes a number of complex and interrelated physiological responses affecting not only respiratory, cardiovascular, and metabolic functions but endocrine functions as well. Such widespread and orchestrated control implies that the adjustments to hypoxia involve the nervous system. This is indeed the case. Primary responsibility seems to lie with the sympathetic portion of the autonomic nervous system. Numerous studies have shown that catecholamine levels in the plasma and urine are increased during exposure to hypoxia and altitude (15,27,53). Furthermore, the increase in catecholamine levels is nearly totally due to an increase in norepinephrine and not epinephrine (15,27). This observation indicates that the rise in norepinephrine is due to increased release from terminal endings

of the sympathetic nerves only. A rise in epinephrine as well as norepinephrine would suggest that adrenal medulla release is also involved. Thus, a rise in circulating plasma norepinephrine has been determined to be a useful, though indirect estimation of overall sympathetic hyperactivity (31).

At rest, a significant increase in plasma catecholamines to a hypoxic stress is usually not measurable within the first several hours of exposure. This does not necessarily mean that the activity of the sympathetic nervous system is not enhanced during the onset of hypoxia. Rather, it may simply reflect the fact that an increase in plasma catecholamine levels is not a perfect indicator of a low level of sympathetic activity. It is possible that during the first several hours of exposure, a small and gradually increasing rate of sympathetic activity may occur. The amount of norepinephrine that is secreted normally does not exceed both the capacity of the nerve endings to re-uptake the released norepinephrine and the rate at which monoamine oxidase (nerve endings) and catechol-O-methyl transferase (liver) degrade norepinephrine. In fact, it has been shown that splanchnic removal rate of norepinephrine either during normoxia or hypoxia (10% O₂) rises in proportion to its arterial concentration (4). When the rate of noradrenergic outflow greatly exceeds the rate of re-uptake and degradation, norepinephrine concentration in the blood is significantly raised. This scenario may partially explain why an increase in resting plasma levels of catecholamines are not usually measured until 14-18 hours of exposure to 4300 m (27,53). At plasma concentrations above approximately 1.8 ng·ml⁻¹, the transmitter has a more widespread action, similar to a circulating vasoconstrictor hormone (71).

Other metabolic and endocrine responses to acute exposure to altitude or hypoxia are also little affected during rest. Blood concentrations of glucose, lactate, free fatty acids, cortisol, glucagon, 4-androstenedione, testosterone, luteinizing hormone, insulin, growth hormone, arginine vasopressin, prolactin and thyroxine have been found not to be altered significantly from normoxic resting values (3,38,39,66,70,76). Resting levels of plasma renin activity, aldosterone and angiotensin II have been found to be reduced slightly or not at all (39,40,53).

Exercise

Exercise during normoxic conditions causes marked changes in sympathetic, metabolic and hormonal activity (1). Whether these responses to exercise are altered during acute exposure to altitude or hypoxia are still questionable (3,25,53,57,66,70,76). It is highly probable that much of what is unclear arises from differences in experimental design between protocols. Sutton (76) reported that blood concentrations of glucose, lactate, free fatty acids, cortisol and growth hormone were higher, and the concentration of insulin lower in subjects pedalling for 20 minutes while at a simulated altitude of 4550 m compared to normoxia. However, the subjects exercised at the same absolute exercise intensity (125 watts) during each condition. Because the exercise load used at altitude was not reduced in proportion to the reduction in $\dot{V}O_{2\max}$, the subjects at altitude were working at a

significantly higher percentage of their sea-level $\dot{V}O_{2\max}$. At sea level, the exercise load was between 30% and 50% $\dot{V}O_{2\max}$, but at altitude the load was 70% to 90% of their sea level $\dot{V}O_{2\max}$. In other words, the differences between the normoxic and hypoxic condition may have been totally due to changes in relative intensity and not to the effects of hypoxia per se.

Bouissou (3) compared metabolic and endocrine responses to graded exercise during normoxic and hypoxic conditions (3000 m) after adjusting for the 17% hypoxia-induced reduction in $\dot{V}O_{2\max}$. Comparisons were therefore made at the same relative intensity (40%, 60%, 80% $\dot{V}O_{2\max}$ and at $\dot{V}O_{2\max}$). Each exercise intensity lasted 5 minutes. As the intensity of the exercise increased, blood levels of lactate, cortisol, 4-androstenedione, testosterone, epinephrine and norepinephrine also increased. However, except for a small difference in norepinephrine at $\dot{V}O_{2\max}$, no environmentally-induced differences were found in the above blood values as well as in blood glucose, free fatty acids, glucagon, insulin and luteinizing hormone. It was concluded that acute, moderate hypoxia does not affect metabolic and hormonal responses to short periods of exercise performed at similar relative exercise intensities. Similar results are also found at higher levels of hypoxia. Escourrou (25) had subjects pedal an ergometer at intensities requiring 40, 60 and 75% of their $\dot{V}O_{2\max}$ for 15 minutes at each intensity during normoxia and while breathing a hypoxic gas (11-12% O_2 in N_2 ; 4500-5000 m equivalent). The exercise intensities were adjusted during hypoxia to reflect the 24% reduction in $\dot{V}O_{2\max}$. It was found that the concentrations of epinephrine and norepinephrine were higher for any absolute level of $\dot{V}O_2$ during hypoxia. When the catecholamine values were compared to $\dot{V}O_2$ expressed as a relative

