Poor relationship between arterial [lactate] and leg net release during exercise at 4,300 m altitude

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Brooks, George A., Eugene E. Wolfel, Gail E. Butterfield, Allen Cymerman, Amy C. Roberts, Robert S. Mazzeo, and John T. Reeves. Poor relationship between arterial [lactate] and leg net release during exercise at 4,300 m altitude. Am. J. Physiol. 275 (Regulatory Integrative Comp. Physiol. 44): R1192–R1201, 1998.—We evaluated the hypotheses that on acute exposure to hypobaric hypoxia, sympathetic stimulation leads to increased muscle lactate production and circulating [lactate] through a β-adrenergic mechanism and that β-adrenergic adaptation to chronic hypoxia is responsible for the blunted exercise lactate response after acclimatization to altitude. Five control and 6 β-blocked men were studied during rest and exercise at sea level (SL), on acute exposure to 4,300 m (A1), and after a 3-wk sojourn at altitude (A2). Exercise was by leg cycling at 49% of rate exercise is due to increased net lactate release rate (L) from contracting muscle, the phenomenon is little studied. The few reports in which arterial lactate levels and net lactate release rate from working muscle beds were measured simultaneously during submaximal exercise (1, 5, 29, 30) show that muscle lactate release occurs at exercise onset, but net release declines as exercise continues. The change in L during constant rate exercise is due to the decrease in the venous-arterial concentration ([v-a]) for lactate, which falls to zero or becomes negative while muscle blood flow remains elevated compared with rest. Moreover, this “Stainsby effect” (28) of transient muscle lactate release at exercise onset followed by net uptake of lactate from the blood by working muscle is observable in men working at altitude (5, 6) as well as at SL (1, 5, 30). Furthermore, studies on canine muscles studied in situ, both with (27) and without adrenergic stimulation (28), indicate a role of epinephrine in promoting lactate release from skeletal muscle. Thus it is uncertain whether working skeletal muscle is the sole source of blood lactate in men during whole body exercise (3, 5). Similarly, it is uncertain to what extent β-adrenergic signaling is responsible for either the muscle or blood lactate responses in men exercising at altitude.

During continuous progressive exercise tasks at SL, arterial epinephrine and lactate concentrations are closely related (6, 20). In a previous study conducted on...
men exposed acutely and chronically to 4,300 m altitude on Pikes Peak, we (5, 6) observed that blood lactate and epinephrine concentrations and 13C-tracer measured lactate flux rates were highly correlated. Moreover, we observed that acute altitude exposure resulted in the greatest blood epinephrine and lactate responses, whereas continued residency resulted in diminished responses during exercise (23).

Based on previous observations on men studied at altitude and canine muscles studied in situ, we hypothesized that 1) sympathetic stimulation on acute exposure to hypobaric hypoxia leads to augmented lactate production and circulating lactate through a b-adrenergic mechanism and 2) b-adrenergic adaptation to chronic hypoxia is responsible for the paradoxical blunted exercise lactate response after acclimatization to altitude. Additionally, we felt it necessary to confirm our previous observation of transient muscle lactate release during exercise at altitude. For these purposes we studied young men under the influence of dense b-adrenergic blockade at SL, acutely on the summit of Pikes Peak (4,300 m, barometric pressure (Pb) 462 Torr), and after a 3-wk residency at altitude. Our results confirm the presence of a lesser blood lactate response to exercise after acclimatization to altitude; however, whereas b-blockade significantly reduced circulating [lactate] during exercise at SL and altitude, b-blockade did not effect working muscle lactate content or net lactate release rate at SL or altitude.

METHODS

Subject Selection and Diet

Our procedures have been reported previously (20, 25, 26); briefly, 11 nonsmoking untrained male sea-level inhabitants were recruited by advertisements in local newspapers. Subjects gave their written informed consent for participation in the study, which was approved by the institutional ethical review boards of responsible institutions. Food intake was controlled at SL and at altitude with a food and formula diet provided in amounts sufficient to cover energy needs as determined by maintenance of body weight and nitrogen balance as described previously (7). One week before the altitude period, outpatient subjects were provided with quantities of diet similar to those previously found to maintain body weight and nitrogen balance during the SL phase. During the time at altitude, basal metabolic rate was measured every other day and energy intake was adjusted to cover increased needs at altitude. All subjects were given a basal diet that provided 30% of energy from fat, 58% from carbohydrate, and 12% from protein. The same foods were given daily at SL and at altitude; the quantity of nonprotein foods was increased at altitude to cover measured energy needs. Carbohydrate-to-fat ratio of added energy was held constant across all conditions. Fluid intake at altitude was a minimum of 2 l/day as water in addition to fluid in foods. Compliance to the dietary regimen was enforced by weighing subjects daily, monitoring fluid balance, and by investigators taking meals with subjects. SL weights of control and b-blocked subjects (control 74.0 ± 6.6, b-blocked 69.3 ± 2.6 kg) were not different from each other and were maintained during the period of altitude exposure (weights at the end of exposure were control 73.8 ± 5.9, b-blocked 69.5 ± 2.3 kg).

