

# Effects of hypercapnia and hyperoxia on metabolism during exercise

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## ABSTRACT

GRAHAM, T.E. and B.A. WILSON. Effects of hypercapnia and hyperoxia on metabolism during exercise. *Med. Sci. Sports Exerc.*, Vol. 15, No. 6, pp. 514-519, 1983. It has been postulated that the respiratory acidosis associated with hyperoxia (HO) may mediate some of the metabolic effects that are traditionally attributed to the elevation in  $Pao_2$ . Five subjects performed 30 min of steady-state exercise (65%  $\dot{V}O_{2\text{max}}$ ) on eight occasions while inspiring either 21 or 60%  $O_2$  in combination with 0, 2, 4, or 6%  $CO_2$ . Statistical significance was accepted if  $P < 0.05$ . The four HO tests were associated with increased  $\dot{V}O_2$  and lower R and blood lactate. However, when compared to the four normoxic tests, all of the hypercapnic (HC) conditions (independent of the inspired  $O_2$  percent) had statistically lower blood lactate. Hypercapnia was associated with lower R values and increased blood  $H^+$ . Regression analysis demonstrated relationships between  $H^+$  and R, as well as between  $H^+$  and blood lactate. These findings are independent of whether 21 or 60%  $O_2$  was inspired, and support the hypothesis that acidosis, not  $PO_2$ , mediates the effects related to HO.

BLOOD LACTATE, CARBON DIOXIDE, HYPEROXIA, FAT METABOLISM, ACID-BASE BALANCE

Increasing  $Pao_2$  inspiration of hyperoxic gas mixtures or hyperbaric air has been associated with increased whole-body  $\dot{V}O_2$  (when derived from pulmonary measures), decreased blood lactate concentration, and increased muscular performance (1,3,14,17,26-30). Several studies (24, 28,30) have questioned whether these effects are due directly to increased oxygen availability to exercising muscle. Direct cardiovascular measures have failed to show an increase in either whole-body (28) or muscle  $\dot{V}O_2$  (24,30); the latter studies found that muscle blood flow was reduced in proportion to the increase in arterial oxygen content. Thus, oxygen delivery was unaltered.

Recently, Adams and Welch (1) proposed that the acidosis observed during hyperoxia experiments, rather than the elevated  $PO_2$  itself, is the mediator of the "hyperoxic effect." Several studies (15,25) have demonstrated that altering acid-base balance can influence performance. Investigations using isolated muscle have shown that lactate

release is suppressed by acidosis (15,18), and lowering of intracellular pH is generally recognized as a negative modulator of glycolysis (22,23,25). During exercise, alkalosis has been associated with elevated blood lactate levels (8,25), and acidosis lowers the blood lactate (11, 12,21,25). The present study compared the effects of inspired hyperoxic and/or hypercapnic gases during exercise to investigate the effects of acid-base alterations on lactate metabolism.

## METHODS

Five subjects, one female and four males, volunteered for the study. After giving written informed consent, which clearly stated the nature and possible risks of the experiments, each subject completed a series of nine cycle ergometer (Monark) tests. The first test for each subject was a standard, progressive  $\dot{V}O_{2\text{max}}$  test. Subsequently, an exercise intensity requiring 65% of  $\dot{V}O_{2\text{max}}$  was established. The subjects then completed eight 30-min work tests at 65%  $\dot{V}O_{2\text{max}}$  while inspiring either 21 or 60%  $O_2$  in combination with 0, 2, 4, or 6%  $CO_2$  (balance nitrogen). The tests were assigned in a random-order, single-blind design, with at least 2 d between tests. The subjects reported to the laboratory after fasting overnight. Each subject breathed the test gas at rest for 10 min and then performed 30 min of exercise. The test gas was humidified, passed through a dry-gas meter (Parkinson-Cowan CD4), and made available for inspiration by the method described by Wilson et al. (29).

The subject inspired through a low-resistance, 60-cc dead-space Daniels valve and expired into a 8.5-l mixing box. The total pressure drops across the system on the inspired side were: 0.1, 1.8, and 6.0 cm  $H_2O$  at flow rates of 100, 200, and 400  $l \cdot min^{-1}$ , respectively, while corresponding pressure drops for the expired side were 0.1, 0.3, and 0.9 cm  $H_2O$ , respectively.

A Perkin-Elmer 1100 mass spectrometer was used for  $CO_2$  and  $O_2$  gas analysis. Throughout the experiment, one sampling channel collected gas from either the mixing

chamber (mixed expired gas) or the inspired gas line. The other sampling channel drew samples from either the Daniels valve (for end-tidal gas analysis) or from calibration tanks (previously analyzed by using the micro-Scholander technique). The procedure followed during the 30 min of exercise was as follows: calibration gases and inspired gas were sampled during the first minute; end-tidal gases were monitored from the second to the fourth minutes; and mixed expired O<sub>2</sub> and CO<sub>2</sub> concentrations were determined during the fifth minute. This sequence was repeated six times during the exercise bout. In addition, inspired and expired gases were also analyzed by using the micro-Scholander technique for the hyperoxic and normoxic experiments. Furthermore,  $\dot{V}O_2$  was calculated via the Haldane and Fick equations which, as described in previous studies (27,29), support the accuracy of volume measures and substantiate that there was not significant room air contamination of either the inspired or expired gases.