percent of $\dot{V}O_{2\text{max}}$, no differences were found between the two environmental conditions.

Blood lactate concentration during maximal exercise in males has been reported to be approximately equal between normoxic and hypoxic conditions even though the absolute exercise intensity is lower during hypoxia (3,75). Females, however, may have a different lactate response. In a study by Drinkwater (21), each of the females had significantly higher plasma lactate values during maximal exercise in hypoxia (12.58% O_2) compared to their respective sea-level values. However, much more comparative work needs to be done to be able to determine whether there is a true gender difference with regard to lactate accumulation in hypoxia.

While the majority of endocrine and sympathetic responses to exercise seem to be similar under normoxia and acute hypoxic conditions when the intensity of exercise is expressed in relative terms, there does exist an example where there are differences between the environments. That example is provided by the renin-angiotensin-aldosterone system (RAAS). During exercise at sea level, plasma renin activity is enhanced due to a redistribution of blood to the working muscles and away from the juxtaglomerular cells of the kidney. Renin is secreted when the cells sense a reduction in perfusion pressure or flow. These cells, being directly innervated by sympathetic nerves, also release renin when sympathetic activity is high as it is during exercise. Renin reacts with the plasma protein angiotensinogen to form angiotensin I which in turn, reacts with angiotensin converting enzyme (ACE) in the lung. After losing two amino groups, angiotensin I is converted to angiotensin II. Aldosterone is

secreted from the adrenal cortex when stimulated by angiotensin II. Both angiotensin II and aldosterone have a direct effect on the kidneys to reabsorb sodium and water thereby increasing extracellular fluid.

There is much evidence to suggest that hypoxia affects the RAAS differently. (10,11,53,57,58,70,72). Slater et al. (72), after measuring a reduction in aldosterone and an increase in plasma renin activity concluded that altitude must affect the control mechanism. Maher (53) confirmed and extended this conclusion to include exercise at altitude. More recent studies have attempted to determine the point at which the RAAS control mechanism(s) differ from sea level. Milledge (57) had subjects exercise on an ergometer for two hours at 50 watts. Ambient, normoxic air was breathed the first hour and a hypoxic gas mixture (12.8% O₂, 4000 m equivalent) for the rest of the time. Throughout the entire 2 hours, plasma renin activity (estimated by measuring angiotensin I), aldosterone and ACE were sampled from a forearm vein. During normoxia, plasma renin activity and aldosterone rose together while ACE concentration was not altered. With the onset of hypoxia, plasma renin activity continued to rise (50% above control values), while aldosterone and ACE fell significantly. The authors concluded that the reduction in ACE activity resulted in a reduction in angiotensin II concentration which directly affected aldosterone secretion. These results were later confirmed in a similar study at 3100 m altitude by some of the same authors (58).

Shigeoka (70) also reported similar findings but provided a different conclusion. Because they found that aldosterone concentration did not relate to changes in plasma renin activity during the normoxic phase which followed

the hypoxia (17% O₂) phase in a crossover designed study, they hypothesized that an inhibitor, possibly of angiotensin II-stimulated secretion of aldosterone, was responsible. In an effort to determine if an inhibitor does indeed exist at this point of the RAAS, these authors (70) infused angiotensin II into their subjects at different rates while the subjects were normoxic and while moderately hypoxic (90% saturation). It was hypothesized that if the aldosterone response to infusion of angiotensin II was inhibited during hypoxia and not during normoxia, then an inhibitor between angiotensin II and the release of aldosterone existed. They found that hypoxia did not significantly inhibit the aldosterone response to angiotensin II and had to conclude that hypoxemia does not cause release of an inhibitor of angiotensin II-mediated aldosterone release.

