Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise

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Stringer, William, Karlman Wasserman, Richard Casaburi, János Pórszász, Kazuhira Maehara, and William French. Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. *J. Appl. Physiol.* 76(4): 1462–1467, 1994.—The slow rise in O_2 uptake ($\dot{V}O_2$), which has been shown to be linearly correlated with the increase in lactate concentration during heavy constant work rate exercise, led us to investigate the role of H^+ from lactic acid in facilitating oxyhemoglobin (O_2Hb) dissociation. We measured femoral venous P_{O_2}, O_2Hb saturation, pH, P_{CO_2}, lactate, and standard HCO_3^- during increasing work rate and two constant work rate cycle ergometer exercise tests [below and above the lactic acidosis threshold (LAT)] in two groups of five healthy subjects. Mean end-exercise femoral vein blood and $\dot{V}O_2$ values for the below- and above-LAT square waves and the increasing work rate protocol were, respectively, P_{O_2} of 19.8 ± 2.1 (SD), 18.8 ± 4.7, and 19.8 ± 3.3 Torr; O_2 saturation of 22.5 ± 4.1, 13.8 ± 4.2, and 18.5 ± 6.3%; pH of 7.26 ± 0.01, 7.02 ± 0.11, and 7.09 ± 0.07; lactate of 1.9 ± 0.9, 11.0 ± 3.8, and 8.3 ± 2.9 mmol/l; and $\dot{V}O_2$ of 1.77 ± 0.24, 3.36 ± 0.4, and 3.91 ± 0.68 l/min. End-exercise femoral vein P_{O_2} did not differ statistically for the three protocols, whereas O_2Hb saturation continued to decrease for work rates above LAT. We conclude that decreasing capillary P_{O_2} accounted for most of the O_2Hb dissociation during below-LAT exercise and that acidification of muscle capillary blood due to lactic acidosis accounted for virtually all of the O_2Hb dissociation above LAT.

femoral vein; oxygen pressure; pH; partial pressure of carbon dioxide; lactate; standard bicarbonate; constant work rate exercise; increasing work rate exercise

AFTER THE ONSET of constant work rate (CWR) exercise, O_2 uptake ($\dot{V}O_2$) reaches a constant value by 3 min if the work rate does not induce a lactic acidosis (9, 10, 14, 16, 19, 30). However, if the exercise is performed at a level that induces a lactic acidosis, $\dot{V}O_2$ continues to increase past 3 min of exercise (6, 19, 22, 30) and the rate of rise in $\dot{V}O_2$ after 3 min correlates linearly with the increase in lactate (6, 8, 15, 22, 32). This finding led us to hypothesize that lactic acid production might be important in facilitating oxyhemoglobin (O_2Hb) dissociation (Bohr effect) when capillary P_{O_2} reached a minimum value.

The initiating event in this mechanism would be the fall in capillary P_{O_2} to a critically low value when O_2 demand exceeded O_2 supply in the muscle during heavy exercise. Wittenberg and Wittenberg (31) postulated that the "critical" capillary P_{O_2} is between 15 and 20 Torr. Below this value, adequate transport of O_2 cannot occur because of physical factors that limit diffusion between the red blood cell and the sarcoplasm of metabolically active muscle. Therefore, net lactate accumulation should occur in the exercising muscle (4, 13, 23, 24). The newly formed lactic acid (acidic dissociation constant = 3.8) must be virtually completely buffered in the cell on formation because it is >99.9% dissociated at cellular pH. Because HCO_3^- is the predominant buffer of lactic acid (1, 28), CO_2 is released from the cell in excess of that formed from aerobic metabolism. Simultaneously, there is exchange of HCO_3^- for lactate between the cell and the extracellular fluid, resulting in a decrease in blood HCO_3^-. Both the increase in CO_2 production over that from aerobic metabolism and the decrease in extracellular HCO_3^- acidify the blood, causing a downward and rightward shift in the O_2Hb dissociation curve and allowing continued O_2Hb dissociation during heavy exercise.

The objectives of this study were to determine *1)* whether end-capillary P_{O_2} as approximated by femoral venous P_{O_2} reaches a minimum (critical) value before femoral vein lactate begins to increase and *2)* whether the primary mechanism for O_2Hb dissociation changes from one of decreasing P_{O_2} during moderate exercise to one of decreasing pH during heavy work rate exercise.

METHODS

Subjects

After institutionally approved informed consent was obtained, five healthy nonsmoking male subjects participated in an increasing work rate protocol and five different healthy nonsmoking male subjects participated in two CWR exercise protocols. Before the study day, each participant performed a preliminary increasing work rate exercise test on an electromagnetically braked cycle ergometer (Godart, DeBilt, The Netherlands) to establish his exercise capacity, lactic acidosis threshold (LAT; by the V-slope method) (2), and maximal $\dot{V}O_2$ ($\dot{V}O_{2\,max}$; $\dot{V}O_2$ averaged over last 30 s of exercise).

