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EFFECT OF HYPEROXIA ON MAXIMAL OXYGEN UPTAKE, BLOOD ACID-BASE BALANCE, AND LIMITATIONS TO EXERCISE TOLERANCE

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ABSTRACT

EFFECT OF HYPEROXIA ON MAXIMAL OXYGEN UPTAKE, BLOOD ACID-BASE BALANCE, AND LIMITATIONS TO EXERCISE TOLERANCE. **Todd A. Astorino And Robert A. Robergs**. **JEP**online. 2003;6(2):8-20. Hyperoxia, or an increase in inspired oxygen concentration, has been used by scientists to examine exercise metabolism and physical work capacity. It is apparent that hyperoxia increases VO_2max and exercise tolerance due to an increase in O_2 supply to contracting muscle. Furthermore, hyperoxia increases P_aO_2, which may promote an enhanced diffusion of O_2 in skeletal muscle. Compared to normoxia, hyperoxia may reduce PCr degradation during the metabolic transient, attenuating the magnitude of cellular disturbance characteristic of near-maximal to maximal exercise. These aforementioned increases in exercise tolerance during hyperoxia are not due to alterations in ventilation, lactate (La^-), or acid/base balance in hyperoxia, as previous data report no change in these parameters compared to normoxia. In addition, it is recommended that researchers take special precautions to ensure the accuracy of gas exchange data in hyperoxia.

Key Words: VO_2max, central limitation, S_aO_2, O_2 breathing, lactate

INTRODUCTION

Hyperoxia is defined as an increase in the inspired oxygen (O_2) concentration. Hyperoxia can be administered via autologous blood reinfusion (1,2), breathing oxygen-rich air (fractional inspired oxygen content (F_IO_2) > (0.2093) (3-7), and exposure to hyperbaria (arterial partial pressure of oxygen (P_aO_2) ~ 500 Torr) (8). During the last two decades, hyperoxia has been widely used by researchers to examine limitations to maximal oxygen uptake (VO_2max), so it is necessary to summarize these findings. In addition, since much additional research has been completed since the most recent review of hyperoxia and exercise tolerance (4), a thorough and more current review of the effects of increased O_2 content on exercise tolerance, cardiovascular function, and acid/base balance is warranted. Search criteria for this review included all studies in which healthy subjects completed incremental exercise to volitional fatigue under hyperoxic conditions.

EFFECT OF HYPEROXIA ON EXERCISE TOLERANCE

Soon after the discovery of O_2, its effects on exercise capacity were determined. Early anecdotal reports (9-10) suggested that breathing pure O_2 increased exercise tolerance, but shortcomings in research design and laboratory equipment minimized the validity of these data. During the next 30 years, research with improved experimental design and methodology supported early findings showing that hyperoxia improved work tolerance independent of exercise mode. However, psychological effects of breathing hyperoxic gas could not be eliminated as a cause of improved performance since control groups, trial randomization, and masking of subjects were not employed. One of the first well-controlled studies (11) to investigate changes in exercise tolerance in hyperoxia required active men to complete treadmill exercise to exhaustion in room air and four hyperoxic inspired gas fractions (40, 60, 80, and 100 %O_2). Results are shown in Figure 1.

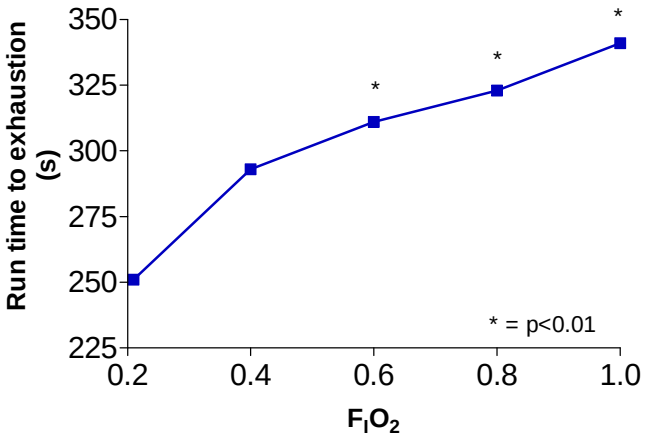

Figure 1. Increases in exercise tolerance with increasing F_IO_2. Adapted from Wilson and Welch. (11).

Run time to exhaustion increased in a near-linear fashion from 40 to 100 $\%O_2$. It is interesting to observe that compared to 80 $\%O_2$, run time was still increased in 100 $\%O_2$, contrary to earlier reports (12) that exercise tolerance plateaus at F_IO_2 greater than 0.66. Subsequent work has shown that compared to normoxia, acute administration of hyperoxia enhances exercise capacity during treadmill running (13-15), submaximal cycle ergometry (16-18), and all-out rowing (Table 1) (6-7). The magnitude of the performance benefit varies, however, with the specific variable measured in the study, as it appears that peak workload increases to a lesser degree than time to exhaustion during maximal or supra-maximal exercise. These data suggest that hyperoxia increases the capacity to complete submaximal and/or high-intensity exercise.