Heart rate and inspired volume, along with the various O<sub>2</sub> and CO<sub>2</sub> concentrations described previously, were monitored continuously and were recorded on an 8-channel recorder (Hewlett-Packard 7888A.) Standard calculations of  $\dot{V}O_2$  and  $\dot{V}CO_2$ , and R were performed on these data for each 5-min exercise period and the values were averaged. It has been demonstrated that the Haldane transformation equation for  $\dot{V}O_2$  can be used with hyperoxic inspirates, although care must be taken if bag-collection systems are used (1,27).

A 21-gauge butterfly catheter (Travenol) was placed in a superficial, dorsal hand vein before the subject began breathing the test gas. Blood samples were taken at rest and every 5 min during the exercise. The catheter was kept patent throughout the experiment with a continuous infusion of sterile, normal saline. The hand was wrapped in a heating pad (approximately 43°C) to obtain arterialized samples. Anaerobic blood samples were obtained by occluding the saline flow, discarding the saline filling the dead space of the catheter, and subsequently collecting 2–4 ml blood in a glass syringe. Two hundred  $\mu$ l of the sample were transferred to 2 ml of chilled 0.33 M HClO<sub>4</sub> and used for lactate determination (4). This deproteinized sample was chilled until the completion of the experiment. The remaining blood sample was chilled in ice water immediately. Following the experiment, these samples were analyzed in duplicate for pH, PO<sub>2</sub>, and PCO<sub>2</sub> (Instrumentation Laboratory, model 213), and the hydrogen ion concentration (H<sup>+</sup>) was calculated from the pH. Forster et al. (9) have demonstrated that the arterialized venous technique gives pH and PCO<sub>2</sub> values that closely approximate arterial levels. A body temperature of 37.0° was assumed; exercise of similar intensity and duration to that used in the present study produces less than a 1°C increase in body temperature and is not affected by hypercapnia (7,19). We did not attempt to correct our measurements for such temperature effects. Plasma bicarbon-

ate was calculated by incorporating the PaCO<sub>2</sub> and pH data into the Henderson-Hasselbalch equation. To evaluate the consistency of the steady-state situation, the coefficient of variation was calculated for each measurement for each subject in every test. The mean values of all subjects for blood PaCO<sub>2</sub>, H<sup>+</sup>, HCO<sub>3</sub><sup>-</sup>, pulmonary  $\dot{V}I$ ,  $\dot{V}O_2$ ,  $\dot{V}CO_2$ , R, and HR for each test gas were analyzed by repeated-measures two-way analysis of variance and Duncan's multiple-range test. In addition, blood lactate and R vs H<sup>+</sup> were compared by linear and curvilinear regression analysis. A value of  $P < 0.05$  was selected as the significance level for all comparisons.

## RESULTS

The subjects ranged in  $\dot{V}O_{2\text{max}}$  from 42.5–65.2  $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ . The mean  $\dot{V}O_2$  for the 30-min exercise bouts was significantly higher on the hyperoxic gas, averaging 71.7%  $\dot{V}O_{2\text{max}}$  compared to 66.9%  $\dot{V}O_{2\text{max}}$  for normoxia. Mean values for the parameters collected are given in Tables 1 and 2. The mean coefficients of variation for the parameters were all less than 5%, with the exception of blood lactate. This measure had values ranging from 12–32% for the various gas treatments.

The  $\dot{V}CO_2$  showed no significant difference for any of the conditions. The  $\dot{V}I$  and PaCO<sub>2</sub> were significantly elevated for each increase in FICO<sub>2</sub> for both normoxia and hyperoxia. The  $\dot{V}I$  was also significantly lower for hyperoxia as compared to normoxia. When the two 0% FICO<sub>2</sub> conditions were compared, the PaCO<sub>2</sub> was significantly greater when hyperoxic gas was inspired. The H<sup>+</sup> con-

TABLE 1. Mean heart rate and respiratory data for all subjects.\*

Parameter	%O <sub>2</sub>	%CO <sub>2</sub>				
		0%	2%	4%	6%	
$\dot{V}I(\text{l} \cdot \text{min}^{-1}\text{BTPS})$	21%	$\bar{x}$	67.5	81.2	101.6	115.9
		SD	14.2	13.3	11.2	8.0
	60%	$\bar{x}$	62.8	77.1	99.4	109.5
		SD	8.3	11.0	11.8	9.2
	21%	$\bar{x}$	2.39	2.34	2.35	2.39
		SD	0.48	0.46	0.40	0.46
$\dot{V}O_2(\text{l} \cdot \text{min}^{-1}\text{STPD})$	21%	$\bar{x}$	2.49	2.56	2.55	2.55
		SD	0.60	0.58	0.62	0.72
	60%	$\bar{x}$	2.24	2.14	2.13	2.05
		SD	0.41	0.49	0.31	0.23
	21%	$\bar{x}$	2.24	2.19	2.13	2.04
		SD	0.45	0.46	0.37	0.39
R	21%	$\bar{x}$	0.94	0.90	0.91	0.87
		SD	0.03	0.04	0.06	0.09
	60%	$\bar{x}$	0.91	0.85	0.85	0.81
		SD	0.06	0.02	0.11	0.08
	21%	$\bar{x}$	156	154	158	164
		SD	12.5	12.3	13.3	12.7
HR (beats · min <sup>-1</sup> )	60%	$\bar{x}$	151	149	156	158
		SD	15.1	17.6	14.4	15.8

\*For a single experiment the six values (at 5, 10, 15, 20, 25, and 30 min) were averaged. The mean values presented here are based on the average values for the five subjects.