NEUROPSYCHOLOGICAL IMPAIRMENT

The neuro-psychological effects of immediate, or gradually progressive hypoxia were observed from the earliest experiences dealing with low pressure chambers, high-altitude balloon flights, and motorized aviation (see ref. 41). There is a progression in the sensitivity of various nervous tissues to oxygen deprivation. The higher cortical centers appear to be the most sensitive followed in order by the cerebellum, medulla, spinal cord, and sympathetic ganglia - producing a reasonable correlation with the observed pattern of behavioral and neurological dysfunction (20,33). Relatively small reductions in arterial oxygen saturation can significantly impair mental and motor coordination, personality, and judgement to the extent that individuals

may deny any functional impairments (13). This is especially true at hypoxia levels above 3,000 m where hemoglobin saturation lies on the beginning of the steep portion of the oxygen dissociation curve (see Table 1 for the progressive reduction in arterial saturations).

Initial hypoxia effects progress from subtle, almost imperceptible, changes in personality, judgement, and short-term memory to gross derangements. In susceptible individuals, signs can occur with a $P_{I\text{O}_2}$ as high as 100 torr (equivalent altitudes of 3,000 m). A number of individuals may experience euphoria and be cheerful and complacent, while others appear less tolerant and may become irritable and uncooperative. When these behavioral changes are acknowledged by cohorts, some individuals will attempt to disprove and deny that hypoxia affects them, in much the same manner as an individual who is intoxicated and tries to hide the fact that he/she has imbibed alcohol (14). This is of special concern in situations where a person is in a potentially dangerous situation (e.g. mountain climbing or piloting a non-pressurized plane). Furthermore, the poor mental and motor performances and personality changes usually precede but can be independent of any feelings of sickness (14). Symptoms of impending illness usually begin after four or more hours exposure at altitudes exceeding 3000 m. Illness caused by hypoxic exposure is presented in detail in Chapter 14.

Human performance on different types of tasks are affected at different levels of hypoxia. Impairment on a specific task relates to factors such as: (a) the level of hypoxia, (b) the type of task or function being performed (sensory or motor), (c) the complexity of the task, (d) the familiarity of the individual with the task, and (e) whether the task has been learned prior

to or during exposure (12,13,18,32). These factors plus the large interindividual variability in personality traits and motivation obviously have the potential to bias the results of experiments where a high degree of consistency, motivation, and attentiveness is required (13).

Through the years, a number of experiments have been performed to determine how various levels of hypoxia affect a number of different psychomotor and cognitive tasks (12,13,18,32,33,45). From these studies and others (81), some generalizations have been made (14,56). These are briefly summarized below and illustrated in Figure 6.

FIGURE 6 HERE

Sensory

Decreases in light sensitivity (the amount of light required for perception of a given stimulus) can be detected at an altitude as low as 1200 m. At 4900 m, twice as much light would be required for perception (14,56). At approximately the same level of hypoxia, central field extent is reduced 10%, central brightness, 30%; and dark adaptation, 34%. Visual acuity (ability to resolve a given target at a given distance) is affected at about 2400 m and reduces to 50% of the sea-level value at 5200 m if the illumination is dim. If the illumination is bright, there is little or no impairment until an altitude of 5500 m is attained (56). In tasks requiring

an alignment response to a changing input (visual pursuit tasks), no decrement from sea-level values are measured until the altitude exceeds 5200 m. Above this altitude, performance falls off very rapidly (18,56). It is generally accepted that auditory sensitivity is little affected by exposure to acute altitude (56).

Mental Functioning

The ability to do mathematical calculations, make decisions, and perform coding and conceptual reasoning tasks are affected at altitudes beginning at approximately 3000 m, with performance steadily declining down to 4900 m. Above about 4900 m, the quality of performance decreases extremely rapidly (32,33,45). Tasks take longer to perform, and errors are more frequent, in direct proportion to the increase in altitude (14). Short-term memory is affected at levels of hypoxia beginning at altitudes as low as 1800 to 2400 m and declines rapidly after 3700 m (12,14). At 4300 m, performance during word association, position and pattern as well as immediate recall and delayed recall (15 and 30 min) are reduced by 17%. At 5500 m, there is a 25% reduction in short-term memory (12,56). The ability to detect a reduction in attentiveness occurs at approximately 3000 m with a linear decline approximating 22% per 1000 m, thereafter (45).

In summary, percent decrements can be assigned to general types of tasks which demonstrate sensitivity to hypoxia. Figure 6 illustrates the progressive decline in vision and psychological tests with increases in altitude. No decrement in sensory or mental performance can be detected at

altitudes less than 1500 m (14,45,56). In general, there is an 25% reduction in sensory performance at 3700 m which may be an acceptable decrement in performance, and a 40% reduction at 4300 m which is usually unacceptable (56). Performance on many mental tasks can be improved significantly at higher altitudes if the tasks are well learned at lower altitudes or at sea level (18,32). Tests of mental function show a 10% reduction at about 4300 m and a 25% reduction at about 5200 m (33).