Catheter Placement

On the day of testing, the subjects reported to the exercise laboratory after consuming a light meal with no caffeinated beverages. The right groin was shaved, cleaned, and anesthetized with lidocaine. Under sterile conditions, a 10-cm 8-Fr sheath (Cordis, Miami, FL) was inserted percutaneously into the right femoral vein at 2 cm below the inguinal ligament using the Seldinger technique. The sheath was secured with a single suture, and the catheter tip was positioned ~4 cm above the inguinal ligament. The catheter was attached to an infusion apparatus (ContinuFlo, Baxter Healthcare, Deerfield, IL) that provided a slow continuous flow (15 ml/h) of heparinized normal saline (1,000 U heparin/l) and facilitated periodic bolus flushing of the catheter.

During the progressive increasing work rate protocol, a brachial artery catheter was placed before exercise using the Seldinger technique and was flushed in the same way as the femoral vein catheter described above.

Exercise Protocols

Increasing work rate test. Five subjects performed increasing (25–40 W/min) work rate exercise to maximum tolerance.

Heart rate and gas exchange measurements were made continuously during the 3 min of rest, 3 min of unloaded cycling, and increasing work rate exercise to exhaustion.

CWR tests. Five subjects performed 6-min CWR exercise tests at two different exercise intensities (in randomly selected sequence) separated by a 2-h rest period. One CWR test was performed at an exercise intensity equivalent to 80% of LAT $\dot{V}O_2$ determined from the screening increasing work rate exercise test ("moderate"). The other test was performed at an exercise intensity of LAT $\dot{V}O_2$ plus 75% of the $\dot{V}O_2$ difference between LAT and $\dot{V}O_{2\,max}$ ("very heavy"). Heart rate, ventilation, and gas exchange measurements were made continuously during 3 min of rest and 6 min of exercise.

Respired gas analysis. The subjects respired through a mouthpiece. Expired air was directed to a Fleisch-type no. 3 pneumotachograph via a breathing valve (100 ml dead space). Respired O_2, CO_2, and N_2 partial pressures at the mouthpiece were continuously measured by mass spectrometry (model MGA-1100, Perkin-Elmer, Pomona, CA). Minute ventilation (BTPS) and $\dot{V}O_2$ and CO_2 production (both at STPD) were calculated as whole breath averages for each 30-s exercise period.

Blood Sampling

Increasing work rate test. Blood was sampled from the femoral vein and brachial artery at rest, during unloaded cycling, and during each minute of increasing work rate exercise.

CWR tests. During CWR exercise tests, blood was sampled from the femoral vein at rest, every 5 s during the first 120 s of exercise [using a computer-driven anaerobic collector with a time correction for the dead space of the catheter, as previously described (7)], and every 30 s thereafter until the end of exercise. During manual blood sampling, ~1.5 ml of blood were withdrawn from the catheter before each sample to ensure clearance of saline from the catheter.

Blood Analysis

The blood samples were agitated and immediately chilled in an ice slurry. Blood gas analysis was performed with a blood gas machine (model 1306, Instrumentation Laboratory, Lexington, MA) and a CO-oximeter (model 482, Instrumentation Laboratory). The samples from each exercise study were analyzed on the same blood gas machine. The blood gas machines underwent a one-point calibration after each sample and a full calibration with acid, alkaline, and normal standards each study day. In addition, tonometered blood samples with low P_{O_2} (20 Torr) were analyzed before the study to verify machine accuracy. The standard HCO_3^- values were calculated with an equation previously derived from the Siggard-Andersen nomogram (28). During the increasing work rate exercise protocol, a 1-ml sample of whole blood was pipetted into a 1-ml volume of iced perchlorate solution. A clear supernatant was obtained by centrifugation, separated from the stroma, and frozen for analysis. The samples were subsequently analyzed spectrophotometrically (17). During CWR protocols, the lactate measurement was made on whole blood with a lactate analyzer (model 2300, Yellow Springs Instruments, Yellow Springs, OH).

Data Analysis and Statistics

Group mean values for femoral vein P_{O_2}, O_2Hb saturation, P_{CO_2}, pH, standard HCO_3^-, lactate, and $\dot{V}O_2$ were compared by analysis of variance to detect differences between rest and exercise values. The Newman-Keuls multiple-range test was used to isolate differences between groups and to correct P for repeated measures. $P < 0.05$ was considered significant. All values are expressed as means ± SD unless otherwise specified.

RESULTS

The five subjects who participated in the incremental exercise protocol (mean age 25 ± 6 yr, height 179 ± 4.2 cm, weight 72 ± 4.9 kg) were young and physically fit (mean $\dot{V}O_{2\,max}$ 3.91 ± 0.68 l/min; LAT/$\dot{V}O_{2\,max}$ of 64 ± 7%). The five individuals who participated in the square-wave protocol had nearly identical average physical characteristics and parameters of aerobic fitness as those who participated in the incremental exercise protocol. The work rates utilized for CWR tests in the second group of subjects averaged 113 ± 17 and 265 ± 23 W for the below- and above-LAT exercise intensities, respectively.