TABLE 2. Mean blood lactate and acid-base related data for all subjects.\*

Parameter	%O <sub>2</sub>	%CO <sub>2</sub>			
		0%	2%	4%	6%
La(mM)	21%	X̄ 3.95	2.24	2.17	2.33
		SD 1.38	1.37	1.24	1.18
	60%	X̄ 3.17	2.48	2.43	1.97
		SD 1.26	0.89	0.93	1.26
PaCO <sub>2</sub> (mmHg)	21%	X̄ 33.7	38.6	44.0	51.7
		SD 2.1	3.0	2.1	2.2
	60%	X̄ 35.5	39.5	44.1	50.8
		SD 2.3	2.0	2.4	1.2
HCO <sub>3</sub> <sup>-</sup> (mM)	21%	X̄ 18.4	20.0	20.8	20.9
		SD 1.8	1.7	1.3	1.5
	60%	X̄ 19.0	19.9	19.9	20.4
		SD 1.4	0.8	0.8	1.1
H <sup>+</sup> (nM)	21%	X̄ 43.4	45.0	50.9	58.6
		SD 2.1	2.3	1.2	3.7
	60%	X̄ 44.9	47.5	53.0	60.0
		SD 1.5	2.2	1.3	2.7

\*For a single experiment the six values (at 5, 10, 15, 20, 25, and 30 min) were averaged. The mean values presented here are based on the average values for the five subjects.

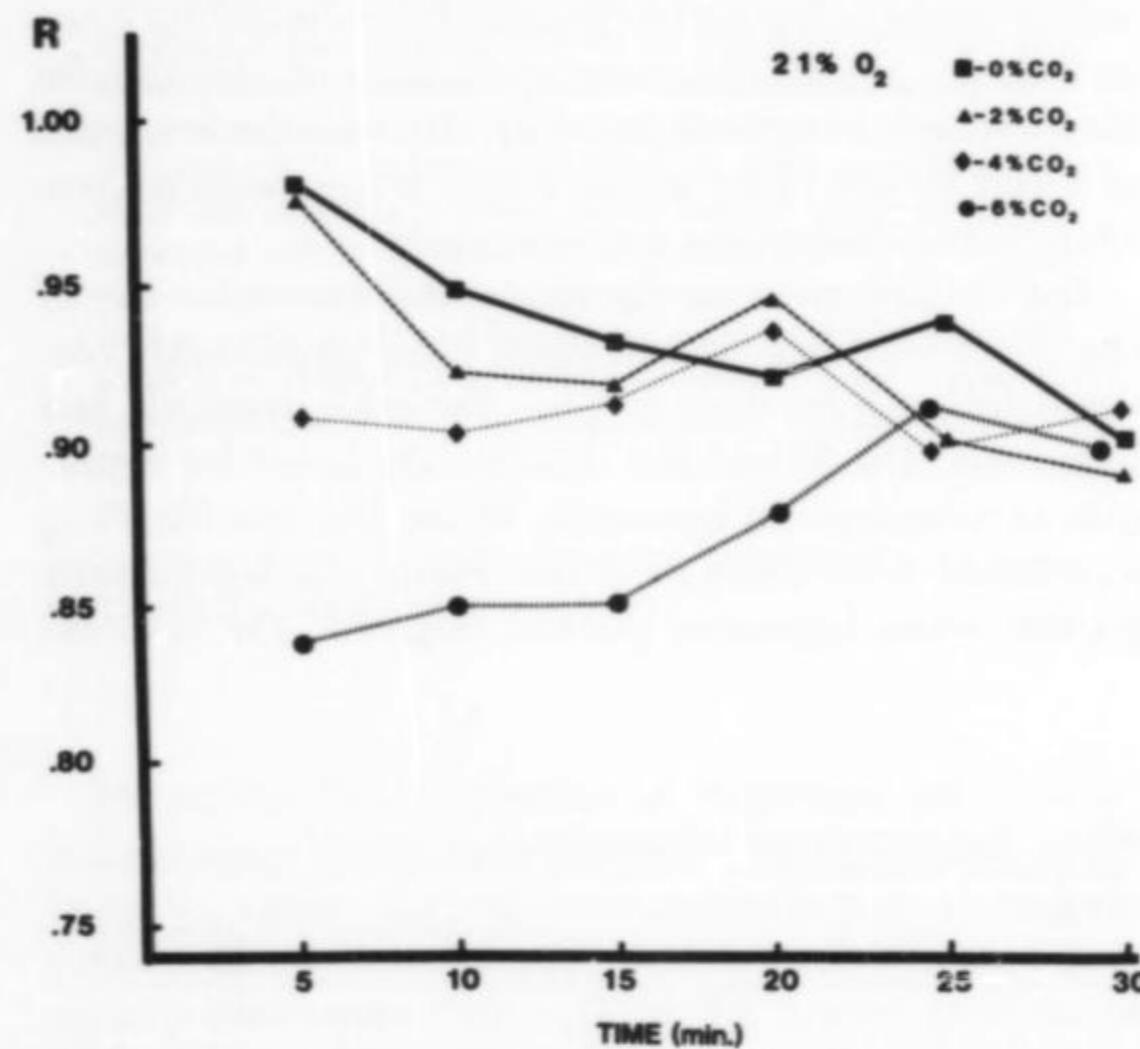


Figure 1—The time course for the mean R data during inspiration of normoxic gases. Each point represents the mean for the five subjects for a given time sample.

centration was significantly greater with hyperoxia and also increased significantly with increasing F<sub>i</sub>CO<sub>2</sub> with the exception of a comparison between 0% and 2% F<sub>i</sub>CO<sub>2</sub> within the normoxic treatments. The mean H<sup>+</sup> for 21% O<sub>2</sub> and 0% CO<sub>2</sub> corresponded to a pH of 7.36, while the 60% O<sub>2</sub> and 6% CO<sub>2</sub> values corresponded to a pH of 7.22.