SUMMARY

The effects of a reduction in ambient oxygen pressure occurring within four hours are dependent to a large extent on one principal factor: the degree of hypoxia and the resultant arterial hypoxemia. As the degree of hypoxia increases, a series of compensatory responses occur in various organ systems which are directly proportional to the severity. Above approximately 1500 m, demonstrable changes become evident in ventilation, cardiac output, circulation, blood endocrine levels, and sensory and mental function. With a level of hypoxia equivalent to approximately 4000 m, the changes can become considerable and can be discerned for almost any physiological and psychological function. The problems are further accentuated when exercise is superimposed on the hypoxia.

With physical performance, reductions of both maximal and endurance exercise capacity are observed almost immediately due to the reduction in oxygen content of arterial blood despite potentially beneficial changes in alveolar ventilation, distribution of ventilation/perfusion ratios, cardiac

output distribution, shifts in the oxygen-dissociation curve, increases in sympathetic nervous system activity, and changes in fluid control hormones. Nevertheless, individuals can function reasonably well due to compensatory responses which act to minimize the effect of the reduction in oxygen pressure.

With regard to the senses it appears that vision is particularly sensitive to hypoxia. Mental functioning and performance on complex tasks are complicated by many factors, but in general the better a task is learned at sea level, the less will be the decrement at altitude. With moderately severe, acute altitude exposures there are demonstrable changes in personality and behavior which may be subtle but recognizable.

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Table 1. Typical acute reduction in arterial P_{O_2} and saturation with increasing altitude for unacclimatized men.^a

Elevation m	ft	P_B torr	$P_{I_{O_2}}$ torr	$P_{A_{O_2}}$ torr	$P_{a_{O_2}}$ torr	$P_{A_{CO_2}}$ torr	$S_{a_{O_2}}$ %
0	0	760	149	104	86	40	96
1600	5248	627	122	82	69	38	94
3100	10169	522	100	62	57	33	89
4300	14104	448	84	53	40	30	84
5500	18000	379	70	38	35	27	75

^areferences (41,43,62, and 76).

FIGURE LEGENDS

- Figure 1. Oxygen transport cascade at sea level and at 4300 meters. Modified from West (88).
- Figure 2. Time course for arterial P_{O_2} to become equilibrated with alveolar P_{O_2} in a pulmonary capillary at rest and exercise, at sea level (A) and altitude (B). Modified from West (88).
- Figure 3. Effect of increasing altitude (or reducing $P_{I}O_2$) on arterial saturation at rest (open circles) and during exercise (closed circles). Modified from Banchero (2).
- Figure 4. Percent reduction in $\dot{V}O_{2\max}$ as a function of altitude exposure. Note that $\dot{V}O_{2\max}$ is not measurably altered until the altitude exceeds 1500 m (or inspired P_{O_2} is less than 120 torr). Above 1500 meters, there is a linear decrease in $\dot{V}O_{2\max}$ at the rate of 10% per 1000 meters. Adapted from Buskirk (7).
- Figure 5. Pulmonary ventilation (BTPS) in relation to oxygen uptake at different exercise intensities at sea level and during exposure to 2000 m and 4000 m simulated altitude. Modified from Åstrand (1).
- Figure 6. Effect of increasing in altitude (or reduction in $P_{I}O_2$) on sensory and mental functions. Redrawn from data presented by McFarland (56) and Cudaback (14).

