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Effect of Altitude and Acute Hypoxia on VO₂max

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ABSTRACT

EFFECT OF ALTITUDE AND ACUTE HYPOXIC RESPONSES ON VO_{2MAX} . **Daryl L Parker. JEPonline.** 2004;7(3):121-133. As people ascend to higher terrestrial altitudes or are exposed to other hypoxic conditions, VO_{2max} declines. The declines in VO_{2max} are variable from person to person. Sea-level VO_{2max} , arterial saturation, muscle mass, and red cell mass have all been shown to play a role in determining VO_{2} under hypoxic conditions. Models that have examined the effect of hypoxia on VO_{2max} suggest that O_2 consumption is decreasingly reliant on O_2 delivery and more reliant on peripheral O_2 extraction with increasing hypoxia. The two most prominent acute responses to hypoxia are hyperventilation and increased diuresis, both of which have previously been considered detrimental to VO_{2max} and therefore human performance. Both diuresis and hyperventilation can decrease fluid volume and subsequently the delivery of oxygenated blood and therefore decrease VO_{2max} in normoxia. Yet this decrease in delivery may not have the same impact under hypoxic conditions. In contrast the fluid loss due to diuresis and hyperventilation may aid in maintaining saturation and facilitate muscle diffusion. Thus, a short acclimatization period may be beneficial to the hypoxic exercise response rather than detrimental.

Key Words: Acid-Base, Fluid Balance, Muscle Volume, Exercise.

VO_{2MAX} CHANGES AND HYPOXIA

Early studies

While it is important to note that West (49) has chronicled man's interest in the affects of altitude on human physiology back to the days of Aristotle, the real push to understand the affects on altitude on exercise performance began in the mid-1960's with the announcement of the Olympic games in Mexico city (2250 m). At this time it was not clear what affect this moderate altitude would have on the outcome of the games, if any at all. One of the earliest studies conducted by Balke, Nagle, and Daniels (3) in Red River, NM (2300 m) suggested that indeed this moderate altitude would have an affect on cardiovascular capacity and running performance. Upon arrival at altitude they observed an immediate decrease in VO_{2max} (~6%) and one-mile time trial performance (~9%). After ten days at altitude VO_{2max} had returned to normal, but time trial performance was still approximately 4.5% less than sea-level values. The results of this study suggest that even with ten days of acclimatization to restore VO_{2max} to normal, performance was still suppressed at altitude.

In an effort to better understand the metabolic changes at altitude, Consolazio et al. (9) measured expired gas in three different groups of soldiers ascending to various altitudes. They reported an 8% drop in VO_{2max} from sea level to 1610m and a 14% drop in VO_{2max} from 1610m to 3475m. This represents a greater percent drop than that reported by Balke et al. (3). During the 19 days at altitude Consolazio et al. documented a decrease in O_2 debt (EPOC) and found it to be the primary adaptation to altitude with very little change in VO_{2max} . The finding of Consolazio et al. suggested that acclimatization would have little effect on the recovery of sea level VO_{2max} . This finding is in direct disagreement with the findings of Balke et al. (3).

To examine the effect of hypoxia on VO_{2max} and work capacity Dill et al. (13) conducted maximal incremental exercise tests on the cycle ergometer at 535, 485, and 455 Torr in a hypobaric chamber. His group found that VO_{2max} dropped 10, 14, and 19% respectively, while maximal work capacity on the bike only dropped 5, 9, and 14% respectively. The decline in VO_{2max} observed by Dill et al. was similar to the declines reported by others (3,9), however, the smaller change in maximal workload than the decrement in maximal running performance was a perplexing finding. Dill et al. attributed the differences observed to the shorter duration of exposure that they had in a hypobaric chamber relative to the studies done on running at terrestrial altitudes.

To determine the rate of adaptation and to see if a more prolonged bout of exposure would affect running performance on the return to sea level from training at high altitude Buskirk et al. (8) took a group of track athletes to an elevation of 4,000m to train. The training involved a mix of intervals, repetition runs, callisthenic exercise, and

soccer. Upon arrival at altitude the athletes dropped their intensity and duration to 40% of their sea-level training. Over the duration of their stay the athletes were able to increase their intensity and duration to 75% of their sea-level training. Buskirk et al. reported a 26% drop in VO_{2max} at this altitude and reported that it required a four to five month period for the athletes to compete in soccer on equal terms with the residents. However, the important discovery in this paper was that as long as the athletes were in training at altitude that they would not suffer an appreciable loss in performance on return to sea level.