Study Design

 Sites. Measurements were made at rest and during steady-state exercise while subjects were breathing ambient air at SL (Pb 751 Torr), within the first 4 h of arrival at 4,300 m altitude (A1 Pb 462 ± 1 Torr), and after 21 days residence at altitude (A2). Studies at high altitude began 4 wk after those performed at SL. Subjects were flown from SL to Colorado Springs, Colorado, where they slept at 1,954 m the night before ascending to 4,300 m (Pikes Peak). During the 45-min ascent via automobile, subjects breathed from a tank which contained 100% O2. Subject arrival at altitude was staged so that all subjects were studied promptly on arrival and after an equivalent period of residence at altitude. The SL studies were performed at the Geriatrics Research, Education and Clinical Center of the Palo Alto Veterans Affairs Health Care System, whereas the altitude studies were performed in the United States Army Research Laboratory on the summit of Pikes Peak, Colorado.

Experimental conditions. Six subjects were randomly assigned according to age and weight to the experimental altitude group. Six subjects of similar age and weight were randomly assigned to the control group. One control subject was dropped during SL studies for lack of compliance. Oral propranolol (80 mg) was administered three times daily (total 240 mg/day) as the experimental condition. The condition was double blind; all subjects were administered a pill (either a placebo or propranolol) with the code retained by the principal investigator. Pills were taken for 1 wk before study at SL, for 1 wk before ascent to altitude, and continuously at altitude. Adequacy of b-adrenergic blockade was documented by monitoring the heart rate responses to progressive intravenous doses of the b-agonist isoproterenol.

Ergometry and indirect calorimetry. V\textsubscript{O2peak} was defined as the highest 1-min value of pulmonary oxygen consumption measured during leg cycling exercise on a Collins electrically braked cycle ergometer during a continuous, progressive protocol, with increments of 25 W every 2 min. V\textsubscript{O2peak} was assessed twice at SL and on days 4 and 19 after arrival at altitude (20). Respiratory gas exchange was determined in real time with a PC-based system described previously (5). The same equipment was used for determinations of V\textsubscript{O2} during maximal and continuous exercise testing at SL and at altitude. To determine effects of exercise, altitude, and b-blockade on lactate metabolism, subjects were studied at rest and during leg cycle ergometer exercise at a power output that elicited 49% of SL V\textsubscript{O2peak}. At SL work output during continuous leg cycle ergometry was 88.6 ± 2.4 and 86.7 ± 3.1 W in control and blocked subjects, respectively. Thus at altitude the same absolute power output as at SL elicited ~65% of the altitude V\textsubscript{O2peak}, an intensity that could be maintained for 45 min (5). Chronic altitude exposure did not further affect either maximal (peak) or submaximal V\textsubscript{O2} (20, 26).

Limb catheterization. After local xylocaine anesthesia, the femoral artery and vein of the same leg were cannulated by the use of standard percutaneous techniques as previously described (32). After catheterization and acquisition of an initial blood sample, subjects rested semisupine for ≥90 min.

Blood measurements and sampling time points. In each trial subjects were studied 8-10 h postabsorptive. Simultaneous blood samples were drawn, anaerobically, over 5 s from arterial and venous leg catheters when V\textsubscript{O2} reached a steady state at 75 and 90 min of rest, and at 5, 15, 30, and 45 min during exercise.

Blood sampling and analysis. Blood samples (6 ml) obtained for determination of lactate and glucose (24, 26) were mixed with 17.5 mg of sodium fluoride and 14 mg of potas-
sium oxalate to inhibit glycolysis. All samples were immediately stored on ice until centrifugation (DuPont Instruments Sorval RC-5) for 10 min at 1,000 g; supernatants were decanted and stored at –20°C or on dry ice until enzymatic analysis as previously described (5, 6).

Hemodynamic measurements. Heart rate was determined by an electrocardiogram. After blood sampling iliac venous blood flow was estimated from a 10-ml bolus injection of sterile saline cooled to near 0°C through an American Edwards Laboratories-set II (93–520) by the thermodilution technique using a cardiac output computer (American Edwards Laboratories model 9520). Measurements were made in triplicate at rest and each sampling period during exercise. Validity of the measurements was determined by obtaining appropriate thermodilution morphology curves on a Soltex (model 8K22) recorder with each measurement. Measurements were made in triplicate at rest and each sampling period during exercise. These methods are described in detail elsewhere, and reliability and reproducibility have been discussed (32).