Figure 1

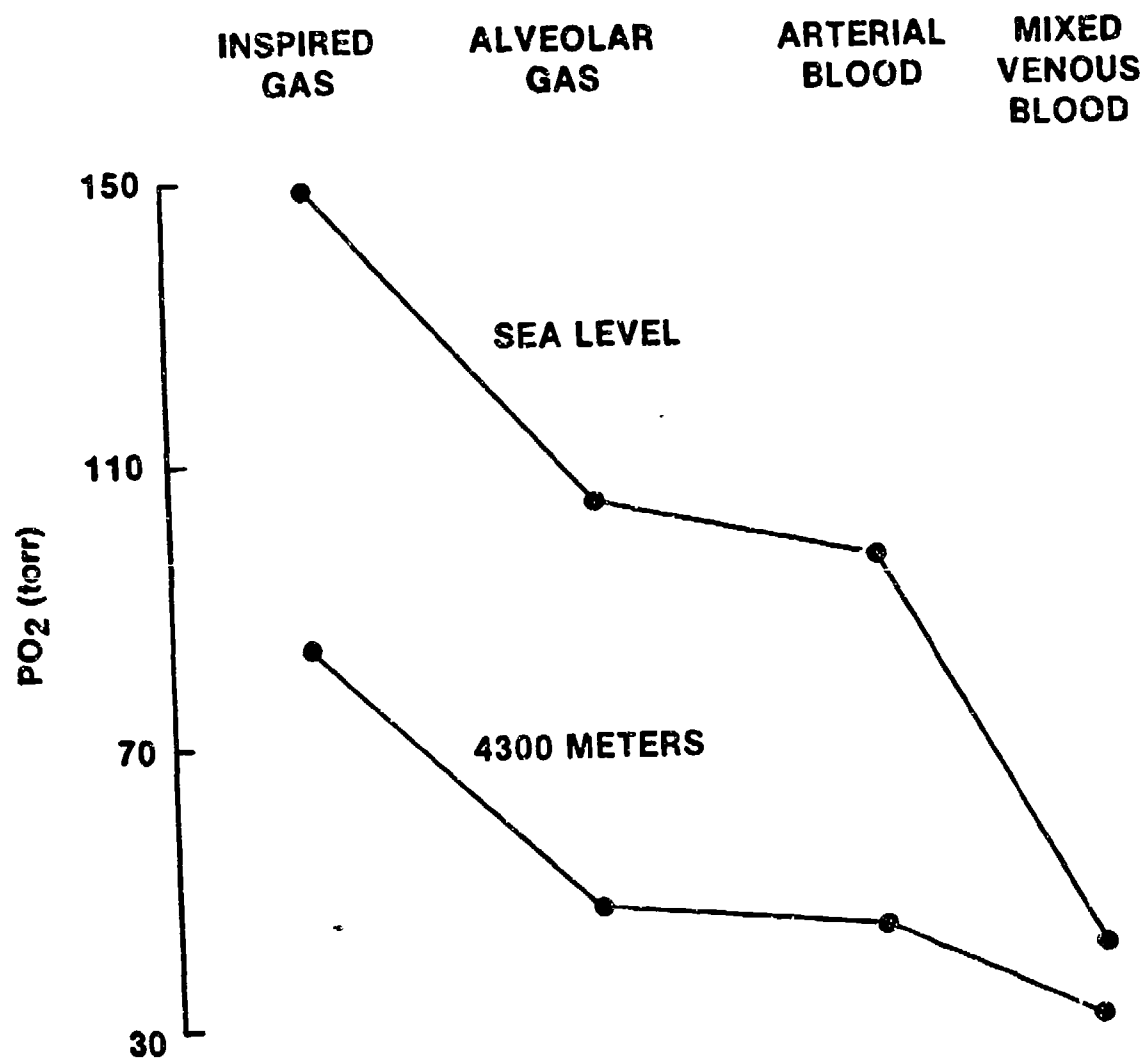


Figure 2