Buskirk's (8) finding that a prolonged stay at altitude did not hurt performance on return to sea level was an important consideration in the training of athletes for the games in Mexico City. However, Faulkner, Daniels, and Balke (16) had theorized that if athletes trained at a moderate altitude for a long enough period of time they would be able to compete at moderate altitude as if they were at sea level. Using two groups of athletes, runners and swimmers, each took part in a training camp at a moderate altitude (~2300 m). What they found was similar to their original investigation in Red River, NM. First they found no decrement in performances in distances less than 800 m. Second they found that in distances greater than 800 m, performance was decreased significantly at altitude and stayed significantly reduced even after the 21-day acclimatization period. Finally they found that after the 21 days VO_{2max} was regained to the sea level value. This finding regarding VO_{2max} is in contrast to their original investigation suggesting that VO_{2max} could be regained in 10 days at moderate altitude. Although it received little attention, it was interesting that the authors reported that altitude had almost no effect on swim performance, suggesting that swimming differed from the running response.

While the Olympic games in Mexico City served as an impetus for this early research, it is hard to draw any real conclusion from it. Most of the investigations did not have a clear-cut objective and therefore were not well controlled. Many of them were only descriptive studies with small samples making it even more difficult to draw conclusions. However, there were a few similarities in the findings of the studies. First, it appears that the decline in VO_{2max} and performance become increasingly worse over the first week at altitude until the acclimatization process begins. Secondly, even if an athlete can regain their sea level VO_{2max} at altitude it is unlikely that they will regain their sea level performance. And thirdly, because there were so many conflicting reports about the amount of decrement in VO_{2max} for a given altitude it seems obvious that there is a large amount of variability from person to person in the amount of decline they will experience.

Acute Changes

Due to the lack of control in the earlier studies many scientists began to take on more controlled studies using hypobaric chambers and hypoxic gas systems. These studies brought about a characterization of the VO_{2max} response to increasing hypoxia.

Elliot and Atterbom (15) documented the decrement in VO_{2max} from hypobaric conditions equivalent to 1576 m to 3962 m during leg ergometry in moderate altitude (~ 1500 m) residents. Both male and female subjects displayed an 18% decrement in VO_{2max} . The 18% drop observed in this study was slightly low compared to 26% drop at 4,000 m reported by Buskirk (8), but may be due to the subject's acclimatization to moderate altitude. Squires and Buskirk (45) documented the changes in VO_{2max} in a hypobaric chamber at 730, 681, 656, 632, and 574 Torr. The pressures are equivalent to 362, 914, 1219, 1524 and 2286 m respectively. Squires and Buskirk (45) found that the first statistically significant drop in VO_{2max} was at a barometric condition equivalent to 1219 m. At 1219 m they found a 5% drop in VO_{2max} and 12% drop at 2286 m. The pattern of the decrement in this investigation suggested that the VO_{2max} decline is linear with decreasing barometric pressure. Levitan et al. (28) had similar findings using inspired gas at 20.9% and 15.5% O_2 (2440 m equivalent). Levitan observed an 8.3% decrement in VO_{2max} , a finding similar to the 12% decrement at 2286 m of Squires and Buskirk (45).

A better understanding of the pattern of decrement in VO_{2max} was obtained by the data of Andersen et al. (2). Andersen et al. conducted cycle ergometry tests at barometric conditions equivalent to sea level, 2500, 3750, 4375, 4690, and 5000 m. They discovered VO_{2max} declined in a curvilinear fashion rather than in a linear fashion such as that reported by Squires and Buskirk (45). Extrapolation of the data reported by Andersen et al. (2) suggests the more severe decrements in VO_{2max} begin at 525 Torr (3,050 m). The authors suggest that this was due to a

ventilation limitation, as the authors noted a plateau in maximal ventilation at P_iO₂ of 93 Torr, which is close to the P_iO₂ of 100 Torr at 3,050 m. Dill et al. (12) had also speculated a drop in pulmonary function played a role in the decrement of VO₂max. Using data pooled over years of study at the White Mountain research facility, Dill et al. had found a drop of 20% or more in vital capacity in older subjects (age 58 – 71) at altitude. Dill et al. further speculated that this drop in vital capacity would lead to greater decrements in VO₂max in the older subjects. However, he found that the rate of decrement in VO₂max was similar in both the younger and older subjects. Suggesting changes in vital capacity were not related to the decrement in VO₂max.

To better understand the sex differences in response to VO₂max during hypoxia Paterson et al. (36) studied four females and three males using inspired O₂ concentrations of 20.93%, 17.39%, 14.4%, and 11.81% (Equivalent to sea level, 1500, 3000, and 4500 m). Paterson found a 24% decline in females and 29.5% decline in males at 11.81%, the equivalent of 4500 m. While these numbers suggest that males and females respond differently to altitude, it is important to point out that the numbers are very similar to the 26% drop demonstrated by Buskirk et al. (8) at 4000 m.

The majority of these studies were conducted at altitudes and gas partial pressures equivalent to altitudes where many people travel for recreation and competition. However, little has been done to examine the more extreme environment of high altitudes. Therefore a group of scientists took on the task of examining the drop in VO₂max during a simulated ascent to Mount Everest. The study was referred to as Operation Everest II (10). The findings of this investigation indicated a 70% drop in VO₂max at the hypobaric equivalent of ~8,932 m.