Increasing Work Rate Exercise

Figure 1, *A–F*, displays the group mean femoral venous P_{O_2}, measured O_2Hb saturation, pH, P_{CO_2}, standard HCO_3^-, and lactate measurements as a function of $\%\dot{V}O_{2\,max}$ during the progressively increasing work rate exercise test. The simultaneous arterial values for pH, P_{CO_2}, standard HCO_3^-, and lactate are shown for comparison. Arterial P_{O_2} and O_2 saturation values are not shown because they were normal, unchanging, and off-scale. The mean LAT for the group is identified, and the statistical analyses of the rest, LAT, and peak exercise group mean femoral vein measurements are presented. The group mean $\dot{V}O_2$ at rest was 0.39 ± 0.05 and increased to 2.5 ± 0.40 l/min at LAT and to 3.91 ± 0.68 l/min at peak exercise.

From rest to LAT, the group mean femoral vein P_{O_2} decreased significantly from 27.4 to 21.2 Torr ($P < 0.05$). However, from LAT to $\dot{V}O_{2\,max}$ there was only a small, nonstatistically significant further decrease (from 21.2 to 19.8 Torr) in femoral vein P_{O_2}. In contrast to P_{O_2}, femoral vein O_2Hb saturation fell continuously throughout exercise (from 46.8% at rest to 26.8% at LAT to 18.5% at $\dot{V}O_{2\,max}$; Fig. 1*B*). Femoral vein pH decreased a small amount (7.34 to 7.27) from rest to LAT. However, above LAT, there was a dramatic decrease (from 7.27 to 7.09; Fig. 1*C*) in femoral vein pH. Therefore, during increasing work rate exercise, 64% of the total O_2Hb desaturation occurred below LAT (substantially related to P_{O_2} decrease) and 36% occurred above LAT (primarily related to a fall in pH).

The femoral vein P_{CO_2} was ~48 Torr at rest and continued to rise throughout exercise. Femoral vein standard HCO_3^- remained constant until LAT was reached and then decreased for the remainder of exercise. Femoral vein lactate did not increase significantly until the gas exchange LAT was reached. Thereafter, lactate increased to a peak value of 8.3 mmol/l at end exercise.

Several items are noteworthy on Fig. 1, including *1*) the femoral vein lactate values always slightly exceed the arterial values in the work rate range above LAT, *2*) arterial and femoral vein standard HCO_3^- values were nearly superimposable, and *3*) femoral vein P_{CO_2} and H^+ concentrations were much greater than the arterial values. In addition, the reciprocal changes in lactate and standard HCO_3^- as well as the marked fall in pH during exercise above LAT were evident.

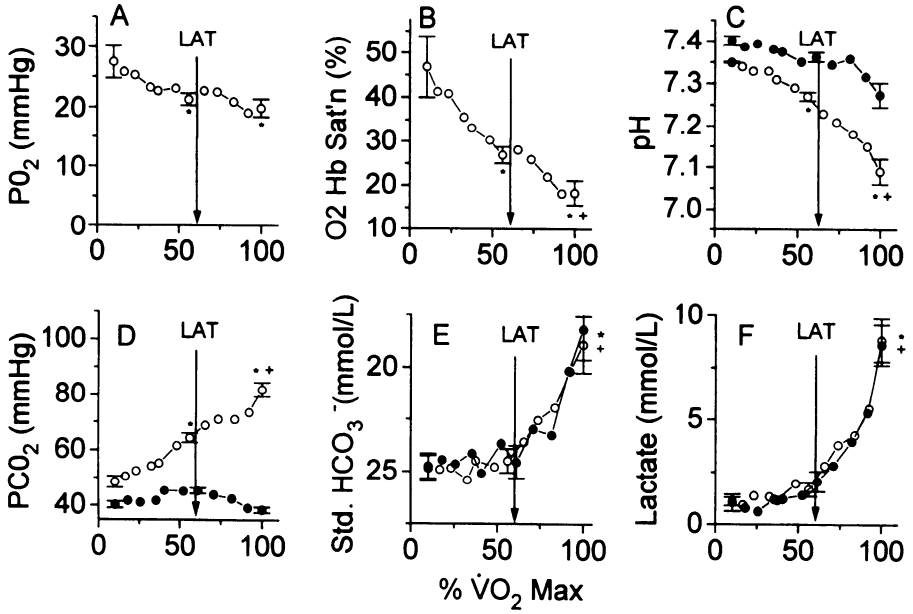

FIG. 1. Group mean ± SE [at rest, lactic acidosis threshold (LAT), and maximal O_2 uptake ($\dot{V}O_{2\,max}$)] femoral vein P_{O_2}, oxyhemoglobin (O_2Hb) saturation, pH, P_{CO_2}, standard HCO_3^-, and lactate values as function of $\%\dot{V}O_{2\,max}$ during progressively increasing work rate exercise in 5 healthy subjects. Simultaneous arterial values are shown for comparison. Arrow, average LAT for group. Standard HCO_3^- values shown on inverted scale to emphasize stoichiometric relationship between standard HCO_3^- decrease and lactate increase. ○, Femoral; ●, arterial. * Significantly different from rest, $P < 0.05$. + Significant difference between LAT and peak exercise, $P < 0.05$.