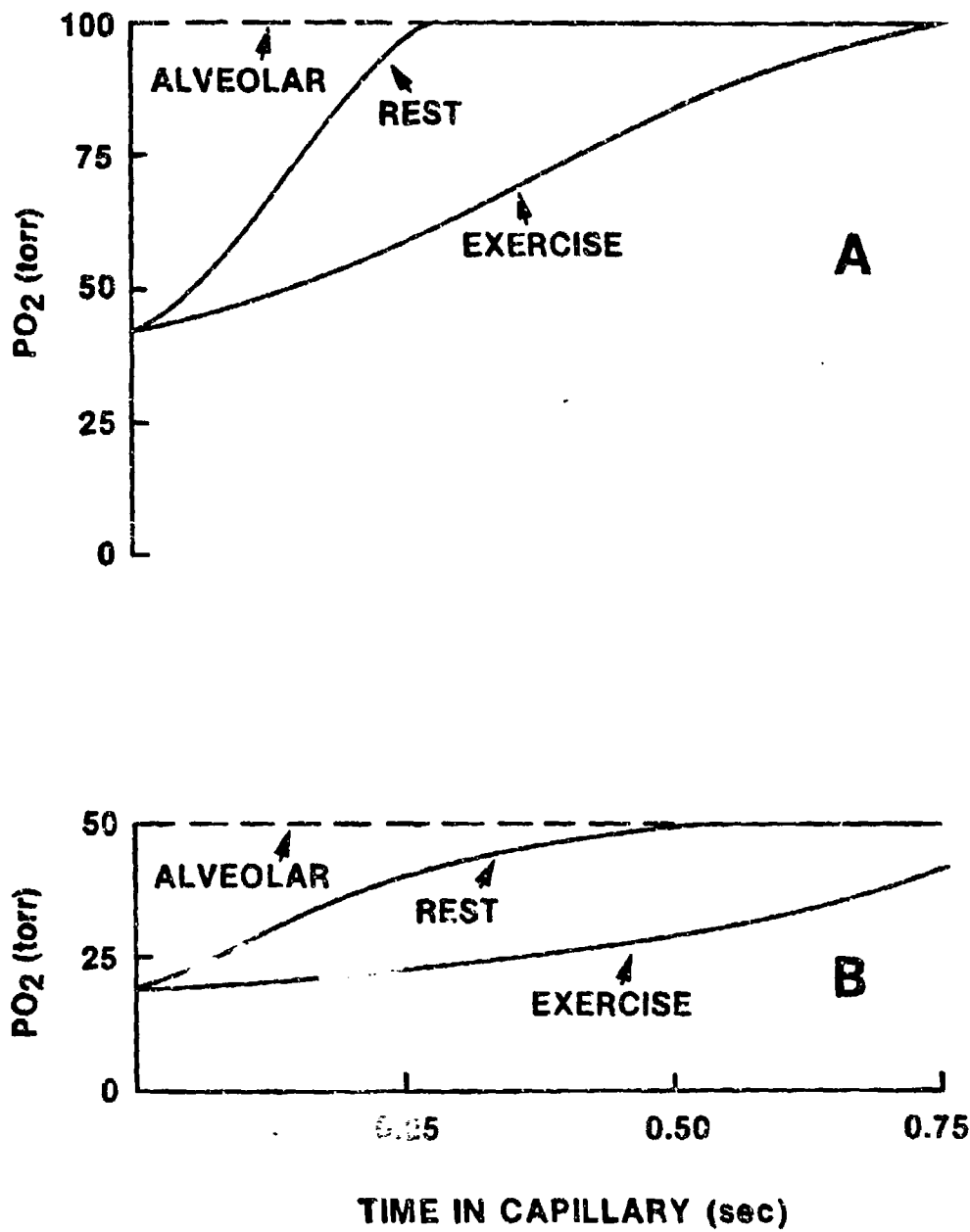


Fig 3

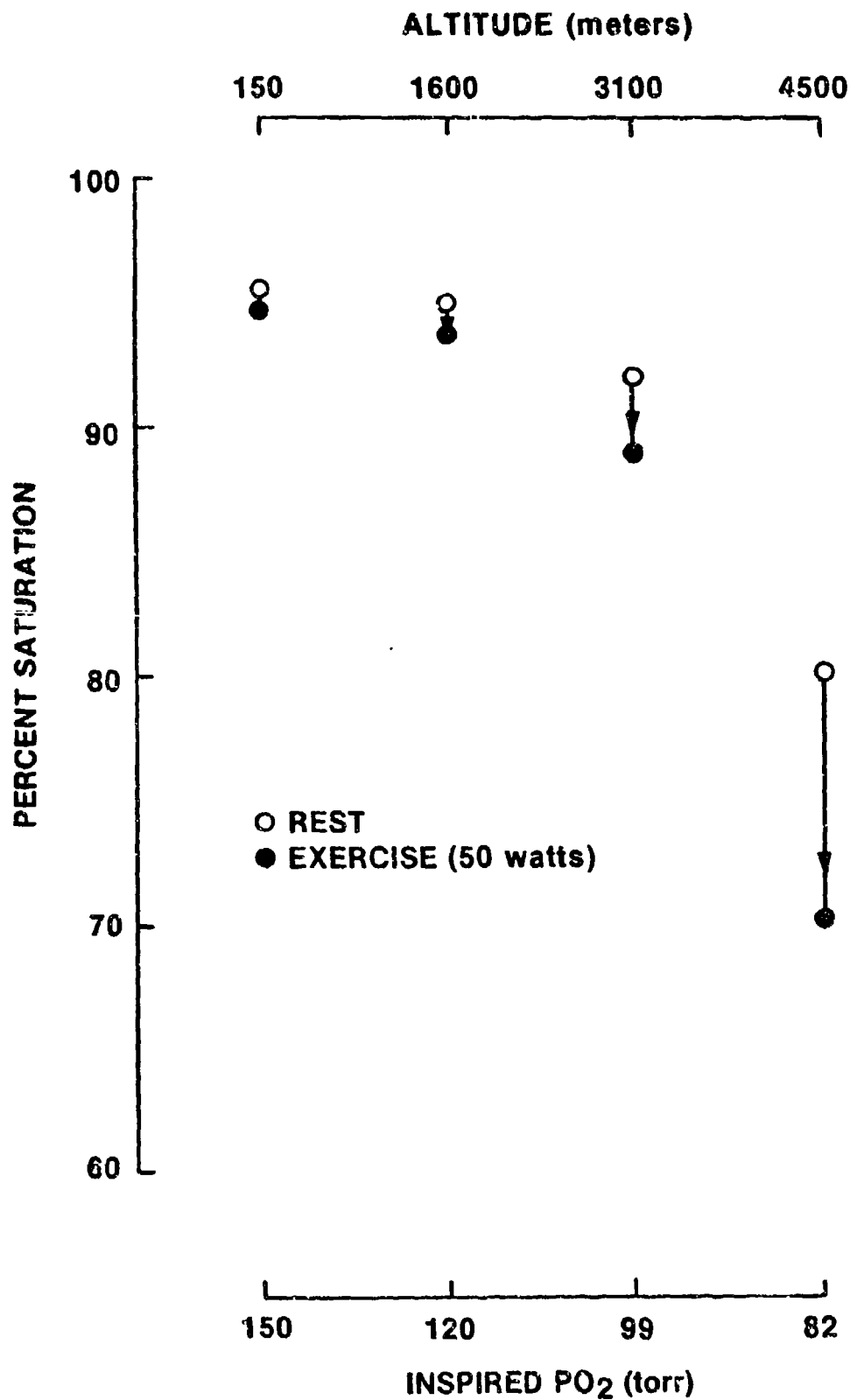