The R data (Figures 1 and 2) and heart rate were significantly lower with hyperoxia and also significantly different between 0% and 6% CO<sub>2</sub>. Regression analysis between R and H<sup>+</sup> demonstrated a significant, inverse, linear relationship ( $r=0.75$ ) (Figure 3).

Blood lactate levels (Figures 4 and 5) were significantly

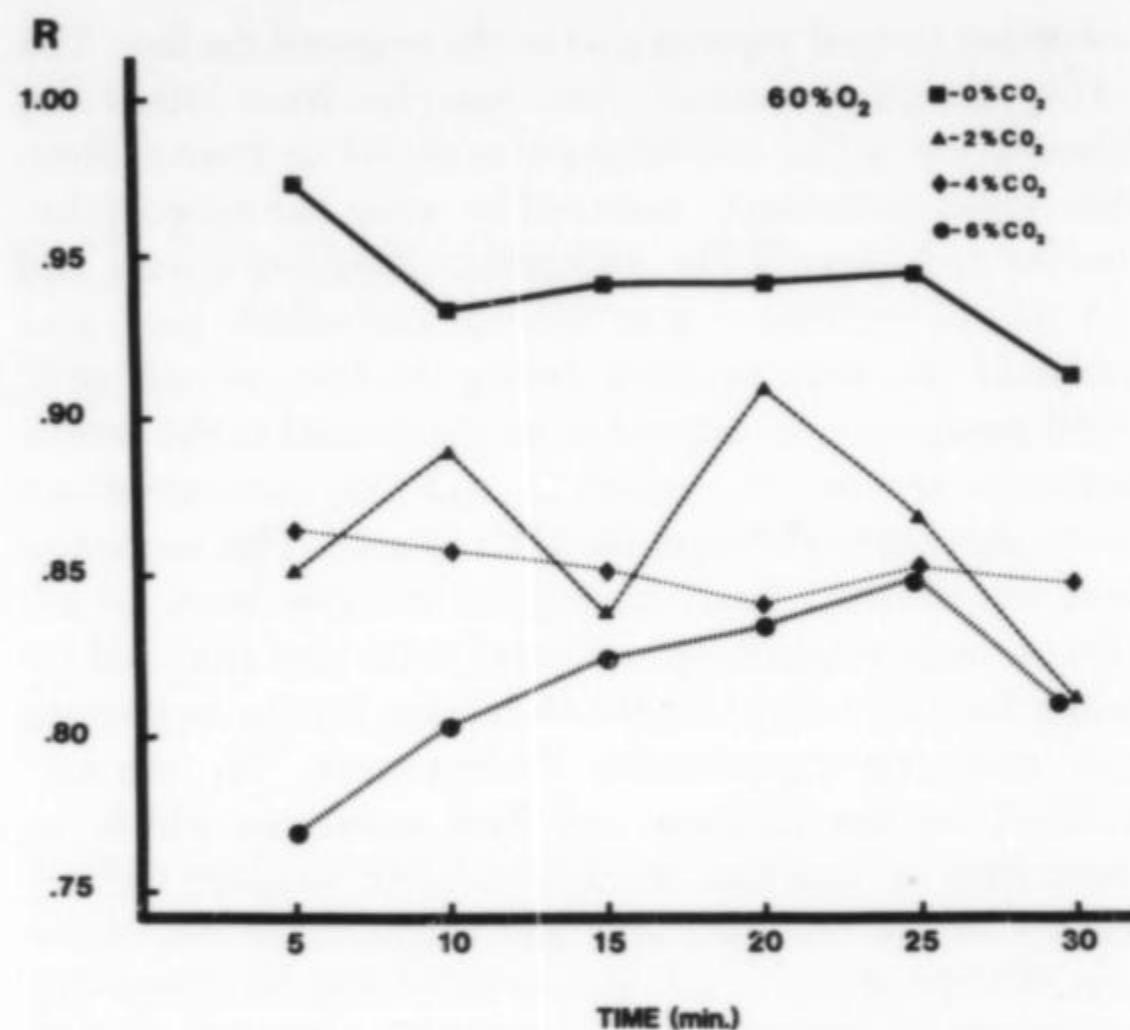


Figure 2—The time course for the mean R data during inspiration of hyperoxic gases.