CWR Exercise

Figure 2, *A–F*, displays the group mean values and statistical analyses for femoral venous P_{O_2}, measured O_2Hb saturation, pH, P_{CO_2}, standard HCO_3^-, and lactate responses as a function of time for CWR exercise below and above LAT. During exercise at the work rate below LAT, the femoral vein P_{O_2} fell to 20 Torr within the 1st min and was relatively constant for the remainder of exercise (Fig. 2*A*). During exercise above LAT, P_{O_2} decreased at virtually the same rate and to the same value as the below-LAT work rate (there was no statistical difference) despite the fact that the average $\dot{V}O_2$ at rest and at 3 and 6 min of below-LAT exercise (0.37 ± 0.05, 1.76 ± 0.25, and 1.77 ± 0.24 l/min, respectively) differed remarkably from the corresponding above-LAT $\dot{V}O_2$ values (0.37 ± 0.04, 3.16 ± 0.49, and 3.36 ± 0.44 l/min). The average observed $\dot{V}O_2$ drift in this study between 3 and 6 min of heavy exercise was 0.2 l/min.

O_2Hb saturation fell more slowly to a nadir at ~2 min during exercise below LAT (Fig. 2*B*). In contrast, O_2Hb saturation during CWR exercise above LAT continued to fall throughout (Fig. 2*B*), with a contour similar to that of the pH curve (Fig. 2*C*). It should be emphasized that these measurements are methodologically independent, since they were obtained from different machines. Femoral vein pH decreased to 7.27 at ~2 min of exercise in the below-LAT test and remained relatively constant throughout the remainder of exercise (Fig. 2*C*). During exercise above LAT, the pH decrease by 2 min was more marked (as was the case for O_2Hb saturation) and continued to fall for the entire 6 min of heavy exercise and reached an average end-exercise value of 7.02.

The group mean femoral vein P_{CO_2}, standard HCO_3^-, and lactate as a function of time for the five subjects during CWR exercise tests below and above LAT are shown in Fig. 2, *D–F*. The femoral vein P_{CO_2} averaged 48 Torr at rest for both the below- and above-LAT intensi-

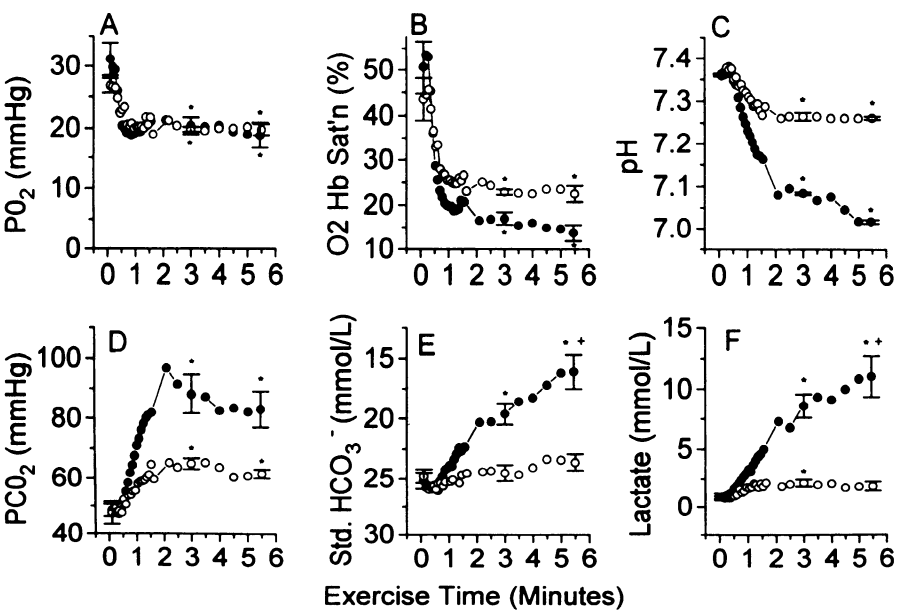

FIG. 2. Group mean ± SE (at rest and at 3 and 6 min of exercise) femoral vein P_{O_2}, O_2Hb saturation, pH, P_{CO_2}, standard HCO_3^-, and lactate values as function of time during 6 min of 2 constant work rate (CWR) exercise tests in 5 healthy subjects. ○, Test performed at work rate below LAT; ●, test performed at work rate above LAT. * Significantly different from rest, $P < 0.05$. + Significant difference between LAT and peak exercise, $P < 0.05$.