Finally, Maresh et al. (30) examined the effect of short term and long-term residency on VO₂max at altitude. He observed no significant differences in VO₂max between short term and long-term residence. This finding suggests that the acclimatization process only aided the sub-maximal and not the maximal exercise response.

Studies during this period further demonstrated the variability in the responses of VO₂max to hypoxia. However, these studies did provide a description of the pattern of the changes in a more controlled environment that was not confounded by training, travel, or other environmental conditions. While these studies did provide a characterization of the declines in VO₂max, it was still of considerable debate as to which factors influenced VO₂max at altitude.

Individual Factors Affecting VO₂max in Hypoxia

One of the most notable changes in the acclimatization process is the increase in red cell mass. Robertson et al. (47) speculated that polycythemia augmented VO₂max at altitude. Five male climbers completed VO₂max testing at sea level and under hypoxic conditions (inspired O₂ fraction = 13.5%, equivalent to 3566m). Following the tests they underwent blood draws for the subsequent storage of their red blood cells. Eight weeks later the climbers were re-infused with their red cell, thus increasing their red cell mass. The re-infusion increased hematocrit by 26.5% and hemoglobin by 27.7%. These hematological changes increased VO₂max at sea level by 20.9% and 9.8% under hypoxic conditions. This finding suggests that red cell adaptations play a role in the changes in VO₂max at altitude. However, in contrast to this article, Young et al. (51) conducted a red cell reinfusion on 16 healthy males and despite the re-infusion increasing hemoglobin concentration it had little effect on the decrement in VO₂max in comparison to a matched control group that was infused with an equal volume of saline. These findings suggest that red cell mass has little to do with the VO₂max response to chronic altitude exposure. The findings of these two articles also suggest that it is unclear what role red blood cells play in influencing VO₂max at altitude.

Tucker et al. (47) examined arterial oxygen saturation at altitude in 12 of the Colorado State University track team members. Tucker et al. found that from 760 Torr to 635 Torr (~1500 m) SaO₂ fell an average of 9.4% and then fell an additional 10.8% from 635 Torr to 525 Torr (~3,000 m). In relation to these decrements in SaO₂, Tucker also found a drop of 6.5% and 22% in VO₂max at 635 and 525 Torr respectively. These findings indicated that the greater the decrement in SaO₂ the greater the decrement in VO₂max. The outcome of this investigation indicates that arterial desaturation also contributes to the changes in VO₂max under hypoxic conditions. Lawler et al. (40) and Powers et al. (49) were collapsed across gender to simplify the graph.

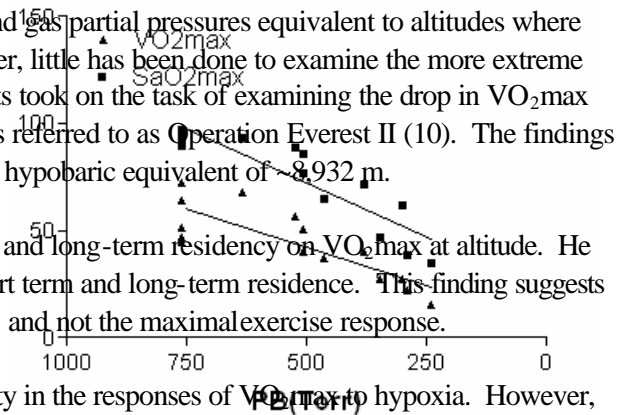


Figure 1. The data show the % decrements in arterial O₂ saturation and VO₂max with decreasing barometric pressure (PB). Data are redrawn from Cymerman et al. (10), Lawler et al. (27), Sutton et al. (46) and Tucker et al. (47) and show a parallel decrease. The slopes of each line are not statistically different from one another (p = 0.14).

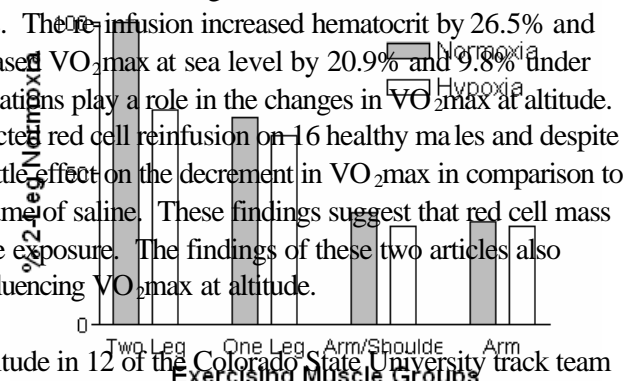


Figure 2. Percent decrement in VO₂max when exercising with different volumes of muscle. Note that the effect of hypoxia on VO₂max is much less with smaller muscle groups. Data are redrawn from Shepard et al. (4) and were collapsed across gender to simplify the graph.

