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## **Physiological Responses to Altitude: A Brief Review**

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### **ABSTRACT**

**Wyatt, FB.** Physiological Responses to Altitude: A Brief Review. **JEPonline** 2014;17(1):90-96. Hypoxia has been defined as conditions with lower than normal oxygen availability. Altitude exposure and acclimatization have been areas of research for a considerable time. The immediate (acute) effects of lowered ambient pressure of oxygen ( $PO_2$ ) pertaining to the human response and the adaptations to prolonged exposure (chronic) are complex. Several systems (i.e., cardiovascular, pulmonary, and endocrine) react to the hypoxia associated with altitude exposure. Adding to the complexity, these systems rarely react in isolation but rather interact to allow the work of the individual to be accomplished in this type of environment. While generalities exist relating to acute and chronic adaptations (acclimatization) to altitude exposure, current evidence indicates individual responses may facilitate or hinder the acclimatization process. Responders and non-responders have been identified in the literature during attempts to understand the human response to a lowered partial pressure of oxygen. This review summarizes the affects of acute and chronic exposure to altitude as it relates to exercise and work output. Several sub-categories will be addressed. Included in these categories are the following: (a) acute and chronic exposure; (b) performance and length of events; (c) substrate utilization; and (d) various adaptations associated with various increasing altitudes. While much research has been conducted regarding living high/training low (LHTL) scenarios, this review will only discuss findings associated with acute and chronic exposure to altitude. Thus, the purpose of this brief review is to summarize two basic tenets of altitude and exercise: (a) acute exposure response; and (b) chronic adaptations.

**Key Words:** Altitude, Acclimatization, Acute / Chronic Adaptations

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## BASIC CONCEPTS WITH ALTITUDE EXPOSURE

### Acute Exposure and Response

Immediate exposure to altitude places the body in an environment with reduced partial pressure of oxygen ( $PO_2$ ). Because of this reduction of  $PO_2$ , as the body works there is a diminished supply of oxygen to the tissues thereby resulting in a condition of hypoxia. Hypoxia is a Greek term meaning “less than normal amount of oxygen.” As it relates to acute exposure to altitude the human body experiences a condition known as hypoxic hypoxia. This describes reduced arterial blood oxygen content as a result of decreased partial pressure of inspired oxygen (6). The response by the human body to reduced  $PO_2$  depends on the intensity of work of the individual, the altitude at which the individual is exposed, and the fitness level of the individual. Utilizing maximal oxygen capacity ( $VO_2$  max) as a benchmark for work performed at altitude, evidence suggests that decrements upon acute exposure begin to occur above 700 m (~2,333 ft.). However, declines in  $VO_2$  max up to 1500 m (~5,000 ft.) are shown to be curvilinear and appear more linear after 1500 m (8). The variability up to 1500 m may reveal a concept at acute exposure that is seen with acclimatization known as responders and non-responders.

General physiological changes upon acute exposure to altitude include increased resting and sub-maximal heart rate (HR), increased resting and sub-maximal ventilation ( $V_E$ ), increased blood pressure (BP), increased catecholamine secretion, and decreased  $VO_2$  max. These changes result in increased oxygen transport to the tissue, increased alveolar  $PO_2$  with a concomitant decrease in carbon dioxide ( $CO_2$ ) and hydrogen ions ( $H^+$ ), increased vascular resistance, increased lactate production, and decreased work capacity, respectively (1). Several systems (i.e., cardiovascular, pulmonary, and endocrine) react to the hypoxia associated with altitude exposure.

### Cardiovascular Response to Acute Exposure to Altitude

With acute exposure to altitude, resting and sub-maximal cardiac output (Q) increase. As compensation for reduced  $PO_2$  and tissue hypoxia, an increase in Q is provided primarily by an increase in HR ( $\text{beats}\cdot\text{min}^{-1}$ ). The blood flow increase at altitude seems to be in response to arterial desaturation (7). The increase in HR is also in response to the increase in peripheral resistance, thus allowing for the decrease in stroke volume (SV). To maintain a necessary Q to pump the oxygenated blood to the tissues, HR increases. In addition, the increase in catecholamine response also further increases HR. Utilizing hypobaric chambers with simulated altitudes between 4000 m and 8000 m, reports have indicated an increase in Q despite reduced blood volume and reduced ventricular filling. The increase in Q seems to confirm that HR is responsible for this adjustment. It has been reported that the increase in HR is a result of increased sympathetic nervous system activity resulting from increased blood norepinephrine concentrations (5). Increases in HR and blood pressure with altitude exposure have coincided with increased levels of norepinephrine.