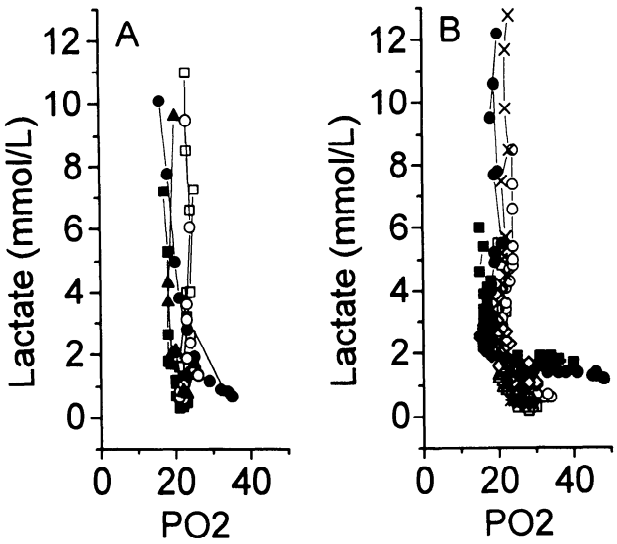

FIG. 3. Femoral vein lactate as function of femoral vein P_{O_2} for increasing work rate (*A*; 5 studies in 5 subjects) and CWR (*B*; 10 studies in 5 subjects) exercise below and above LAT. Different symbols, responses of different subjects.

ties. P_{CO_2} rose to ~62 Torr at end exercise for the below-LAT test and to nearly 82 Torr at end exercise for the above-LAT test ($P < 0.05$). These values are similar to the P_{CO_2} values observed during the increasing work rate exercise test at rest, LAT, and $\dot{V}O_{2\,max}$ shown in Fig. 1. Noteworthy is the P_{CO_2} overshoot at a time coincident with the most rapid rise in lactate (Fig. 2*F*), fall in pH (Fig. 2*C*), and fall in standard HCO_3^- (Fig. 2*E*) for the CWR test above LAT. This rise in P_{CO_2} most likely represents CO_2 produced by the rapid HCO_3^- buffering of lactic acid.

Femoral vein standard HCO_3^- and lactate changed by an average of 1 mmol/l over the course of exercise for the below-LAT exercise test. In contrast, during the above-LAT test, standard HCO_3^- had fallen at end exercise by 9 mmol/l and lactate had increased by 10 mmol/l relative to resting values. The patterns of lactate increase (Fig. 2*F*) and standard HCO_3^- decrease (Fig. 2*E*) mirror each other, changing in an equal and opposite fashion after 1 min of exercise. This is consistent with previous observations (1, 28).

Relationship Between Femoral Vein P_{O_2} and Lactate

Femoral vein lactate is plotted in Fig. 3 as a function of femoral vein P_{O_2} for the progressively increasing work rate (Fig. 3*A*) and the two CWR exercise periods (Fig. 3*B*). In both, the lactate values remain <2 mmol/l as the femoral vein P_{O_2} falls to ~20 Torr. Subsequently, femoral vein P_{O_2} does not decrease further, whereas femoral vein lactate increases dramatically. As previously noted in Fig. 2*A*, the rapid decrease in femoral vein P_{O_2} to 20 Torr occurs within 30 s of the onset of exercise and remained relatively constant during below- and above-LAT exercise, and femoral vein lactate begins to increase at approximately the same time (30 s).

Figure 4 shows the group mean values of femoral venous O_2Hb saturation as a function of P_{O_2} for the two CWR exercise tests. During exercise below LAT (Fig. 4*A*), the femoral venous P_{O_2} decreased to ~20 Torr, resulting in a decrease in O_2Hb saturation to ~27.5%. This fall in O_2Hb saturation was due primarily to the decrease in P_{O_2}. A further 5% decrease in O_2Hb saturation was due to the subsequent fall in pH (primarily related to an increase in P_{CO_2} from 48 to 60 Torr and a small increase in lactate from 0.9 to 1.9 mmol/l). During exercise above LAT (Fig. 4*B*), the O_2Hb saturation again decreased to ~27.5% as P_{O_2} fell to 20 Torr. However, the subsequent additional 15% observed decrease in O_2Hb saturation was primarily due to the fall in pH related to H^+ from lactic acid.

DISCUSSION

We were interested in understanding the mechanism by which lactate increases during CWR exercise was related to the slow increase in $\dot{V}O_2$ previously demonstrated in a number of studies (6, 15, 22, 32). Casaburi et al. (8) and Poole et al. (19) have reviewed the putative mechanism for increasing $\dot{V}O_2$ by the cells during CWR exercise. The objective of this investigation was to determine the relationship between end-capillary P_{O_2} (as approximated by the femoral venous P_{O_2}) and the exercise lactic acidosis as well as the role of lactic acid in facilitating O_2Hb dissociation. The present study shows that the femoral vein lactate does not start to increase until femoral vein P_{O_2} has reached its minimum value and that O_2Hb dissociation above LAT is due to the Bohr effect primarily as a result of the exercise lactic acidosis.