Thompson (27) who tested subjects using 21% and 14% inspired O_2 later confirmed these findings. The greatest decrements in VO_{2max} were seen in subjects with the greatest arterial desaturation. The importance of high V_E and therefore high SaO_2 was further reinforced by the finding of Sutton et al. (46) that examined O_2 transport during the OEII studies and by Shepard et al. (42) who similarly found that high V_E limited the decrease in SaO_2 . The relationship between barometric pressure and its effect on VO_{2max} and SaO_2 at VO_{2max} can be seen in Figure 1.

To better understand the role of hormonal function in determining VO_{2max} under hypoxic conditions Boissou et al. (7) studied eight males performing cycle ergometry at 40, 60, 80, 100 percent of VO_{2max} . He found no differences in insulin/glucagon ratios, Δ -4 androstene/testosterone ratios, and no significant differences in catecholamines with hypoxia. These findings indicated that hormonal function does not play a role in determining VO_{2max} .

To determine the effect of working muscle mass on VO_{2max} decrement Shepard et al. (41) conducted VO_{2max} tests on eight male and eight female volunteers. Each subject completed a two-leg, one-leg, shoulder/arm, and arm only exercise test to VO_{2max} . Each test was conducted under both normoxic and hypoxic conditions (12% O_2). Each decrease in working muscle mass resulted in a smaller decrement in VO_{2max} . On average the two-leg test resulted in a 30% decrement in VO_{2max} , while the arm only test resulted a 2% decrement in VO_{2max} . Furthermore, each decrement in muscle mass resulted in a corresponding smaller decrease in VO_{2max} (Figure 2). These data show that muscle mass is a major contributing factor to the decrement in VO_{2max} under hypoxic conditions, and may explain why Faulkner, Daniels, and Balke (16) found very little drop in swim performance at altitude. Research in swim exercise has documented that most of the propulsion comes from the arms and would therefore represent a smaller exercising muscle mass.

The most prominent of all variables in determining the drop in VO_{2max} under hypoxic conditions is sea-level VO_{2max} . Young et al. (52) was the first to show that as an individual's sea level VO_{2max} increases the percentage of drop in VO_{2max} will be greater under hypoxic conditions. This finding is somewhat counter intuitive as it would be expected that a person with a higher sea level VO_{2max} would show less decrement not more since their body had an enhanced ability to use oxygen. Shepard et al. (42) showed that a higher sea level VO_{2max} was indeed protective of the drop in VO_{2max} during hypoxic conditions up to a VO_{2max} of ~ 48 ml/kg/min. Above a VO_{2max} of ~ 48 ml/kg/min a higher VO_{2max} was associated with a larger decrease VO_{2max} during hypoxia. The effects of sea level VO_{2max} on the decrement of VO_{2max} during hypoxia were supported by the work of Lawler et al. (27) and Martin and McKroy (31) who each demonstrated greater drops in VO_{2max} during hypoxia with greater sea level VO_{2max} .

These studies demonstrate that several factors relate to the decrement in VO_{2max} . Arterial desaturation, red cell mass, working muscle mass, and sea level VO_{2max} all contribute the decrement in VO_{2max} . Collectively they explain the wide range in the decrements in VO_{2max} shown in the early studies of VO_{2max} during hypoxia.

MODELS OF THE CHANGE IN VO_{2MAX}

Because a number of variables have been demonstrated to play a role in the decrement of VO_{2max} under hypoxic conditions, investigators began modeling these factors to determine how they interacted with one another.

Ferretti (17) had observed that the decline in VO_{2max} was a mirror image of the oxy-hemoglobin dissociation curve. This observation tied together the work of both Squires and Buskirk (45) and Andersen et al. (2). Squires and Buskirk had suggested that the VO_{2max} response to altitude was linear; however they had only tested up to an equivalent elevation of 2286 m leaving them on the relatively flat portion of the oxy-hemoglobin dissociation curve. Testing above the equivalent of ~ 3000 m would have put them on the steeper portion of the oxy-hemoglobin dissociation curve and they would have also observed the curvilinear response of Andersen et al. since they tested up to an equivalent of 5,000 m

Ferretti also derived a mathematical model of the changes in VO_{2max} at altitude. The data for this model was based on the previous observations of other researchers. In this model Ferretti put forth that approximately 70% percent of VO_{2max} was determined by maximal cardiac output at sea level. As altitude increases to approximately 4300 m maximal cardiac output only determined 48% of VO_{2max} and that the balance of the VO_{2max} response was determined by peripheral O_2 transport.