Figure 4

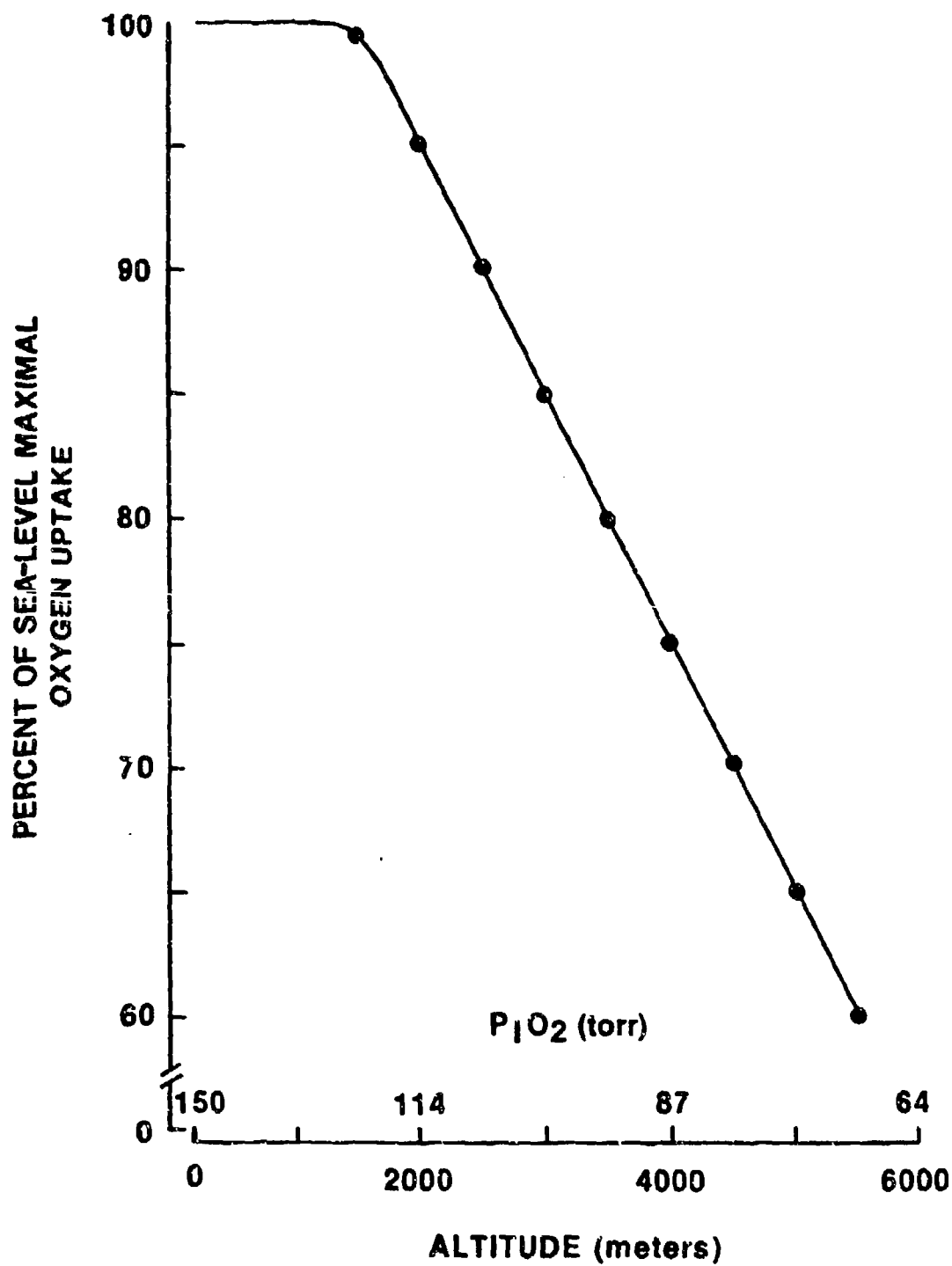