Several previous investigators have sampled femoral venous blood during leg exercise and determined that, on average, femoral venous P_{O_2} reaches a value between 15 and 25 Torr at peak exercise during air breathing (5, 11, 12, 18, 20, 21). Although variability in this range could be due to methodology, state of training, subject characteristics, or other physical variables, these values are remarkably similar to the critical capillary P_{O_2} value postulated by Wittenberg and Wittenberg (31). The pattern of change in femoral vein P_{O_2} with different work rate ranges, however, was not addressed in previous studies.

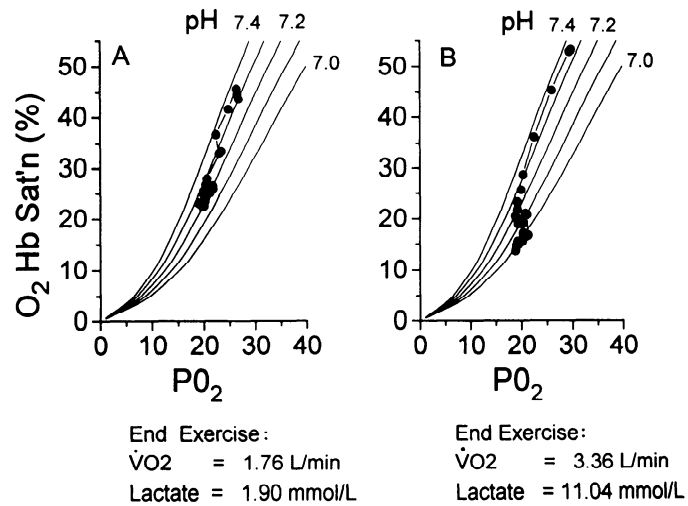

FIG. 4. Group mean femoral vein O_2Hb saturation as function of mean femoral vein P_{O_2} for 6-min CWR exercise periods below (*A*) and above (*B*) LAT. Highest O_2Hb saturations are those at start of CWR exercise, followed by sequential samples until end of exercise. pH lines were calculated from equations of Severinghaus (27).

The importance of lactic acidosis in maintaining capillary P_{O_2}, and thereby permitting increased extraction of O_2 from capillary blood during heavy exercise, has only recently been addressed. Wasserman et al. (29) described the effect on P_{O_2} when lactic acid was added to an in vitro closed system. They found a 6% increase in P_{O_2} for each 1-mmol/l increase in lactic acid concentration. Böning et al. (3) also used a closed system and reported an increase in P_{O_2} of 8.1% for each 1-mmol/l increase in lactic acid.

Both papers speculated on the importance of the associated pH decrease on facilitation of O_2Hb dissociation at low capillary P_{O_2} values; however, the data in the literature do not allow us to address our hypotheses that *1*) end-capillary P_{O_2} reaches a minimum value by LAT and *2*) exercise lactic acidosis, rather than decreasing P_{O_2}, is the primary mechanism promoting O_2Hb dissociation after the capillary P_{O_2} has reached its critical value. In this investigation, we found only small changes in femoral vein P_{O_2} from moderate to peak exercise despite the continued fall in femoral venous O_2 saturation related to increasing work rate exercise (Fig. 1, *A* and *B*). During CWR exercise, the pattern of decrease in femoral vein P_{O_2} was identical irrespective of the exercise intensity (Fig. 2*A*). After the first 2 min of exercise below LAT, O_2Hb saturation and pH remained constant for the remainder of the exercise period. However, during CWR exercise above LAT, femoral O_2Hb saturation decreased below that for the below-LAT work by 45 s and continued to decrease in a similar pattern as the decrease in pH (Fig. 2, *B* and *C*). The additional H^+ generated by increasing femoral vein P_{CO_2} (aerobic metabolism and HCO_3^- buffering of lactic acid; Fig. 2, *D* and *E*) and increasing HCO_3^- consumption as lactic acid concentration increases (Fig. 2*F*) allowed continued O_2Hb desaturation despite a relatively constant femoral vein P_{O_2} (~20 Torr).

Reaching a "floor" value (~20 Torr) for femoral vein P_{O_2} (despite an increase in muscle $\dot{V}_{O_2}$) was associated with an abrupt rise in femoral vein lactate concentration during increasing work rate and CWR exercise (Fig. 3, *A* and *B*). The additional H^+ from lactic acid during CWR exercise above LAT (relative to below LAT) changes the mechanism of O_2Hb dissociation from decreasing P_{O_2} to decreasing pH by 1 min of exercise. As illustrated in Fig. 4*B*, P_{O_2} stops decreasing when the pH falls below 7.3 and O_2Hb dissociation continues solely due to decreasing pH.

Because the increase in muscle temperature during 6 min of heavy cycle ergometer exercise has previously been determined to be <1°C (25), this factor could account for no more than a 1-Torr change in the P_{O_2} observed at 6 min into exercise, as estimated from the nomogram of Severinghaus (26). Therefore, the rightward shift of the O_2Hb saturation curve related to changes in muscle temperature must be quite small relative to the change in O_2Hb saturation due to pH.