Within a few days of exposure Q declines, and above 3500 m there have been reported declines in maximum HR (4). This is partially due to increased parasympathetic influence and the decrease in responsiveness to catecholamines with prolonged exposure. The reduced SV could be due to the decrease in plasma volume (PV) although there are reports of diminished myocardial contractility occurring 2 to 8 days after exposure. One possible explanation for reduced Q after exposure is the increase in arterial-venous oxygen difference ( $a-vO_2$  diff).

### Pulmonary Response to Acute Exposure to Altitude

There is an increase in resting and sub-maximal ventilation upon arrival to altitude. This is accomplished through both an increase in tidal volume ( $T_V$ ) and frequency of breaths ( $F_b$ ) (5).

Known as the hypoxic ventilatory response, there is considerable evidence of individual variation (i.e., responders vs. non-responders) (2). It is reported that those with a strong hypoxic ventilatory drive perform better at extreme altitudes compared to those with a diminished hypoxic ventilatory response (7). In addition, there is less reported symptoms of acute mountain sickness (AMS) (5). Ascending to altitude stimulates ventilation as a result of carotid bodies in the arch of the aorta and the aortic bodies in the bifurcation of the carotid artery sensitivity to reduced  $PO_2$  in arterial blood ( $PaO_2$ ). This hyperventilation increases the  $PO_2$  in the alveoli ( $PAO_2$ ) and at the same time reduces the partial pressure of carbon dioxide ( $PCO_2$ ) (6). With an increase in ventilatory drive, a reduced  $PCO_2$  allows for reduced  $CO_2$  in the blood and a lowered  $H^+$  concentration in the blood. In compensation, bicarbonate ( $HCO_3^-$ ) is gradually reduced through excretion from the kidneys (renal diuresis) during the first few days of exposure. This excretion is associated with a decrease in plasma volume and subsequent effects on the cardiovascular system as outlined above. The increased ventilatory drive also reduces total body water through loss of water vapor during respiration. This coupled with the above-mentioned renal diuresis and increased evaporative cooling can lead to rapid dehydration upon acute exposure to altitude (8).

### **Catecholamine, Hematological, Bioenergetics: Responses to Acute Exposure to Altitude**

As mentioned earlier, there is an increase in catecholamine release upon acute exposure to reduced  $PO_2$ . Norepinephrine increases progressively during rest and exercise peaking inside of a week of exposure (7). This response is associated with increases seen with HR and BP. The sympathetic neural activity increases as an indication of the increased concentrations of blood norepinephrine (5). Additionally, catecholamine activity regulates SV, peripheral vascular resistance (PVR), and affects substrate utilization with altitude exposure. The increase in catecholamine secretion allows for a greater reliance on glycolysis for energy production and thus carbohydrate utilization.

Upon exposure to lowered  $PO_2$  and subsequent tissue hypoxia, there are many hematological adjustments to allow for increased  $PaO_2$ . Hemoglobin (Hb) concentration and hematocrit (Hct) have been shown to increase within 24 hrs of exposure to altitude. The stimulation of red blood cell (RBC) production occurs as  $PO_2$  sensitive cells within the kidneys stimulate the release of erythropoietin (EPO) (8). However, with the aforementioned reduction in plasma volume and the lag between EPO secretion and new RBC production, the true initial increases in Hb and Hct actually occur after ~3 to 4 days of exposure. This increase allows for greater  $PaO_2$  and oxygen content per liter of Q (4). Within the RBC another change occurs subsequent to ascents to high altitude. There is an elevation of 2,3-diphosphoglycerate (2,3-DPG) that is stimulated by a rise in intracellular pH. This allows for an increase in oxygen ( $O_2$ ) dissociation and, therefore, a rightward shift of the oxyhemoglobin dissociation curve. At altitude, increased levels of red blood cell 2,3-DPG promote oxygen unloading at the muscle tissue level and, theoretically, an increase in oxygen utilization. However, because  $O_2$  extraction is already highly efficient, the advantage 2,3-DPG affords in dissociation may be negligible.

Interestingly, there is conflict literature concerning substrate utilization at altitude. While increased catecholamines and reduced  $PaO_2$  upon acute exposure favors reliance on carbohydrate via an increase in glycolytic rate, the determining factor seems to be relative exercise intensity. Because carbohydrates have a high yield of ATP per mole of oxygen, tissue hypoxia resulting from reduced  $PO_2$  indicates a greater use of muscle glycogen and blood glucose. Reports indicate that hypoglycemia and reduced liver glycogen content are common with acute altitude exposure (1). If carbohydrate supply is inadequate, fat catabolism increases at altitude. In addition, significant changes have been noted in negative nitrogen balance and muscle mass loss with a subsequent increase in gluconeogenesis. Yet, in a study of trained cyclists exercising at 2300 m, there was a

reduction in the activity of 6-phosphofructokinase (PFK), a glycolytic rate-limiting enzyme (4). This may indicate that those training at altitude may reduce glycolytic reliance over time. However, in this same study the reduced muscle glycogen depletion over time was associated with a concomitant increase in blood glucose dependence for fuel. The increase in glucose metabolic clearance rate is related to increased arterial norepinephrine levels and activation of the sympathetic nervous system.