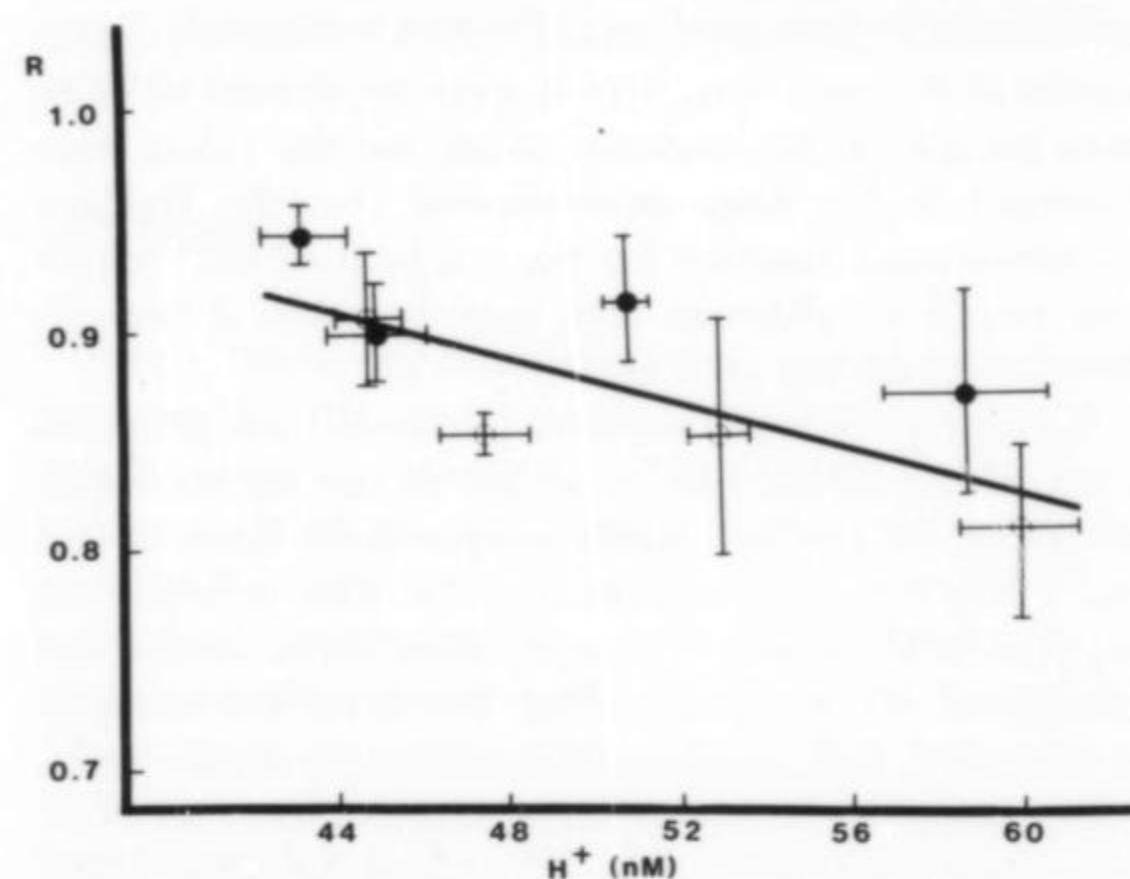


Figure 3—The relationship between H<sup>+</sup> and R. Each point represents the mean data for all five subjects for a given experimental condition. The vertical and horizontal lines represent the standard error. The solid circles represent the normoxic treatments and the open circles represent the hyperoxic state. The solid line represents the regression equation  $y = 1.13 - 0.005x$ .

lower for hyperoxia vs normoxia, but only for the 0% CO<sub>2</sub> condition. When all treatments were compared there was no evidence of a hyperoxic effect, but blood lactate was significantly lower when 2, 4, and 6% CO<sub>2</sub> were inspired. When the data for individual subjects were expressed as a percent of their lactate values for the 0% CO<sub>2</sub> normoxia test, the lactate decreased to approximately half of the control value (Figure 6) and displayed a significant, curvilinear relationship ( $r=0.69$ ) with H<sup>+</sup>. Individual subjects decreased to as little as 20% of the control value with some of the test gases.