Table 1. Effect of Hyperoxia on Exercise Performance

Author (yr)	*Subjects*	*% Increase in Ex. Performance*	*Parameter*
Margaria (72)	11 healthy men	19.0	Time at supramaximal workload
Fagraeus (73)	11 healthy men	15.1*	Time at supramaximal workload
Linnarsson (74)	6 healthy men	20.0*	Peak workload
Davies (74)	5 healthy men	1.0	Peak workload
Adams (80)	6 male runners	26.4*	Time at 90 $\%VO_2$max
Buick (80)	11 track athletes	31.0	Time at 95 $\%VO_2$max
Wilson (80)	10 healthy men	21.8	Time at 8 mph
Hogan (83)	6 healthy men	5.9	Peak workload
Hogan (84)	6 healthy men	22.0	Time at 90 $\%VO_2$max
Powers (89)	7 trained runners	5.3	Peak workload
Plet (92)	11 young men and women	41.0*	Time at 80 $\%VO_2$max
Chick (93)	5 healthy men	32.3*	Time at 85 %Wmax
Knight (93)	11 trained cyclists	8.7*	Peak workload
Mateika (94)	8 healthy men	13.0*	Incremental exercise time
Peltonen (95)	6 trained rowers	6.5*	Peak workload
Nielsen (98)	11 trained oarsmen	3.2	Peak workoad
Hogan (99)	6 men and women	14.0*	Incremental exercise time
Richardson (99)	5 trained cyclists	12.1	Peak workload
Linossier (00)	5 healthy men	45.0*	Maximal exercise time
Harms (01)	25 female runners	57.0*	Time at peak work rate
Peltonen (01)	6 trained men	5.5	Peak workload
Astorino (01)	20 healthy men	7.4*	Peak workload

* = $p<0.05$

EFFECT OF HYPEROXIA ON VO_2MAX

An initial explanation for this enhanced performance in hyperoxia is a greater VO_2max mediated by enhanced oxygen delivery. The Fick Equation proposes that any observed increase in VO_2max is partly attributed to central cardiovascular function (cardiac output) and/or O_2 extraction (arteriovenous O_2 difference). For example, a simple calculation emphasizes the expected change in VO_2max for a hyperoxia-mediated increase in O_2 delivery due to an increase in arterial oxygen content (C_aO_2). Using previously reported values for cardiac output (Q) and arteriovenous O_2 difference (a-$vO_2\Delta$) in normoxia and 100 $\%O_2$ (5), VO_2max should increase by approximately 11 % (4,547.5 mL/min vs. 4,102.6 mL/min) in hyperoxia. Table 2 shows the magnitude of increase in VO_2max in response to various levels of hyperoxia administered in previous investigations. Recent data from our laboratory (19) revealed that mean VO_2max is 12 % higher in 25 $\%O_2$ (4.34±0.75 L/min) versus normoxia (3.87±0.58 L/min) in moderately-trained young men. This increase is comparable to data reported in

previous research (7,14,17,20) using similar subject populations. So, what factors are responsible for the increase in VO_2max in hyperoxia?

Table 2. Change in VO_2max, Maximal S_aO_2, and HRmax reported in Hyperoxia

Author (yr)	*Subjects*	*Ex. Mode*	F_IO_2	ΔVO_2max (%)	ΔS_aO_2 (%)	ΔHRmax ($b.min^{-1}$)
Margaria (72)	11 men	TM[1]	1.0	+8.1	N/R	+0.8
Ekblom (75)	9 men	TM/CE[2]	0.50	+12.6*	+4.0	+2.0
Buick (80)	11 runners	TM	Blood reinfusion	+5.1*	N/R	N/R
Thomson (82)	4 untrained men	TM	Blood reinfusion	+11.2*	-0.7	+1.0
Byrnes (84)	6 men	CE	0.70	+13.0*	N/R	0.0
Spriet (86)	4 runners	TM	Blood reinfusion	+6.8*	N/R	-12.0
Powers (89)	7 runners	CE	0.26	+6.6*	+5.3*	+1.0
Plet (92)	6 men, 5 women	CE	0.55	+3.7, +11.4*	N/R	+2.0, +5.0*
Knight (93)	12 cyclists	CE	1.0	+8.1*	+3.7	+0.4
Peltonen (95)	6 rowers	RE[3]	0.62	+11.1*	N/R	+11.0
Cardus (98)	6 men and women	CE	1.0	+16.4	N/R	+2.0
Nielsen (98)	11 oarsmen	RE	0.30	+13.3*	+5.4	-4.0
Richardson (99)	5 cyclists	KE[4]	1.0	+18.5*	+1.5	-4.0
Astorino(01)	20 healthy men	CE	0.25	+12.1*	+3.1	+1.9
Harms (01)	25 trained women	TM	0.26	+6.3*	+5.2*	+1.0
Peltonen(01)	6 trained men	CE	0.32	+14.0*	N/R	N/R

[1] = treadmill, [2] = cycle ergometer, [3] = rowing ergometer, [4] = one-leg knee extension, N/R = not reported, * = significant increase ($p<0.05$) in VO_2max, S_aO_2, and HR compared to normoxia

First, an enhanced O_2 delivery (mediated by increases in Q and/or C_aO_2) may explain increases in VO_2max coincident with hyperoxia. In response to reinfusion of 2 U of blood eliciting a 11.2 % increase in VO_2max (2), C_aO_2 was significantly higher (21.9±1.2 mL/dL vs. 19.7±0.7 mL/dL), whereas Q was similar except at VO_2max. In another study, O_2 delivery at VO_2max was 11 % higher in 100 %O_2 (4.18±0.23 L/min) compared to room air (3.77±0.2 L/min), due to an increased C_aO_2 and no change in Qlegs (5). The near-linear increase in VO_2max in response to increasing O_2 delivery in hyperoxia from previous studies is shown in Figures 2a-c.