### **Performance Responses to Acute Exposure to Altitude**

The consensus is that upon acute exposure to altitude performance declines. With endurance performance, the standard measure to determine this decline has been  $\text{VO}_2$  max. For most athletes, oxygen consumption begins to decline at approximately 1500 m with a subsequent rate of decline of 3% per 300 m (1000 ft) (1). There have been reports of declines in athletes as low as 580 m (4). The oxygen cost of work is similar to sea level but with the decline in  $\text{VO}_2$  max this results in a given workload representing a higher percentage of maximal. However, when other considerations are taken into account the performance decline generality may be spurious. For instance, 1-hr distance records on the velodrome are often attempted at altitude to take advantage of reduced air resistance. One may find performances in events of short duration and high power requirements are improved at altitude while events beyond 800 m generally show a decline (1). There is considerable controversy over time to arrive at altitude prior to a performance. Time-lines vary from immediate (within 24 to 48 hrs) to 12 wks of exposure for optimizing performance.

Other reports indicate that short power output is not compromised at altitude. With more prolonged high intensity work there is an increased reliance on glycolysis and increased formation of lactate (8). There is also an increased blood acidosis resulting from diminished blood bicarbonate. This allows for an earlier onset of fatigue upon acute exposure. The generalized trend in performance with acute altitude ascent is one that shows a steady decline with increased distance (7). Under 2 min in length the performance differences between sea level and altitude are negligible. From 2 to 5 min, the athletes' performance times increase at altitude up to 115% of the sea level times at 4000 m. Performances from 20 to 30 min in length show a near linear increase at altitude of >100% of sea level at 1000 m to over 115% of sea level performance at 4000 m. The time increase is even more dramatic with performances over 2 hrs in length. At 1000 m the increase in time compared to sea level is around 102%. Yet, at just under 3000 m, this performance time is increased to over 125% of a comparative sea level time. Overall, the threshold for performance decline seems to begin at approximately 1600 m for events of 2 to 5 min and at 600-700 m with events over 20 min.

## **ACCLIMATIZATION**

By definition, acclimatization describes a chronic adaptation response by the body to allow for improved tolerance to altitude changes. Full acclimatization and the time period that it occurs are still controversial areas of research. While some reports with "responders" indicate a 12-14 day period up to an altitude of 2300 m, others note this process may take several months (7,8). Within the process of acclimatization several systems are involved in the improved tolerance and work ability.

### **Cardiovascular Adaptations to Chronic Exposure to Altitude**

With acclimatization there is a reduction in resting and sub-maximal HR indicating a return to normal homeostasis within this system. Cardiac contractility does not seem to be affected yet SV is decreased due to reduced cardiac filling pressure. The rate pressure product (HR x SBP), used as

an indirect measure of myocardial oxygen consumption ( $MVO_2$ ), has been shown to increase to nearly 100% of that shown at sea level with acclimatization (1). Mean arterial pressure increases due to systemic vascular resistance, increased catecholamine secretion at given workloads and increased blood viscosity resulting from increased hematocrit. The blunted myocardial response during vigorous work at altitude is brought on by a combination of decreased plasma volume, increased total peripheral resistance, and an increase in parasympathetic tone decreasing maximal HR. While it seems that maximal Q decreases along with muscle blood flow with chronic altitude exposure at 4300 m,  $VO_2$  max values increase after acclimatization.

### **Pulmonary and $VO_2$ with Chronic Exposure to Altitude**

Chronic exposure to altitude increases pulmonary BP and vascular density, which allows for an improved pulmonary perfusion (1). Ventilation continues to be elevated with acclimatization and may be an indication of increased chemoreceptor sensitivity to blood gas changes occurring at altitude. In addition, with diureses and the excretion of bicarbonate, hyperventilation allows for normalization of alveolar and arterial oxygen pressures and reduced  $PCO_2$  levels for acid-base balance.