Figure 5

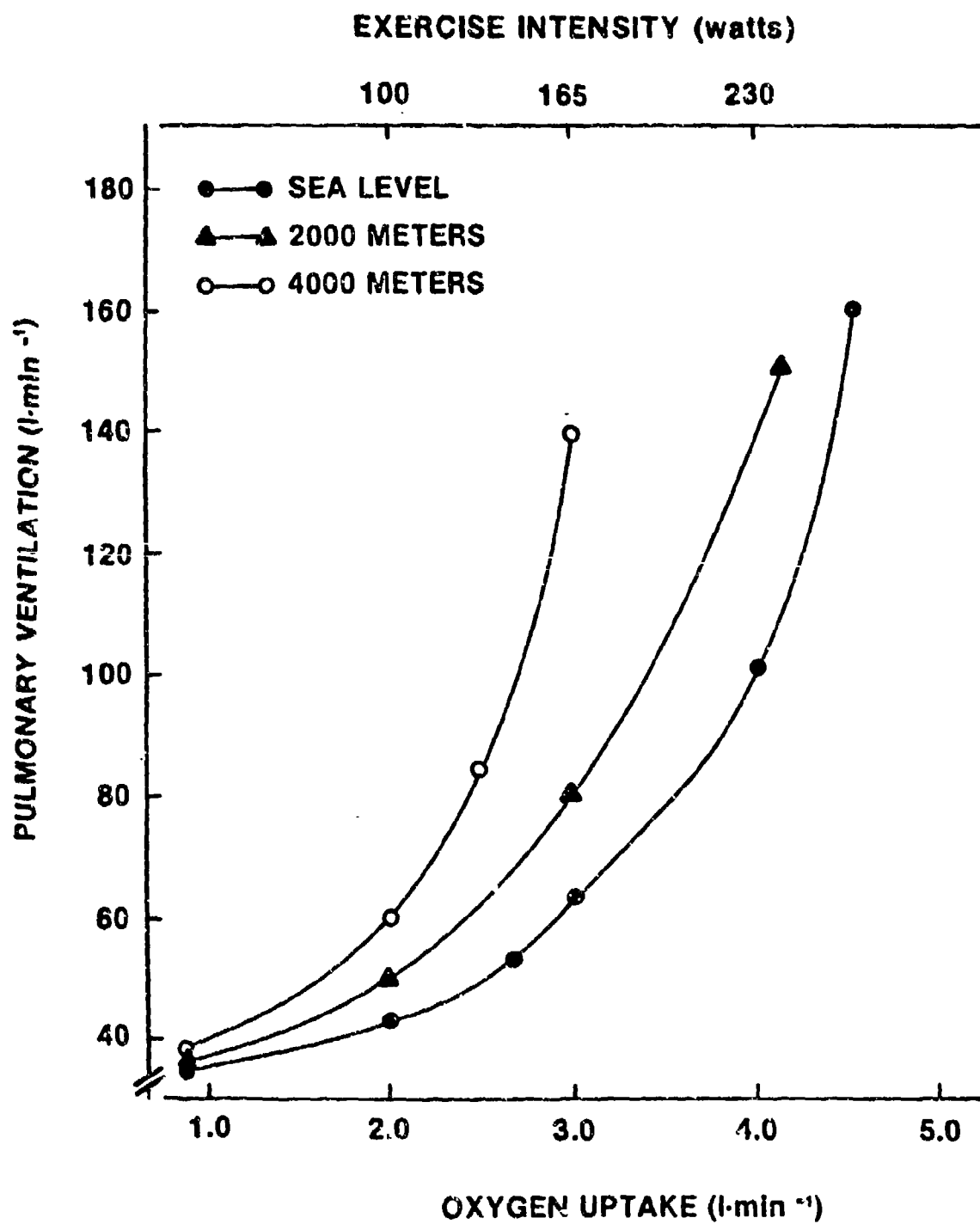


Figure 6