The hyperoxia-mediated increase in C_aO_2 is due to marked increases in S_aO_2 (3,7,19) and to a lesser extent, hemoglobin concentration ([Hb]) (1,14). In fact, pioneering data from Powers et al. (1) demonstrated that acute hyperoxia (26.2 %O_2) eliminates appearance of arterial hypoxemia in highly-trained runners, resulting in a significantly higher VO_2max compared to room air (74.7±1.2 vs. 70.1±1.9 mL/kg/min). Trained runners who did not desaturate (marked decline in S_aO_2) at VO_2max showed no increase in VO_2max while breathing hyperoxic gas mixtures. Consequently, it is evident that hyperoxia enhances VO_2max due to an increase in oxygen delivery to active muscle.

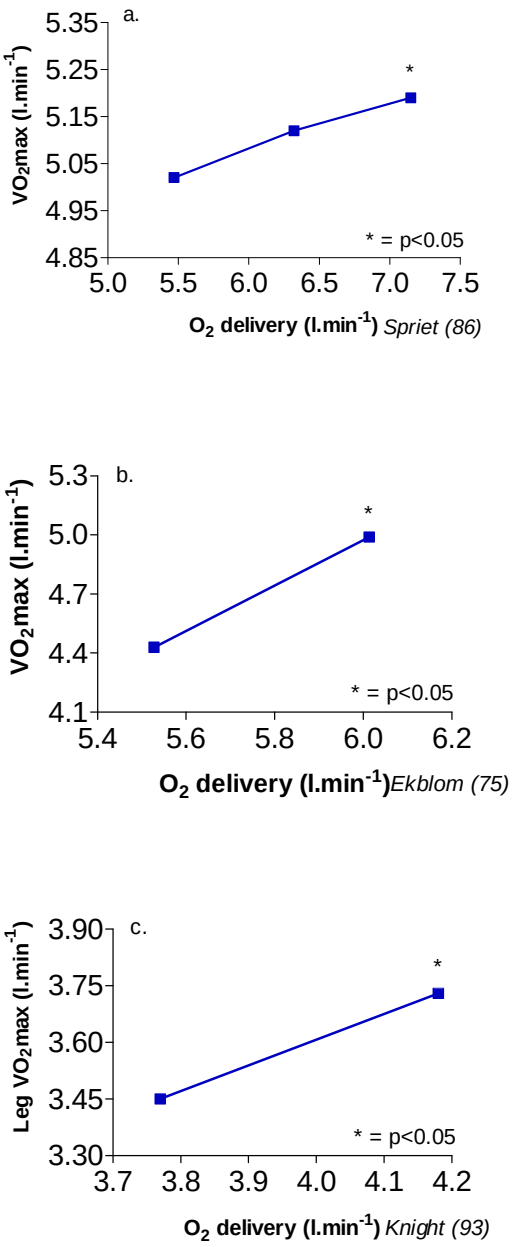

Figure 2. Relationship between VO_2max and O_2 delivery in previous research; (a) in response to blood reinfusion (1), (b) during rowing ergometry in normoxia and 30 %O_2 (7), (c) during cycle ergometry in normoxia and 100 %O_2 (5), and (d) during single-leg knee extension in normoxia and 100 %O_2 (32).

Does this hyperoxia-driven increase in O_2 delivery allow athletes to overcome central limitations to VO_2max? The contention that central cardiovascular function regulates VO_2max is not new, as this theory was originally introduced in classic research from A. V. Hill's laboratory (21,22). During this research, subjects ran on an 85 m grass track at various speeds for three minutes while gas exchange was obtained every 30 s with Douglas bags. Hill and colleagues concluded that a running speed of 16 km/hr and VO_2max equal to 4 L/min represented the maximal athletic performance in man. To explain the leveling off in oxygen uptake at these high running speeds, Hill commented (p. 156)…*"In running, the oxygen requirement increases continuously as the speed increases, attaining enormous values at the highest speeds: the actual oxygen intake, however, reaches a maximum beyond which no effort can drive it. The oxygen intake may attain its maximum and remain constant merely because it cannot go any higher owing to the limitations of the circulatory and respiratory system*."

This brief synopsis of data collected almost 80 years ago represents the initial interpretation of a VO_2 plateau at VO_2max to represent a central limitation to VO_2max. That is to say, at VO_2max, oxygen delivery to the working muscle is interpreted to be inadequate to meet the ever-increasing oxygen demand. Subsequent research (23-25) examining the VO_2 response to discontinuous incremental exercise corroborated the paradigm developed by Hill that O_2 delivery limits VO_2max. Two decades later, in response to 43 % of adult men exhibiting a plateau in VO_2 at VO_2max, Cumming and Borysyk (26) commented (p. 20) that…*"To some extent, they (criteria to confirm incidence of VO_2max) are all indicators that the oxygen transport system is fully taxed and exercise is increasingly carried out anaerobically*." Similarly, Shephard (27) noted (p. 759)…*"During treadmill exercise, maximum effort is halted by central circulatory failure*." In addition, it was reported that in men exercising to volitional fatigue, VO_2max and O_2 delivery are markedly attenuated in 12 %O_2 and 15 %O_2 compared to normoxia (28). Consequently, it is apparent that O_2 delivery to contracting muscle partly limits VO_2max, and increases in O_2 delivery via hyperoxia promote increases in VO_2max and exercise tolerance.