Similarly, Robergs et al. (39) composed a model to explain the variance in the decrement of VO_{2max} . Robergs conducted cycle ergometer tests on 28 subjects at the equivalent hypobaric conditions of sea level and 2439 m. While this range of hypobaric conditions is not very wide, it does represent the typical range for competition and recreation. Using multiple regression they found that a high sea level VO_{2max} , low lactate threshold, low SaO_{2max} , high lean body mass, and the female sex all lead to greater decrements in VO_{2max} at 2439 m. Because lactate threshold serves as proxy variable for peripheral O_2 transport Robergs findings agree very well with the model of Ferretti (17). The greatest amount of variance explaining the decline in VO_{2max} was sea level VO_{2max} . Again this finding agreed well with the previous findings of others. Young, Cymmerman, and Burse (51) as well as Shepard et al. (42) found that volunteers with higher VO_{2max} at sea level had a greater percent decrement. Indeed a high sea level VO_{2max} is still the greatest detriment to VO_{2max} decline at altitude.

The relevance of the high sea level VO_{2max} to the percent decline in VO_{2max} at altitude was made clear by Wagner (48). Wagner found that at sea level more highly trained individuals (higher VO_{2max}) were limited by the delivery of oxygen to the muscle, whereas less trained (lower VO_{2max}) were limited by O_2 utilization in the periphery. This model would explain why even small decrements in SaO_2 would have large decreases in VO_{2max} at altitude in well-trained subjects. Wagner further confirmed the finding of Robergs et al. and Ferretti. In addition to demonstrating the importance of O_2 delivery at sea level he further demonstrated the increased limitation of the periphery under hypoxic conditions. Wagner's model again suggests that individuals with a high lactate threshold would minimize their losses in VO_{2max} at altitude.

The research over the last decade has brought a better understanding of VO_{2max} at altitude. The reasoning behind the curvilinear and linear responses previously reported is now better understood. More importantly, the variance in individual responses that had been documented since the mid-60's has now been replicated, verified as normal, and explained by various models. Furthermore, various laboratory tests may even be suitable to identify who will perform well at altitude and who will not; a question that was originally posed prior to the Olympic games in Mexico City.

ACUTE PHYSIOLOGICAL RESPONSES TO HYPOXIA

Upon arrival at altitude the two most prominent physiological responses to the hypoxia are a renal diuresis and increased minute ventilation. It is unclear what effect these responses will have on VO_{2max} and performance at altitude. The hypoxic ventilatory response has clearly been shown to have little effect on VO_{2max} at altitude (23,33), however it may have secondary effects (i.e. increased fluid loss and increased pH) that may influence VO_{2max} . Furthermore, the increased diuretic response at altitude subsequently leads to dehydration, and would be hypothesized to have detrimental effects on VO_{2max} . These responses to altitude led Daniels (11) to suggest that athletes should either travel to altitude at the last minute for competition or arrive weeks in advance to undergo acclimatization, neither of which is convenient or cost effective; an adage that many athletes still follow today. The next section examines these acute responses and attempts to fit them into the models above to determine their real value or detriment on VO_{2max} .

Fluid Balance at Altitude

Fluid Compartment Changes at Altitude

Altitude has a profound effect on fluid balance. It is often the most common and immediate effect of altitude that can be sensed by people traveling to higher elevation. Jain et al. (25) measured the changes in body fluid compartments at 200 and 3500 m in 18 healthy males. Measurements were taken after 3 and 12 days at 3500 m. What they found were significant decrements in total body water (TBW) on days 3 and 12 (-3.7 and -4.7%, respectively) as well as intracellular water (ICF) (-3.3% and -4.3%, respectively). Extracellular (ECF) water also showed a significant decrease (6%) by the 12th day. Within the extracellular compartment, plasma volume (PV) decreased 16%.

Increased diuresis will lead to dehydration, and it would intuitively seem that fluid loss at altitude would be potentially harmful. However, Hackett et al. (22) speculated that the fluid loss caused by acute and chronic altitude exposure was beneficial and in their study of 102 trekkers in Nepal those that developed high altitude pulmonary edema (HAPE) and AMS symptoms had a decrease in their frequency of urination and increased gains in body weight (BW). Similarly Gunga et al. (20) also examined changes in fluid balance and its effect on tissue thickness at moderate altitude (2315 m). Using ultrasound to measure tissue thickness in the forehead, tibia and sternum, they observed a significant increase in tissue thickness in the forehead and tibia. The increase in tissue thickness was associated with an increase in body weight (75.5 kg to 76.2 kg) and total body water (44.21 L to 45.01 L). Finally Shirlo et al. (43) carried out a similar experiment examining thigh circumference changes with acute exposures to hypoxia. With increasing hypoxia thigh circumference decreased significantly and the decrease in circumference was proportional with the increase in diuresis (Figure 3). This suggests, and that as Hackett (22) had speculated, fluid retention or an antidiuresis is significantly related to edema. With regard to AMS and fluid balance, Richalet et al. (38) measured PV, BW, and AMS in 9