A potential criticism of this paper may concern the use of femoral vein P_{O_2} to approximate end-capillary P_{O_2}. We believe that femoral vein P_{O_2} should approximate end-capillary P_{O_2}, since the blood flow to the exercising muscle far exceeds the blood flow to tissues with small extraction ratios, and, as work rate increases, femoral vein P_{O_2} should be more representative of the muscle end-capillary P_{O_2}. In addition, the observed mean values for femoral vein P_{O_2} reported in this paper and by several other investigators noted earlier agree surprisingly well with the calculated critical capillary P_{O_2} (31). If there is blood flow to areas with small extraction ratios in the leg during cycle exercise, it must be a relatively small amount.

We now return to the original question that launched this investigation. How much of the increase in $\dot{V}_{O_2}$ between 3 and 6 min of CWR exercise (0.2 l/min, on average, in the above-LAT study) can be supplied by the change in femoral vein O_2Hb saturation over this period? A rough approximation can be obtained by estimating leg blood flow ($\dot{Q}$leg) at 3 min [by assuming a constant arterial O_2 content (20.4 ml/100 ml) and assuming that all of the increase in $\dot{V}_{O_2}$ above rest was related to leg exercise]

$$\dot{Q}\text{leg} = \frac{\Delta\dot{V}_{O_{2\,\text{leg}}}}{\Delta(\text{a-fv})\text{C}} = \frac{3.16 - 0.37\ \text{l/min}}{16.2\ \text{ml/100 ml}} = 17.14\ \text{l/min} \quad (1)$$

where $\dot{V}_{O_{2\,\text{leg}}}$ is $\dot{V}_{O_2}$ of leg, 16.2 is arterial-femoral vein O_2 content difference [Δ(a-fv)C], and 0.37 l/min is resting $\dot{V}_{O_2}$. If $\dot{Q}$leg is unchanging, the increase in O_2 extraction can account for 62% of the increase in $\dot{V}_{O_2}$ between 3 and 6 min ($\dot{Q}\text{leg} \times \Delta(\text{a-fv})\text{C} = 17.14 \times 0.72 = 0.123$ l/min; 0.123 divided by 0.2 l/min = 62%). Although the increased O_2 extraction accounts for the majority of the increase in $\dot{V}_{O_2}$ between 3 and 6 min of exercise, the remainder is presumably related to increased $\dot{Q}$leg.

We conclude that the acidification of femoral venous blood by lactic acid during heavy exercise enables continued O_2 extraction while maintaining the required capillary-mitochondrial O_2 driving pressure dictated by the metabolic rate and the physical factors governing diffusion of O_2 from red blood cells to mitochondria (Fick's law). Therefore, lactic acid accumulation is likely to be essential for increasing O_2 transport to muscle during heavy exercise and promoting aerobic metabolism.

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REFERENCES

1. **Beaver, W. L., K. Wasserman, and B. J. Whipp.** Bicarbonate buffering of lactic acid generated during exercise. *J. Appl. Physiol.* 60: 472–478, 1986.
2. **Beaver, W. L., K. Wasserman, and B. J. Whipp.** A new method for detecting anaerobic threshold by gas exchange. *J. Appl. Physiol.* 60: 2020–2027, 1986.
3. **Böning, D., D. Hollnagel, A. Boecker, and S. Göke.** Bohr shift by lactic acid and the supply of O_2 to skeletal muscle. *Respir. Physiol.* 85: 231–243, 1991.
4. **Bylund-Fellenius, A. C., P. M. Walker, A. Elander, S. Holm, J. Holm, and T. Schersten.** Energy metabolism in relation to oxygen partial pressure in human skeletal muscle during exercise. *Biochem. J.* 200: 247–255, 1981.
5. **Carlson, L. A., and B. Pernow.** Studies on the peripheral circulation and metabolism in man. I. Oxygen utilization and lactate-pyruvate formation in the legs at rest and during exercise in healthy subjects. *Acta Physiol. Scand.* 52: 328–342, 1961.