Peripheral Limitations to VO_2max

Limitations to VO_2max may also exist in the periphery, within skeletal muscle. Saltin et al. (29) used a single-leg cycling protocol to examine central and peripheral adaptation to four weeks of different types of training. Results demonstrated that in response to sprint and endurance training, the trained leg expressed significant increases in VO_2max, and significant decrements in blood La^- and heart rate at submaximal work rates, compared to the untrained leg. The authors concluded that peripheral factors play as important a role in limiting exercise performance as central cardiovascular function. It is also regarded that substantial muscle La^-

accumulation during incremental exercise is associated with onset of volitional fatigue. Early reports from Welch's lab (11) stated that enhanced performance with hyperoxia may be due to a decreased anaerobiosis and a subsequent increase in oxidative metabolism. An enhanced carbon dioxide production (VCO_2) may represent greater oxidative ATP production, yet few studies (7,30) have demonstrated significant increases in VCO_2 in hyperoxia. Therefore, it is necessary to examine changes in VCO_2, ventilation, and blood La^- reported in previous research.

Differences in VCO_2, ventilation, and blood La^- from previous studies comparing exercise tolerance in normoxia and hyperoxia are shown in Table 3. Recent data (7) revealed a significantly higher VCO_2 at VO_2max in 30 $\%O_2$ in trained rowers completing incremental rowing, although the unique mode of exercise may explain this finding. In addition, VCO_2 was higher during submaximal cycle ergometry in 55 $\%O_2$ (30), although this result was observed in only ten subjects. Data from our laboratory in 20 healthy men (19) demonstrated no difference in maximal or submaximal VCO_2 when gas fractions ranging from 25-35 $\%O_2$ are inspired, although VCO_2 was higher ($p>0.05$) at VO_2max in hyperoxia. This makes sense, as a greater maximal power output in hyperoxia (19, 31-33) should foster a greater VCO_2 at VO_2max. It has been reported that hyperoxia greater than 60 $\%O_2$ abolishes peripheral chemoreceptor activity (11), thus blunting the ventilatory response. Nevertheless, the majority of previous research (3,5,14,19) reports similar ventilation at VO_2max in hyperoxia and normoxia. If maximal ventilation is similar, non-metabolic CO_2 production may also be similar, leading to no change in VCO_2 at VO_2max in hyperoxia.

Table 3. Alterations in Maximal VCO_2, Ventilation, and Blood La^- in Hyperoxia and Normoxia

Author (yr)	*VCO_2 (L/min)*	*Ventilation (L/min)*	*Blood La^- (mmol/L)*
Fagraeus (73)	4.5(0.2),4.4(0.3)[1,2]	117.6(6.5),134.1(7.5)	14.5(0.6),14.6(0.8)
Ekblom (75)	N/R[3]	139.9(5.4),157.3(7.3)	N/R
Welch (77)	3.1, 3.4	88.8, 107.6	6.1, 8.1
Buick (80)	N/R	78.9, 80.2	1.8, 2.2
Thomson (82)	N/R	137.6(31.4),129.3(29.2)	6.7(0.8),6.1(0.9)
Byrnes (84)	ND[4]	109.2(19.9),115.6(5.0)	9.4(3.5), 9.9(2.6)
Spriet (86)	N/R	N/R	4.7(0.3),12.2(1.7)
Powers (89)	5.8(0.4),5.4(0.2)	129.7(4.4),126.1(4.7)	N/R
Plet (92)	N/R	141.9(5.2),157.3(7.9)	9.3(0.9),10.6(1.1)
Knight (93)	N/R	161.7(4.1),161.4(4.8)	8.5(0.4), 9.5(0.5)
Peltonen (95)	N/R	174.5(18.0),181.8(19.1)	13.2(3.6),13.7(5.4)
Cardus (98)	N/R	95.0(12.0),110.0(6.0)	9.8(0.6), 10.5(0.4)

Central Nervous System Limitations to VO_2max

Previous research demonstrated alterations in catecholamine release with manipulation of F_IO_2. Augmented sympathetic activation has been identified as a mechanism to increase HR and blood flow at a given work rate in acute hypoxia (34). In response to submaximal cycle ergometry in room air and 100 $\%O_2$, a significant reduction in norepinephrine and epinephrine levels was shown after 10 and 15 min of exercise (35). However, during prolonged cycle ergometry at 67 $\%VO_2$max (36), no difference ($p>0.05$) in catecholamine concentration was evident between room air and 60 $\%O_2$, leading the authors to conclude that changes in metabolic or cardiorespiratory function were independent of catecholamines. Consequently, it is unlikely that sympathetic activity alters exercise tolerance in hyperoxia.