mountaineers at 4950 m for a period 4 weeks. During this time they documented decreases in PV of 7% and 10% and BW of 3% and 5% at weeks one and four respectively. The only individual to develop AMS showed increases in BW and PV during the first week and decreases in these variables by the 4th week as the symptoms subsided. In further support of the importance of the diuretic response to AMS, Singh, Raul, and Tyagi (44) found that a group of acclimatized subjects that were being reintroduced to altitude after a previous 4 to 6 month stay at 3500 m had an 11% increase in PV and greater susceptibility to AMS than on their previous induction. Also noted in this study were significant decreases in the fluid compartment after as little as two days. PV decreased significantly by 8%, being similar to the 7% decrement seen by Richalet et al. (38). Significant decreases were also seen in BW, total body water, extracellular fluid, and intracellular fluid of 1.6 kg, 1.14 L, 0.49 L, and 0.65 L respectively. Bartsch et al. (6) published a summary of three previous studies. They observed that increased fluid intake increased urine output. In addition, rather than being protective of AMS development, excess fluid intake may increase the incidence AMS. They also reported that fluid retention in those subjects susceptible to AMS was due to an increase in resting aldosterone.

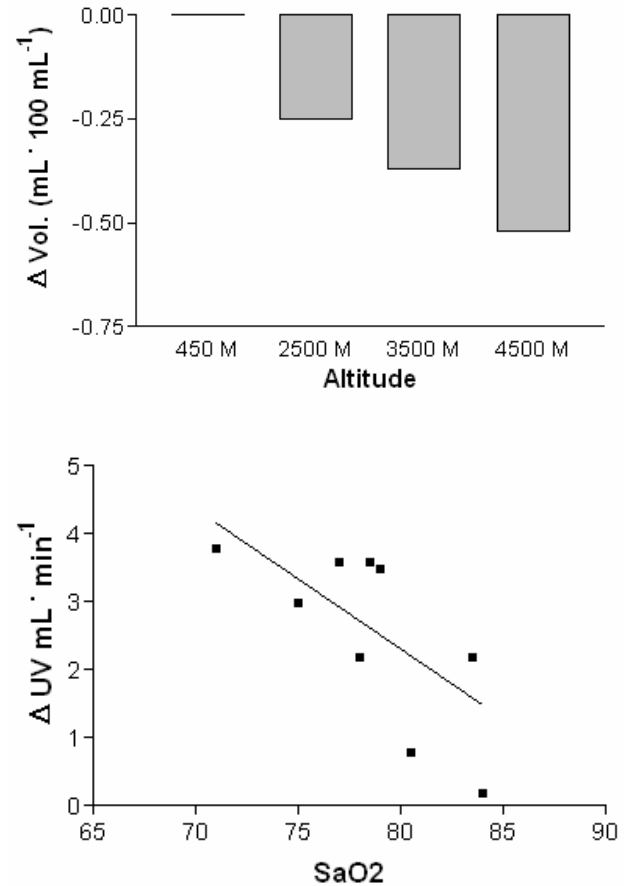


Figure 3. Top graph shows a decreasing muscle volume with increasing altitude. Lower graph shows decrements in SaO₂ increase urine volume (? UV). Data are redrawn from Schirlo et al. (43).

Due to the variability of the previous studies, Hoyt et al. (24) decided to examine the effects of altitude on fluid compartments in goats. Goats were chosen because they provide a good model for fluid balance in humans without AMS complicating the interpretation of the results. Four female goats were examined at sea level and for 16 days at 380 Torr. BW, TBW, ICF, and PV all decreased significantly. Blood volume however remained unchanged due to an increase in red cell volume. ECF increased significantly due to an increase in interstitial fluid. Most of the observed weight loss came from ICF (-4.04 L). Although not mentioned by the authors the data seem to indicate that the increase in interstitial fluid is due to fluid shifts from the PV and ICF compartments. From this data the authors concluded that the majority of the fluid loss at altitude in goats and probably humans is from the ICF compartment.