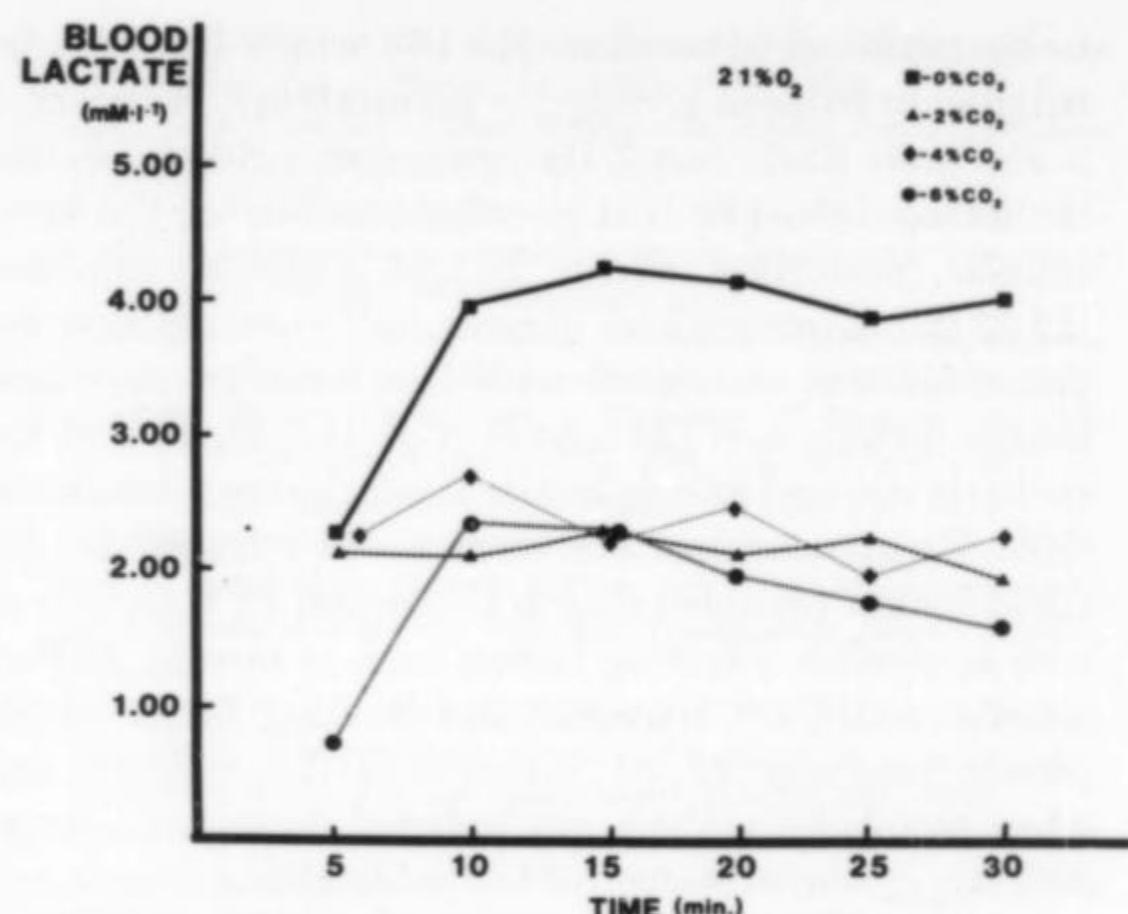


Figure 4—The time course for the mean lactate data during inspiration of the normoxic gases.

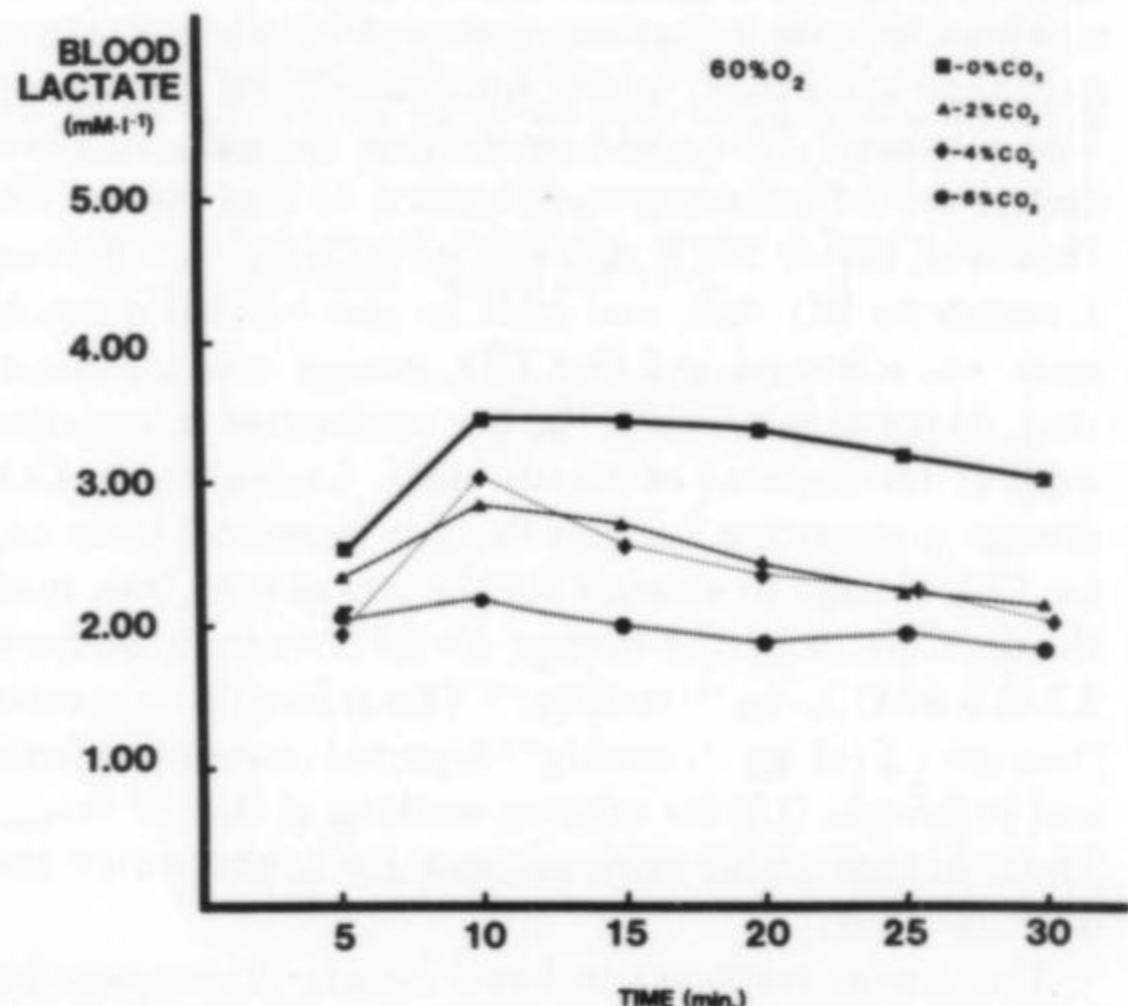


Figure 5—The time course for the mean lactate data during inspiration of the hyperoxic gases.