It is also plausible that enhanced motor unit recruitment may explain increased exercise tolerance in acute hyperoxia. A recent study (34) required six healthy men to perform forearm exercise and cycle ergometry to exhaustion at sea level and after one month of high altitude (5,050 m) acclimatization. During the altitude trial, 100 $\%O_2$ was administered to subjects prior to fatigue, and exercise ensued for an additional 3 min. During all trials, electrodes were placed on the right vastus lateralis to acquire electromyographic (EMG) data. Results

showed that integrated EMG significantly increased throughout the additional 3 min of exercise breathing 100 $\%O_2$, suggesting greater recruitment of inactive fibers during this bout. Nevertheless, these data were obtained in only six subjects, and the additional influence of chronic hypoxia on motor unit recruitment causes these data to be speculative. During incremental treadmill running in healthy men, Mateika et al. (37) reported no differences in root mean square EMG voltage in hypoxia, normoxia, and hyperoxia (66 $\%O_2$). It would be interesting to acquire EMG data from a large number of trained cyclists during incremental exercise in normoxia and hyperoxia to determine if motor unit recruitment is indeed greater under conditions of increased PO_2. This would allow researchers to identify another plausible limitation to exercise tolerance.

EFFECT OF HYPEROXIA ON OXIDATIVE METABOLISM

Past research regarding VCO_2 and ventilation (V_E) does not reveal whether oxidative metabolism is augmented in acute hyperoxia. Early work (38) indicated that glycogen depletion is similar during maximal exercise in normobaria and hyperbaria, a finding supported by a similar rate of glycogenolysis in normoxia and 60 $\%O_2$ (39). However, no change in glycogen breakdown in hyperoxia only infers that aerobic metabolism is similar under conditions of higher inspired PO_2. Eloquent research in *in situ* dog muscle (40) elucidated changes in mitochondrial redox state in normoxia and 100 $\%O_2$. At rest, the cytoplasmic NAD^+/NADH, estimated from lactate/pyruvate, was in a more oxidized state; whereas, during electrical stimulation no differences were observed between normoxia and hyperoxia. In addition, the mitochondrial redox potential, estimated from enzyme activities of the glutamate dehydrogenase system, was not different both at rest and during stimulation. The finding of a more oxidized redox potential in hyperoxia suggests a greater glycolytic rate at the initiation of exercise. This would not only foster greater pyruvate production and resultant flux through the citric acid cycle, but would also provide additional NADH for the electron transport chain. In contrast, work in humans completing maximal exercise in room air and 60 $\%O_2$ (41) revealed an improved maintenance of concentrations of ATP, ADP, and NADH relative to normoxia. This was also associated with reduced accumulation of IMP, La^-, creatine, and glucose-6-phospate relative to normoxia. This reduced perturbation of cellular homeostasis would promote lesser acidosis in hyperoxia, leading to a better maintenance of contractile function and thus improved exercise tolerance. However, these findings are based upon muscle data from only five subjects, so these results should be accepted with caution. Ultimately, it appears that cellular metabolism is regulated by O_2, and further research with greater statistical power is warranted to better investigate the contention that oxidative metabolism is augmented in hyperoxia.

EFFECT OF HYPEROXIA ON THE BLOOD LACTATE RESPONSE

To date, only two studies (1,17) have demonstrated a significantly lower blood La^- at VO_2max in hyperoxia. The former (1) involved the administration of hyperoxia via graded reinfusion of 3 U of blood, while the Plet et al. (17) study required men to complete cycle ergometry in normoxia and 55 $\%O_2$. However, these studies only used four and five subjects, so these data are speculative. In fact, they are in discord with previous data reporting no differences in maximal blood La^- in hyperoxia (Table 3). Previous research (31) not only indicated similar arterial La^- at VO_2max in normoxia (9.5±5 mmol/L) and 100 $\%O_2$ (8.5±0.4 mmol/L), but also documented similar La^- release, calculated from femoral venous flow and arteriovenous difference, in normoxia (23.7±4.2 mmol/min) and hyperoxia (20.1±3.3 mmol/min). In isolated dog muscle (42), La^- production was similar in normoxia (480.0±110.0 *u*mol/g) and 100 $\%O_2$ (390.0±60.0 *u*mol/g). Data from our laboratory (19) in 20 men reveal that maximal blood La^- obtained from a heated dorsal hand vein is not different at F_IO_2 equal to 0.25 relative to normoxia (Table 3). However, a trend ($p>0.05$) was shown for higher blood La^- in 30 and 35 $\%O_2$, which can be explained by the significantly higher power output in hyperoxia (347.7±57.6 and 349.2±62.8 Watts, respectively) versus normoxia (325.7±50.8 Watts). This makes sense, since the rate of glycolytic ATP production must be accelerated at the end of incremental exercise to meet the continually increasing ATP demand. This may be due to the greater recruitment of glycolytic, fast twitch motor units (type IIa and IIb) at near-maximal power outputs. Also, results in isolated dog mitochondria (43) demonstrated La^-

accumulation in fully aerobic muscle, refuting the claim that La^- is not produced in the presence of O_2. To further elucidate the mechanism by which hyperoxia alters the blood La^- response to incremental exercise, future research must address rate of La^- clearance and activity of lactate dehydrogenase and pyruvate dehydrogenase in hyperoxia to discern the mechanism by which hyperoxia alters the blood La^- response to incremental exercise.