Causes of Altitude Diuresis

At altitude a constriction in the pulmonary vasculature occurs in an attempt to better match alveolar ventilation with blood flow. This constriction causes an increase in load to the right side of the heart and will therefore increase the stretch in the right atrium. The stretch in the right atrium will then trigger the release of atrial natriuretic peptide (ANP) (21). The effect of ANP is to increase sodium clearance and will therefore lead to diuresis (37). This mechanism is the most likely the cause of the diuresis observed at higher altitude and has been well demonstrated by Bartsch et al. (4). Bartsch et al. studied 25 mountaineers (9 w/previous HAPE) at 550m and 4559m after 6, 18, and 24 hours of exposure. They found that subjects without AMS has greater urine volume and weight loss, a finding that was similar to others. Also observed were significant decreases in renin, angiotension II, and aldosterone in the non-AMS subjects after 18 hours. ANP was greatest and SaO_2 lowest in subjects with AMS suggesting that ANP may some how be involved in the AMS process. However, when the data was analyzed using multiple regression, where the variance of the other variables could be controlled for, a significant positive relationship was seen between ANP and SaO_2 . In support of this finding Westdorp et al. (50) administered low doses of ANP and under hypobaric conditions (456 Torr (4115 m)) found significant increases in SaO_2 (79.6% vs 84.7%), as well as a decrease in the alveolar-arterial gradient (7.3 vs. 3.5 mmHg). This suggests that ANP is the mechanism of diuresis in non-AMS susceptible subjects and highly related to SaO_2 . Although the subjects with AMS did have greater ANP and less diuresis they also had elevated catecholamines, ADH, and aldosterone. Bartsch et al. (4) attributed the lack of diuresis in the face of elevated ANP to the overriding effects of the catecholamines, ADH, and aldosterone. These conclusions were validated by Koller et al. (29). Koller used two groups of 10 subjects; one acclimatized and the others not. While seated in a chair these subjects were exposed to an equivalent elevation to 6000 m in a hypobaric chamber that was undergoing decompression at rate of 300 m/min. The decompression was stopped every 10 minutes for observation. Koller et al. had similar findings to that of Bartsch et al. (14). Koller et al. found that ANP rose significantly in both groups, as did diuresis. Koller et al. also saw a significant rise in ADH in the non-acclimatized subjects. Unfortunately because of the brevity of the exposure the diuresis was greatest in the non-acclimatized subjects, however because of the hormonal profile if the non-acclimatized subjects had been at altitude for a longer period of time they would have began to retain water and increased their susceptibility to AMS. While aldosterone and ADH may counter balance the rise ANP, the role of catecholamines may need to be re-assessed since Grover et al. (21) administered propranolol to subjects at 4300 m and found no effects of fluid balance during their 3 weeks at this elevation.

While these articles document the changes in fluid balance and the hormonal changes associated with it, Bartsch et al. (5) felt that they were flawed because of the rapid rates of ascent. No mountaineer could travel that fast and therefore the responses were not typical of what would be seen in the mountains. Bartsch et al. theorized that with a less rapid ascent that the time for acclimatization would alleviate the AMS symptoms he had seen previously in those susceptible to AMS. In this study 15 male mountaineers (6 w/previous with a AMS history) trekked from 1170 m to 4559 m with an overnight stop at 2864 m and two nights at 3611 m. Again there was a significant increase in ANP in the subjects with AMS and no increase in ANP, ADH, renin, or aldosterone in the subjects without AMS. This led Bartsch et al. (5) to conclude that a slow ascent will not prevent AMS in those that are susceptible.

The mechanism for release of ANP is a stretch in the right atrium (22). However, it is possible that ANP release is somehow tied into the hypoxic response. Both Barsch et al. (5) and Ponchia et al. (37) examined the causes of ANP release at altitude. As expected both concluded that ANP release was related to atrial volume. However, Ponchia et al. found a significant relationship to the decrease in left atrial volume rather than the right atrial volume as expected. However, closer examination of their data does reveal a mean increase in right atrial volume, but with very high variability, which would preclude them from finding a significant difference.

In opposition to the previous studies, which demonstrate an increase in diuresis at altitude, Anard et al. (1) found an increase in fluid retention in response to altitude. Anard et al. examined 10 subjects at 6,000 m for 10 weeks. During this time he observed an increase in fluid retention in all fluid spaces including a 33% increase in PV and an 84.5% increase in blood volume. This response was attributed to a 37% decrease in renal blood flow and 2-fold increase in aldosterone, and no change in ANP. It is difficult to say why these results are backwards from so many other studies, but it is worthy to note that some subjects may respond the opposite of the expected response.

From these articles it appears that there is an increase in diuresis with increasing altitude or hypoxia. This diuresis also appears to be caused by an increase in ANP relative to the increase in the fluid preserving hormones and tends to have an effect on all of the fluid compartments. The diuresis is an important response to altitude and hypoxia not only because it limits symptoms of AMS, but also because SAO_2 also appears to be higher with an adequate diuretic effect. Further, limb volume appears to decrease with an increased diuresis and may theoretically help facilitate O_2 diffusion in the muscle. Elevated SAO_2 and enhanced muscle diffusion have been shown to be important variables in minimizing the decrease in VO_{2max} at altitude (17,39). This would suggest that fluid loss may be advantageous in minimizing the losses in VO_{2max} at altitude, rather than a detriment as suggested by Daniels (11).

Acid-Base Balance at Altitude

Along with increased diuresis one of the most immediate responses to altitude and hypoxia is an increase in ventilation. The increase in ventilation causes a decrease in the partial pressure of CO_2 in the blood. As the arterial content of CO_2 falls plasma pH will increase developing a gradient between the tissues and plasma and eventually leading to a systemic increase in pH. After a prolonged period of time the kidneys will begin to excrete bicarbonate and the pH of the body will return to normal. This response has been well characterized with previous research and summarized by Milledge (33).