## DISCUSSION

The subjects were able to complete all exercise bouts regardless of the inspired gas condition. Thus, the hypercapnia did not limit the performance at 65%  $\dot{V}O_{2\max}$ . Furthermore, the low coefficients of variation for measurements such as  $\dot{V}O_2$ , HR,  $H^+$ , R, and  $PaCO_2$  indicate the consistency of the steady-state over the 30 min of exercise. Therefore, the experimental protocol presents a situation in which one can use parameters such as R, blood lactate,  $PaCO_2$ , and  $\dot{V}CO_2$  with a certain degree of confi-

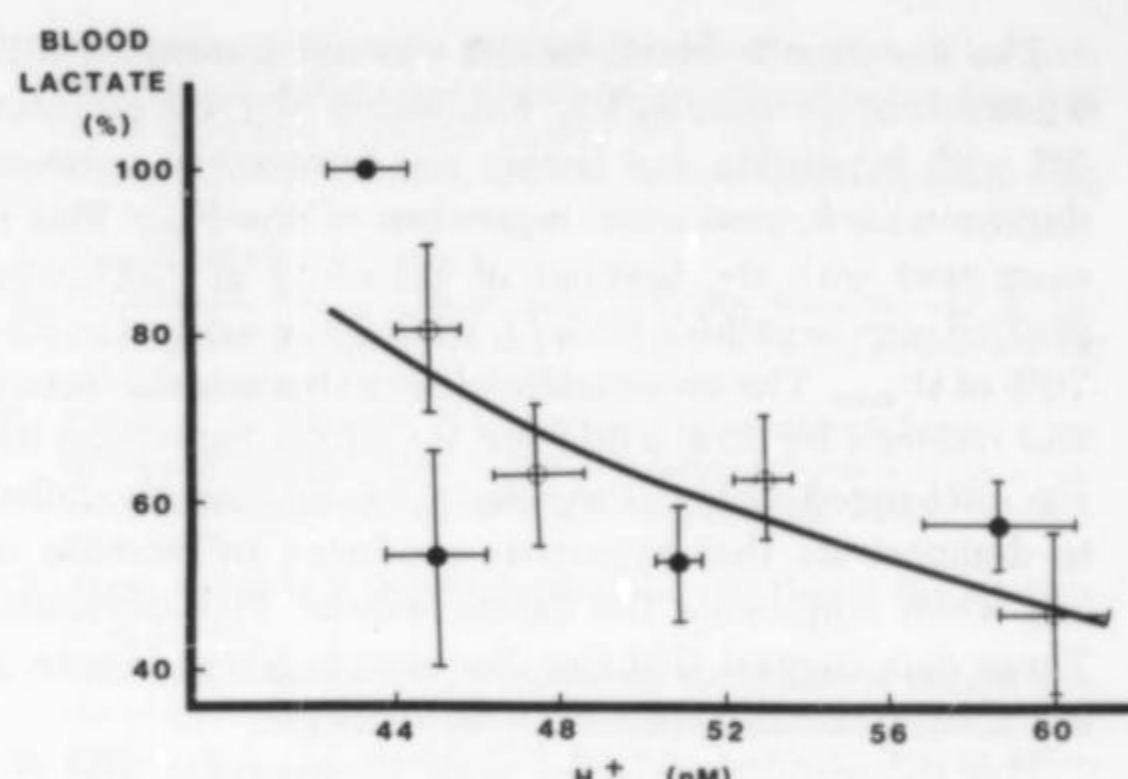


Figure 6—The relationship between the change in mean lactate (as a percent of the data for 21% O<sub>2</sub>, 0% CO<sub>2</sub>) and H<sup>+</sup>. The figure is organized the same as Figure 3. The solid line represents the equation  $y = 435.5 - 94.7 \ln x$ .

dence to examine metabolism and CO<sub>2</sub> storage (12).

The present study agrees with previous reports (7, 11, 12, 19, 21) with regard to hypercapnia increasing  $\dot{V}I$ , HR,  $PaCO_2$ , and  $H^+$  while lowering R and blood lactate. Relative to the control condition (21% O<sub>2</sub>, 0% CO<sub>2</sub>) the hyperoxic treatments resulted in decreases in ventilation, heart rate, and blood lactate as well as an increase in pulmonary  $\dot{V}O_2$  in agreement with previous investigations (1, 3, 14, 26). However, when the four hyperoxic treatments were compared to the four normoxic conditions, there was no significant effect on blood lactate. This supports the hypothesis of Adams and Welch (1) that hyperoxic effects are not mediated directly by  $PaO_2$ . An apparent contradiction to this conclusion is the data for the 0% CO<sub>2</sub> conditions, where hyperoxia resulted in a significantly lower lactate than that for normoxia. Nevertheless, in agreement with the overall findings, this decrease in lactate was associated with significant increases in  $PaCO_2$  and  $H^+$  during the experiments. This is further supported by the relationship between  $H^+$  and blood lactate across all eight conditions. Nevertheless, the relatively-low correlation coefficient ( $r=0.69$ ) implies that the relationship is complex and probably multifactorial.