Effect Of Hyperoxia On Blood Acid/Base Balance

Do the lack of differences in ventilation, VCO_2, pH, and La^- in hyperoxia represent maintenance of blood acid/base balance under conditions of increased PO_2? Past research examining blood acid/base balance in normoxia and hyperoxia is rather sparse (7,16,31,42). Early work (20) revealed similar values for maximal arterial pH in normoxia (7.23±0.02) and 60 $\%O_2$ (7.22±0.01) in response to maximal treadmill exercise. A similar lack of difference in maximal pH was also demonstrated in elite rowers (7), trained cyclists (31), and healthy, active men (19). However, in response to maximal cycle ergometry, arterialized venous pH in 55 $\%O_2$ (7.39±0.02) was significantly higher versus normoxia (7.35±0.01). Interestingly, in canine gastrocnemius muscle exercising to fatigue (42), arterial hydrogen ion concentration ($[H^+]_a$) was significantly higher in 100 $\%O_2$ (49.0±1.0 nmol/L) versus normoxia (42.0±2.0 nmol/L). Data from our laboratory (19) using incremental cycle ergometry and simultaneous sampling from a heated dorsal hand vein indicate that maximal pH is not different ($p>0.05$) in normoxia relative to inspired F_IO_2 equal to 0.25, 0.30, and 0.35 (Figure 3). Consequently, despite a higher maximal power output in hyperoxia, blood pH at VO_2max is similar to normoxia.

So, does the lack of differences in maximal pH in hyperoxia suggest that proton buffering is maintained in hyperoxia? Data from a recent study in our laboratory reveal no differences in maximal arterialized venous bicarbonate concentration ($[HCO_3^-]$) at VO_2max in hyperoxia. Similarly, recent research (7) reported comparable arterial $[HCO_3^-]$ at VO_2max in normoxia (15.0±1.0 mM) and 30 $\%O_2$ (16.0±0.0 mM) in trained rowers. In trained men (16), [HCO_3-] was similar at 91 $\%VO_2$max in normoxia and 60 $\%O_2$, although significant differences were revealed between hyperoxia and hypoxia. Hemoglobin also serves as a potent buffer of protons in skeletal muscle. In response to blood reinfusion, arterial hemoglobin concentration ([Hb]) is significantly higher compared to pre-infusion (1,14), yet no study to date administering hyperoxic gas fractions has demonstrated a similar effect. Therefore, it is likely that acute hyperoxia does not affect blood acid/base balance, leaving other parameters responsible for enhanced exercise tolerance.

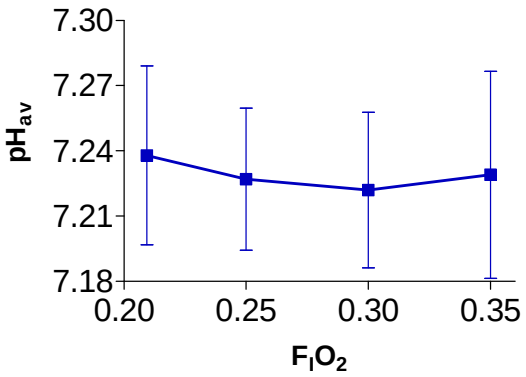

Figure 3. Changes in maximal pH decrement with increasing F_IO_2. Adapted from Astorino (19).

EFFECT OF HYPEROXIA ON PARTIAL PRESSURE OF OXYGEN

An increased arterial partial pressure of oxygen (P_aO_2) is a common result of acute hyperoxia. Several-fold increases in P_aO_2 with hyperoxia have been observed in trained rowers (7), elite cyclists (5,32), elite runners (3), healthy men (17,20,) and in dog muscle (42). In twenty recreationally active men, arterialized venous PO_2 from a heated dorsal hand vein was significantly higher in 25, 30, and 35 $\%O_2$ relative to normoxia (19). These data are shown in Figure 4a. In contrast, maximal P_aO_2 is not enhanced in response to blood reinfusion (1,14). So, does hyperoxia-mediated enhanced PO_2 remove peripheral limitations to VO_2max? Fick's Law of Diffusion states that oxygen uptake is equal to the product of a generalized diffusion conductance (DO_2) and the difference in partial pressure between the red blood cell ($P_{cap}O_2$) and muscle mitochondria ($P_{mt}O_2$). So, it is evident that a direct relationship exists between PO_2 and VO_2max, with alterations in PO_2 via acute hyperoxia causing a commensurate change in VO_2max.