To demonstrate the effect of hypoxia on acid-base status and its effect on human performance, McLellan, Jacobs, and Lewis (32) examined four subjects at sea level and under hypobaric conditions (445 Torr = ~4200 m). The acute exposure lasted two hours and during this time pH increased significantly from 7.396 to 7.446. In performance trials that measured time to fatigue at 90% of the hypoxic specific VO_{2max} they observed an average increase of 3.3 minutes ($p < 0.05$) at altitude. This study makes it impossible to tell if the resulting increase in performance was the result of the buffering of hydrogen ions or a leftward shift in oxy-hemoglobin dissociation curve. An intensity of this magnitude (90% of VO_{2max}) would rapidly accumulate hydrogen ions and an increase in the ability to buffer these ions would be of benefit to performance. Regardless of cause, this study demonstrates that even a short exposure to altitude (2hrs) can have a large effect on both blood pH and exercise performance.

However, the leftward shift in the oxy-hemoglobin dissociation curve cannot be ruled out as an explanation of the improved performance observed by McLellan, Jacobs, and Lewis (32). Gonzalez, Zamagni, and Clancy (18) used rats supplemented with bicarbonate and

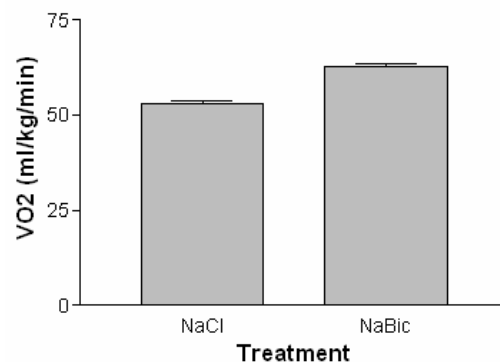


Figure 4. The data illustrate the effect of $NaHCO_3$ supplementation (NaBic) on VO_{2max} under hypoxic conditions in comparison to a NaCl placebo. Data are

exposed them to hypoxic conditions (370-380 Torr). They observed an average of an 18% greater VO_{2max} in the animals supplemented with bicarbonate than the control animal that received a placebo (Figure 4). The authors attributed the elevated VO_{2max} to the increases in arterial oxygen content and found a nearly linear correlation with arterial oxygen content and VO_{2max} . The authors further suggest that the increase in alkalinity served to buffer the hydrogen ions produced during exercise and to attenuate the decrease in arterial oxygen content. This suggestion would seem to indicate that both explanations for the finding of McLellan, Jacobs, and Lewis (32) are correct.

However, yet another explanation for the improved performance observed by McLellan, Jacobs, and Lewis (32) has been suggested by Loeppky et al. (29). Loeppky et al. studied anesthetized dogs that were mechanically ventilated. They found that arterial pulmonary pressure was related to acid-base status, such that the greater the alkalinity the less the pressure in the pulmonary artery. This lower pressure in the pulmonary artery allowed for a better ventilation-perfusion relationship. This was verified by examining differences between end-tidal O_2 and CO_2 and arterial O_2 and CO_2 . This finding led the authors to believe that the hyperventilation that occurs at altitude may facilitate improved SaO_2 by reducing pulmonary pressure via increased alkalinity rather than the traditional view that hyperventilation maintains a higher alveolar oxygen partial pressure. While this data does provide a different view on the effect of acid-base status at altitude, it still suggests that changes in acid-base status after exposure to altitude will have a beneficial effect on SaO_2 and subsequently VO_{2max} .

The changes that occur in acid-base status with acute exposure to altitude or hypoxia appear to be influential on SaO_2 . There does seem to be some controversy over the mechanism by which acid-base status influences SaO_2 . Regardless the increase in alkalinity that increases SaO_2 will tend to positively influence VO_{2max} and therefore theoretically exercise performance.

SUMMARY

Early studies on VO_{2max} suggested that the longer the acute exposure to altitude the greater the decrease in VO_{2max} and exercise performance. Although improvement in exercise performance and VO_{2max} can be seen with acclimatization, the improvement never returns to sea level status. This suggests that for anyone that performs exercise or work at altitude an immediate completion of the task is best, thereby minimizing the deleterious effects of prolonged altitude exposure.

However, some of the immediate responses to altitude or hypoxia including diuresis and increased alkalinity may actually be beneficial. These changes in fluid balance and acid-base status have been shown to be advantageous to altitude exposure and to elevate SaO_2 . The models of Robergs et al. (39), Ferretti (17) and Wagner (48) suggest that better SaO_2 will result in less of a decline in VO_{2max} . Hence an exposure of several hours or even overnight to hypoxia may actually improve VO_{2max} rather than worsen it as is suggested by previous early studies on VO_{2max} .

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