One likely cause for the variability in the relationship is that if hydrogen ion is a prime mediator of the effect, it would be the intracellular, not extracellular, concentration that would be critical (1). There was approximately a 40% difference in  $H^+$  across the various treatments but it is unknown how much of a difference there was in intracellular concentration. Not only is it difficult to predict the magnitude of shift in intracellular pH of active muscle in response to the respiratory acidosis, but it is also likely that the rate of intramuscular metabolic acid production is not constant in the various conditions. Thus, it is not possible to predict the intramuscular pH.

The decrease in blood lactate was not associated with a consistent increase in  $\dot{V}O_2$ . Pulmonary  $\dot{V}O_2$  was elevated 5% with hyperoxia, but lactate was lowered to a similar degree with hypercapnia regardless of the  $FIO_2$ . This is consistent with the findings of Welch et al. (28), who studied men breathing 60% O<sub>2</sub> while they worked at 55–70% of  $\dot{V}O_{2\text{max}}$ . The investigators found that arterial lactate was reduced by 35% while the  $\dot{V}O_2$  of the exercising leg was unchanged. Other researchers (24,30) have also failed to demonstrate that hyperoxia produces an increase in  $\dot{V}O_2$  when employing the cardiovascular Fick equation. These data suggest that the decrease in blood lactate is not always causally related to  $\dot{V}O_2$  changes.

The increased ventilation with hypercapnia and the possibility of enhanced fat metabolism would lead one to anticipate an increase in  $\dot{V}O_2$  in both hypercapnia and hyperoxia. This was not observed in all cases; however, the respiratory acidosis complicates the situation. Cain (6) reported that the oxygen cost of ventilation was directly dependent on pH. According to his data (for anesthetized dogs, passively ventilated), there would be no increase in  $\dot{V}O_2$  if the H<sup>+</sup> was above 44 nM. In the present study most subjects exceeded this concentration. Harken (13) reported a direct linear relationship between resting  $\dot{V}O_2$  of canine skeletal muscle and pH. He found that  $\dot{V}O_2$  decreased 10% for a pH decrease of 0.1 units. According to his data, the mean pH in the present study for a 6% CO<sub>2</sub> and 60% O<sub>2</sub> (pH 7.22) would have a  $\dot{V}O_2$  of 80% of that used at pH 7.4. While one must apply the findings of animal models, such as those of Harken and Cain, to humans with some degree of caution, their findings suggest that the factors contributing to pulmonary  $\dot{V}O_2$  could be altered by the various gas treatments. Alterations in the oxygen cost of breathing or increased  $\dot{V}O_2$  due to fat metabolism could be masked by metabolic changes resulting from acidosis.

The interpretation of blood lactate is complex. It must be appreciated that it is the dynamic integration of lactate release from many tissues ranging from skeletal muscle to bone and lactate uptake by other tissues (predominantly liver, kidney, and slow-twitch muscle). The rate of uptake is proportional to arterial concentration (2,20), so increased lactate uptake, when blood lactate is low, appears unlikely. Thus, the low level probably results from either inhibited glycolytic production and/or reduced membrane permeability (and subsequently, increased lactate storage).

The rate of lactate release from muscle has been shown

to be inhibited by acidosis (15,18), which has been attributed to reduced membrane permeability. However, it is also quite likely that if the respiratory acidosis lowered the intracellular pH, that glycolysis, and hence the intracellular production rate of lactate, could be inhibited (22,23,25). Gimenez and Florenz (10) reported that hypercapnia was associated with low levels of exercising muscle lactate, and Linnarsson et al. (17) found that hyperbaria reduced muscle lactate levels during submaximal (50%  $\dot{V}O_{2\text{max}}$ ) exercise. The decrease in intracellular pH could inhibit phosphorylase b kinase and PFK activity as well as possibly affecting factors such as myosin ATPase activity and Ca<sup>2+</sup> transport and binding in the sarcoplasmic reticulum (22,23). Sutton et al. (24) reported that when metabolic acidosis was induced during exercise at 66%  $\dot{V}O_{2\text{max}}$ , the subjects had lower blood and muscle lactate levels. The relative concentrations of a variety of muscle glycolytic intermediates suggested that the glycolytic flux was inhibited at a level of above glucose 6-phosphate. Thus, a reduced rate of glycolysis is a distinct possibility.

This evidence is further supported by the respiratory exchange ratio data, which implies that fat production was enhanced. This could result from the reduced blood lactate level facilitating mobilization of free fatty acids. However, before the R data can be accepted as reflecting a metabolic RQ shift, one must be assured that a steady state was achieved and that CO<sub>2</sub> storage was not occurring. As noted previously, the low coefficients of variation support the concept of steady state. Undoubtedly, CO<sub>2</sub> storage is occurring because PaCO<sub>2</sub> is increased; however, for CO<sub>2</sub> storage to account for the increase in  $\dot{V}CO_2$  (and the decrease in R), the storage would have to range from 4.5–5.6 ml CO<sub>2</sub>·kg<sup>-1</sup>·mmHg<sup>-1</sup>. This is four times greater than the 1.2 ml·kg<sup>-1</sup>·mmHg<sup>-1</sup> reported recently by Jones and Jurkowski (16) for subjects working at 60% of  $\dot{V}O_{2\text{max}}$ . Thus, storage could only account for a portion of the decrease in R.

The similar responses in blood lactate suppression for hyperoxia and for hypercapnia, together with the relationship between H<sup>+</sup> and lactate, support the hypothesis of Adams and Welch (1) that the effects of hyperoxia are mediated by acid-base shifts rather than by PO<sub>2</sub> directly. Further investigation is required to prove the hypothesis.

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