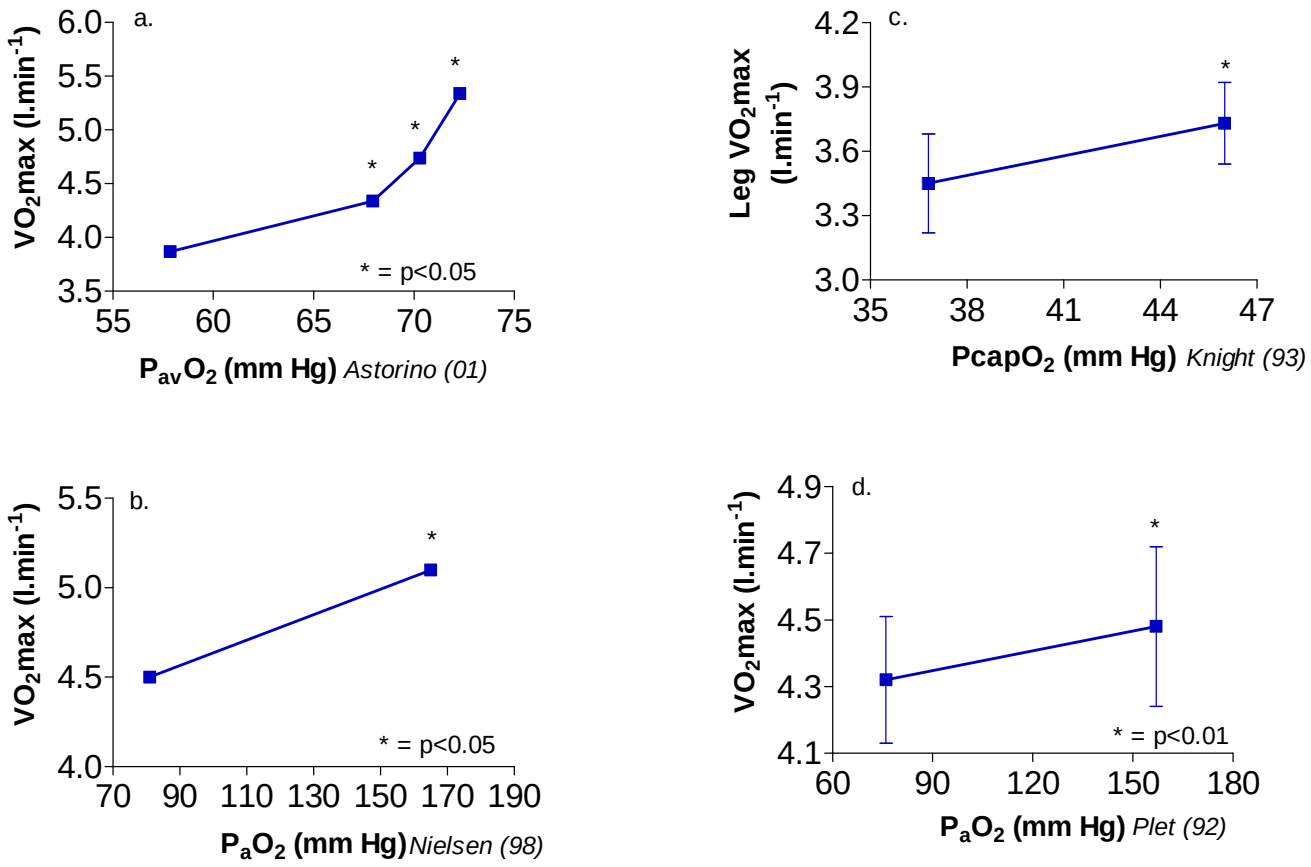

Figure 4a-4d. Relationships between VO_2max and PO_2 reported in previous literature

Eloquent work from Wagner's lab (32) using maximal single leg knee extension demonstrated significantly higher quadriceps VO_2 in 100 %O_2 (1.28±0.2 L/min) compared to normoxia (1.08±0.2 L/min), which was explained by significant increases in $P_{cap}O_2$ and myoglobin-associated PO_2 ($P_{Mb}O_2$). DO_2 was similar in hyperoxia (34.8±6.7 mmHg) and normoxia (38.1±8.5 mmHg). Figures 4b - 4d demonstrate a linear relationship between previously reported values for VO_2max and $P_aO_2/P_{cap}O_2$ in normoxia and hyperoxia. Overall, these data suggest that in hyperoxia, a greater gradient for diffusion of O_2 from the capillary to the muscle mitochondria enhances VO_2max.

EFFECT OF HYPEROXIA ON HIGH-ENERGY PHOSPHATES

Other peripheral factors involved in regulation of exercise tolerance include phosphocreatine (PCr) and inorganic phosphate (Pi). It is believed that fatigue incurred by short-term, intense exercise is due to depletion of PCr and resultant increases in Pi that impair the contractile apparatus (44). Concomitant with depletion of PCr is marked cellular perturbation resulting in La^- accumulation, glycogen degradation, and impending metabolic acidosis, leading to cessation of activity. Early work (38) demonstrated a trend toward greater depletion of PCr during submaximal exercise in normobaria versus hyperbaria; however, no differences were observed during maximal work. More recent investigation (45) using the submaximal plantar flexion exercise model revealed that muscle [PCr] is better maintained in 100 $\%O_2$ compared to normoxia and hypoxia. This suggests a lower rate of PCr degradation in response to increased PO_2. From muscle biopsy data in five healthy, active men (41), a smaller decrement in muscle [PCr] in response to maximal cycle ergometry in 60 $\%O_2$ (48 mmol/kg dm) versus normoxia (71 mmol/kg dm) was reported. Furthermore, ΔPi was lower in hyperoxia (41.6±11.3 mmol/kg dm) compared to normoxia (62.5±2.4 mmol/kg dm), and [ATP] was preserved in hyperoxia (22.9±0.6 to 21.7±1.2 mmol/kg dm) compared to a significant decrement ($p<0.05$) in normoxia (22.9±0.5 to 19.7±0.8 mmol/kg dm). Taken together, these data suggest that PCr hydrolysis may be attenuated in acute hyperoxia, resulting in a lower metabolic disturbance and thus enhanced exercise tolerance.