With a reduction in  $VO_2$  max sub-maximal workloads are generally performed at higher percentages of maximal. Yet, it has been shown that with exposure of approximately 14 days at 4300 m, there is improvement of  $VO_2$  max compared to acute measures. However, the improvement is generally smaller than the decrements shown above 3000 m. The improvement is considerable when looking at the decrements in the cardiovascular system and reduced diffusing capacity of the lungs. Improvements in  $VO_2$  max with acclimatization are due in part to combined hematological and muscular adaptations that allow for increased oxygen transport and utilization, respectively (8).

### **Hematological and Muscular Adaptations to Chronic Exposure to Altitude**

Upon exposure to altitude environments there are several hematological and muscular adaptations that continue during the acclimatization process that allows for increased tolerance to hypoxic conditions. As mentioned above, there is an increase in hemoglobin, red blood cells, and hematocrit. These adaptations are a primary reason athletes sojourn to altitude and stay, to allow for the improvement in oxygen-carrying capacity of the blood. Additionally, with the increased RBC 2,3-DPG the oxygen dissociation curve shifts to the right indicating a facilitated release of oxygen to the muscles. Facilitating the oxyhemoglobin dissociation shift is an increase in chemoreceptor control of ventilation brought on by decreased bicarbonate in the cerebrospinal fluid and excretion of bicarbonate by the kidneys (1). With acclimatization there is also an increase in skeletal muscle vascularity and muscle tissue myoglobin to provide improved oxygen transport and cellular oxygen transport to the mitochondria, respectively.

### **Bioenergetics and Performance Adaptations to Chronic Exposure to Altitude**

After prolonged exposure to altitude the reliance on muscle glycogen stores is reduced with an increase in blood glucose utilization during sub-maximal exercise (8). Green et al. (3) noted that compared to acute exposure measures, chronic exposure to altitude with reduced glycogenolysis appears to be associated with increased control of ATP to ADP ratios. The continued reliance on glycolysis during moderate and intense work after acclimatization has led to research concerning altered blood lactate levels. It has been reported that with prolonged exposure there is a drop in circulating blood lactate levels during periods of exertion. Because this finding was initially contraindicated to hypothetical lactate kinetics, it was termed the "lactate paradox." Current explanations indicate that after acclimatization there is an increase in lactate uptake by active and inactive skeletal muscles, heart, kidney, and liver (1). Additionally, the reduced ability of the central

nervous system and cardiovascular system in hypoxic environments reduces the level of work the body can reach for extended periods of time.

It has been reported that with prolonged exposure to altitude there is a weight loss and associated changes in body composition. Both reductions in lean muscle tissue and body fat have been reported to be in direct association to increased altitude (7). This may stem from reduced appetites experienced at increasing altitudes as well as reported elevation of basal metabolic rates. Fat catabolism may increase as well as gluconeogenesis if diet is inadequate. Further explanations show that for any given workload, the level of exertion is increased as the partial pressure of oxygen is reduced. This is reflected in the decline in  $\text{VO}_2$  max seen with increasing altitudes. Seemingly this decline may begin as low as 589 m above sea level with a steady decline at a rate of 7% to 9% for each increase in elevation of 1000 m. Above 6300 m, there seems to be a curvilinear drop in  $\text{VO}_2$  max with averages of one-half sea level values at approximately 7000 m (7). Because of this apparent decline in  $\text{VO}_2$  max, performance based on oxygen utilization is reduced. It should be noted that this decline is in comparison to sea level performances. When comparing acute values to acclimatized values performance does improve. This is believed to be in response to increases in EPO, total red blood cells, and  $\text{VO}_2$  max (2).

In general, even after acclimatization to altitude, the greater the distance to be covered in performance the greater the time to achieve that distance as altitude is increased. For example, with events less than 5 min in duration the elevation “threshold” where decrements occur is approximately 1600 m while events over 20 min will be adversely affected at 600 to 700 m above sea level. There is also a reduced plasma volume when combined with increases in hematocrit increases blood viscosity and reduce oxygen transport capabilities. Reported decreases in bicarbonate ( $\text{HCO}_3^-$ ) results in decreased lactate efflux to the blood and subsequent decrease in muscle tissue pH. This of course leads to an earlier onset of fatigue (1). The hyperventilatory response at altitude adversely affects performance in that the increased work of breathing leads to an earlier onset of fatigue.

## CONCLUSIONS

From the aforementioned responses to acute exposure and prolonged exposure to altitude, it is evident that the body positively responds to lowered oxygen pressures. There is continued controversy over these responses in relation to the level of altitude, time of exposure, and intensity of work as they combine to provide additional questions in relation to altitude responses. Add to this the current findings on individual responses based on “responders” versus “non-responders” and, then, it is apparent that additional research is needed in the area of altitude exposure.

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