6. **Casaburi, R., T. Barstow, T. Robinson, and K. Wasserman.** Influence of work rate on ventilatory and gas exchange kinetics. *J. Appl. Physiol.* 67: 547–555, 1989.
7. **Casaburi, R., J. Daly, J. E. Hansen, and R. M. Effros.** Abrupt changes in mixed venous blood gas composition after the onset of exercise. *J. Appl. Physiol.* 67: 1106–1112, 1989.
8. **Casaburi, R., T. Storer, I. Ben-Dov, and K. Wasserman.** Effect of endurance training on possible determinants of $\dot{V}O_2$ during heavy exercise. *J. Appl. Physiol.* 62: 199–207, 1987.
9. **Cerretelli, P., D. Pendergast, W. C. Paganelli, and D. W. Rennie.** Effect of specific muscle training on $\dot{V}O_2$ on-response and early blood lactate. *J. Appl. Physiol.* 47: 761–769, 1979.
10. **Di Prampero, P. E.** Energetics of muscular exercise. *Rev. Physiol. Biochem. Pharmacol.* 89: 143–222, 1981.
11. **Donald, K. W., P. N. Wormald, S. H. Taylor, and J. M. Bishop.** Changes in the oxygen content of femoral venous blood and leg blood flow during leg exercise in relation to cardiac output response. *Clin. Sci. Lond.* 16: 567–571, 1957.
12. **Hartley, L. H., J. A. Vogel, and M. Landowne.** Central, femoral, and brachial circulation during exercise in hypoxia. *J. Appl. Physiol.* 34: 87–90, 1973.
13. **Katz, A., and K. Sahlin.** Regulation of lactic acid production during exercise. *J. Appl. Physiol.* 65: 509–518, 1988.
14. **Knuttgen, H. G., and B. Saltin.** Muscle metabolites and oxygen uptake in short-term submaximal exercise in man. *J. Appl. Physiol.* 32: 690–694, 1972.
15. **Koike, A., K. Wasserman, D. K. McKenzie, S. Zanconato, and D. Weiler-Ravell.** Evidence that diffusion limitation determines oxygen uptake kinetics during exercise in humans. *J. Clin. Invest.* 86: 1698–1706, 1990.
16. **Linnarson, D., J. Karlsson, L. Fagraeus, and B. Saltin.** Muscle metabolites and oxygen deficit with exercise in hypoxia and hyperoxia. *J. Appl. Physiol.* 44: 399–402, 1978.
17. **Olsen, C.** An enzymatic fluorimetric micromethod for determination of acetoacetate, beta-hydroxybutyrate, pyruvate and lactate. *Clin. Chim. Acta* 33: 293–300, 1971.
18. **Pirnay, F., M. Lamy, J. Dujardin, R. Deroanne, and J. M. Petit.** Analysis of femoral venous blood during maximal exercise. *J. Appl. Physiol.* 33: 289–292, 1972.
19. **Poole, D. C., W. Schaffartzik, D. R. Knight, T. Derion, B. Kennedy, H. J. Guy, R. Prediletto, and P. D. Wagner.** Contribution of exercising legs to the slow component of oxygen uptake kinetics in humans. *J. Appl. Physiol.* 71: 1245–1253, 1991.
20. **Roca, J., A. G. N. Agusti, A. Alonso, D. C. Poole, C. Viergas, J. A. Barbera, R. Rodriguez-Roisin, A. Ferrer, and P. D. Wagner.** Effects of training on muscle O_2 transport at $\dot{V}O_{2\,max}$. *J. Appl. Physiol.* 73: 1067–1076, 1992.
21. **Roca, J., M. C. Hogan, D. Story, D E. Bebout, P. Haab, R. Gonzalez, O. Ueno, and P. D. Wagner.** Evidence for tissue diffusion limitation of $\dot{V}O_{2\,max}$ in normal humans. *J. Appl. Physiol.* 67: 291–299, 1989.
22. **Roston, W. L., B. J. Whipp, J. A. Davis, D. A. Cunningham, R. M. Effros, and K. Wasserman.** Oxygen uptake kinetics and lactate concentration during exercise in humans. *Am. Rev. Respir. Dis.* 135: 1080–1084, 1987.
23. **Sahlin, K.** Muscle fatigue and lactic acid accumulation. *Acta Physiol. Scand.* 128: 83–91, 1986.
24. **Sahlin, K., A. Katz, and J. Henrikkson.** Redox state and lactate accumulation in human skeletal muscle during dynamic exercise. *Biochem. J.* 245: 551–556, 1987.
25. **Saltin, B., and L. Hermansen.** Esophageal, rectal, and muscle temperature during exercise. *J. Appl. Physiol.* 21: 1757–1762, 1966.
26. **Severinghaus, J. W.** Blood gas concentrations. In: *Handbook of Physiology. Respiration.* Bethesda, MD: Am. Physiol. Soc., 1965, sect. 3, vol. II, chapt. 61, p. 1475–1487.
27. **Severinghaus, J. W.** Simple accurate equations for human blood O_2 dissociation computations. *J. Appl. Physiol.* 67: 2535–2541, 1979.
28. **Stringer, W. W., R. Casaburi, and K. Wasserman.** Acid-base regulation during exercise and recovery in humans. *J. Appl. Physiol.* 72: 954–961, 1992.
29. **Wasserman, K., J. E. Hansen, and D. Y. Sue.** Facilitation of oxygen consumption by lactic acidosis during exercise. *News Physiol. Sci.* 6: 29–34, 1991.
30. **Whipp, B. J., and K. Wasserman.** Oxygen uptake kinetics for various intensities of constant load work. *J. Appl. Physiol.* 33: 351–356, 1972.
31. **Wittenberg, B. A., and J. B. Wittenberg.** Transport of oxygen in muscle. *Annu. Rev. Physiol.* 51: 857–878, 1989.
32. **Zhang, Y. Y., K. Wasserman, K. Sietsema, I. Ben-Dov, T. J. Barstow, G. Mizumoto, and C. S. Sullivan.** O_2 uptake kinetics in response to exercise: a measure of tissue anaerobiosis in heart failure. *Chest* 103: 735–741, 1993.