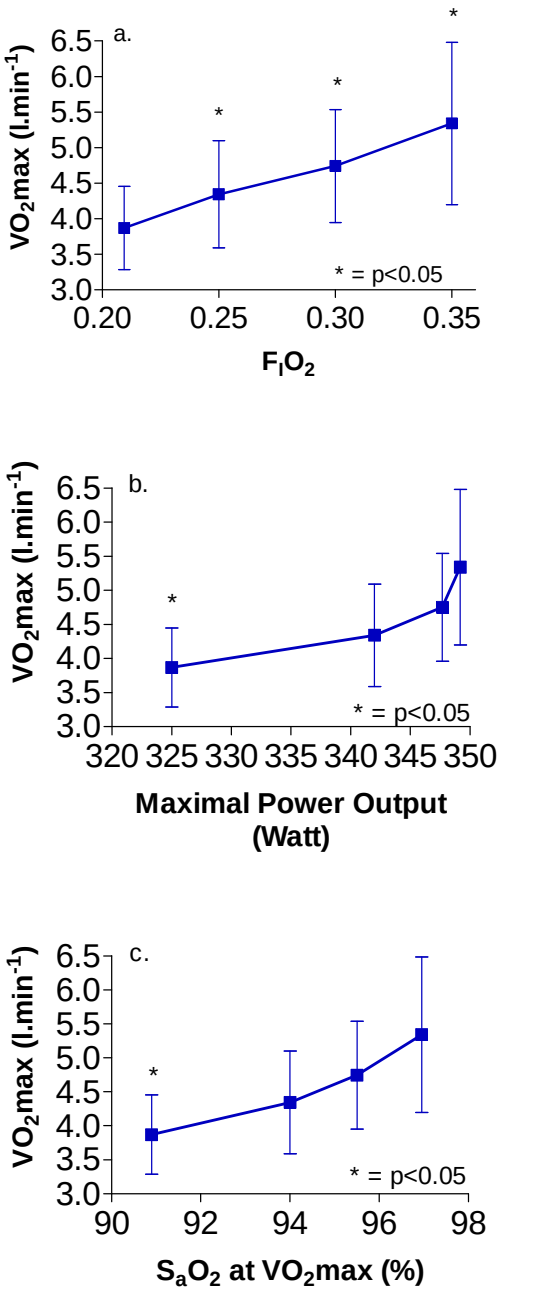

Figure 5. Changes in a) VO_2max in response to graded hyperoxia, and VO_2max versus the change in b) power output and c) S_aO_2 in response to graded hyperoxia.

ACCURACY OF GAS EXCHANGE DATA IN HYPEROXIA

Previous research (46,47) questioned the assumption that nitrogen is physiologically inert in hyperoxia, leading to erroneous values for VO_2. To investigate this, Welch and Pedersen (48) compared Douglas bag estimates of VO_2 to those from the Fick Equation and a third equation ($VO_2 = V_I - V_E - VCO_2$) in normoxia and 60 $\%O_2$. Results showed that compared to normoxia, the Douglas bag method overestimated VO_2 in hyperoxia, whereas the introduction of a mixing chamber resulted in no differences in VO_2 or VCO_2 among the three methods. The authors also recommended that specific precautions, including 10 min equilibration with the hyperoxic gas mixture combined with light exercise, be initiated to ensure that net nitrogen exchange is zero. In our laboratory, these guidelines were followed during research designed to investigate the magnitude of increase in VO_2max in response to 25, 30, and 35 $\%O_2$. Our data (19) are

presented in Figure 5a-c. Compared to normoxia, VO_2max was 12, 22, and 38 % higher with graded hyperoxia. However, the rate of change in VO_2 during incremental exercise in 30 and 35 %O_2 (~ 64 ml O_2/Watt/min) was markedly greater than the accepted value of 9-11 ml O_2/Watt/min. Our data demonstrating an overestimation of VO_2max in 30 and 35 %O_2 are shown in Figures 5b and 5c, indicating a relatively minor increase in both maximal power output and S_aO_2 fostered a dramatic increase in VO_2max in hyperoxia. During all testing, gas analyzers showed zero drift after each trial, and gas exchange data were consistently not different after calibration with 35 %O_2 relative to calibration with room air. However, an unidentified source of error led to this overestimation of VO_2max in 30 and 35 %O_2. It is our recommendation that gas exchange indirect calorimetry may not yield precise estimates of VO_2 in hyperoxia, and cardiac output and arteriovenous difference values should be used to determine oxygen uptake in hyperoxia.

SUMMARY

Hyperoxia has been widely used to examine changes in exercise performance, maximal cardiorespiratory capacity, and blood acid/base balance. It is now apparent that hyperoxia enhances exercise tolerance by partially removing central and peripheral limitations to exercise via increases in C_aO_2 and thus O_2 delivery, and P_aO_2. However, it remains to be clarified whether VO_2max in hyperoxia is limited by the central nervous system. Furthermore, it has been shown that hyperoxia promotes greater oxidative ATP provision during maximal exercise, although additional investigation is warranted to elucidate this contention. In addition, it is plausible that PCr hydrolysis during the metabolic transient is attenuated in hyperoxia, leading to less cellular disturbance at exercise onset. Researchers should take special precautions to confirm the precision of gas exchange data in hyperoxia. Lastly, acute hyperoxia does not alter maximal ventilation, pH, [HCO_3-], or VCO_2, so the increased VO_2max and exercise tolerance in hyperoxia must be due to factors other than improved acid/base balance.

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