Leg net lactate exchange (release or uptake). Because blood flow and lactate [v-a] differences were measured in one leg, net lactate release or uptake rate (L) by the legs was calculated from the product of limb blood flow (Q) and [v-a] difference multiplied by 2

\[ L = 2Q[V-a] \]

where L is [lactate] and the metabolism in the two legs was assumed to be the same.

Muscle sampling and analysis. During preparation for blood sampling, one vastus lateralis was prepared for percutaneous needle biopsy. For each experimental trial, biopsies were taken from two locations separated by 1.5 cm: the distal site for preexercise sampling and the proximal site for subsequent biopsy. For each experimental trial, biopsies were alternated between trials. Biopsies taken at rest and within 10 s of exercise cessation were immediately plunged into liquid nitrogen and subsequently stored under liquid nitrogen or at –80°C until analysis. Lactate contents of biopsy samples were determined by fluorometry as previously described (14).

Statistics. Data on arterial [lactate] and mean net lactate release rates are represented as means ± SE. Representative values (means ± SE) for lactate uptake and release in resting subjects were determined from averaging the two preexercise samples, whereas the mean of values determined at 30 and 45 min of leg cycling provided a representative value for exercise. Because only single pre- and postexercise biopsy samples were obtained, sample averaging to obtain representative values was not possible. Effects of β-blockade and acute and chronic altitude exposure on parameters of leg exchange were assessed by means of two (control and β-block) times three (SL, A1, and A2) ANOVA with repeated measurements using the pooled values from the final 15 min of rest and exercise. Scheffé post hoc comparisons were made to identify significantly different means. An α of 0.05 was used throughout.

RESULTS

\( \dot{V}_O_{2peak} \) in subjects during two-leg cycle ergometry at SL in control and blocked subjects was 45 ± 2.3 and 44.2 ± 1.6 ml·kg\(^{-1}\)·min\(^{-1}\), respectively, and fell to 81% of the SL values during the stay on Pikes Peak with no difference between blocked and unblocked subjects or changes during residency at altitude (26).

Resting rates of whole body \( V_{O2} \) at altitude (A1 and A2, 5.4 ± 0.2 ml·kg\(^{-1}\)·min\(^{-1}\)) were significantly elevated above that at SL (4.3 ± 0.5 ml·kg\(^{-1}\)·min\(^{-1}\)) (Table 1). β-Adrenergic blockade did not affect resting \( V_{O2} \) at SL (4.2 ± 0.1 ml·kg\(^{-1}\)·min\(^{-1}\)), but at altitude β-blockade resulted in lower resting \( V_{O2} \) (4.8 ± 0.1 ml·kg\(^{-1}\)·min\(^{-1}\)), values significantly above those at SL but depressed from those in control subjects at altitude (24).

During exercise at altitude the identical power output as at SL elicited a significantly greater whole body \( V_{O2} \) in all subjects (mean of A1 and A2: 23.9 ± 1.0 ml·kg\(^{-1}\)·min\(^{-1}\)) vs. SL (21.3 ± 0.9 ml·kg\(^{-1}\)·min\(^{-1}\)) (Table 1) (26). At altitude, β-blockade did not affect whole body \( V_{O2} \) during exercise and therefore values were not different between control and blocked subjects (26).

In control subjects, leg \( V_{O2} \) values during rest and exercise at SL averaged 20.9 ± 2.0 and 504.5 ± 70.9 ml/min, respectively (Table 1) (26). During rest at SL, β-blocked subjects had significantly higher leg \( V_{O2} \) (30.1 ± 3.0 ml/min), and the increase in resting leg \( V_{O2} \) persisted in subjects on acute altitude exposure. Dur-

Table 1. Summary of parameters of whole body and leg oxygen consumption, leg blood flow, and net lactate release in control and β-blocked male subjects during rest and from 30 to 45 min of exercise at sea level and after acute and chronic exposure to 4,300 m altitude

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sea Level</th>
<th>Acute Altitude</th>
<th>Chronic Altitude</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td>Rest</td>
</tr>
<tr>
<td>Whole body ( V_{O2} ), ml·kg(^{-1})·min(^{-1})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4.3 ± 0.5</td>
<td>21.3 ± 0.9*</td>
<td>5.4 ± 0.2†</td>
</tr>
<tr>
<td>Blocked</td>
<td>4.2 ± 0.1</td>
<td>21.9 ± 0.8*</td>
<td>4.8 ± 0.1‡</td>
</tr>
<tr>
<td>Single-leg ( V_{O2} ), ml/min</td>
<td>20.9 ± 2.0</td>
<td>504.5 ± 70.9*</td>
<td>21.7 ± 0.02</td>
</tr>
<tr>
<td>Control</td>
<td>30.1 ± 3.0</td>
<td>503.7 ± 32.4*</td>
<td>38.2 ± 4.1†</td>
</tr>
<tr>
<td>Blocked</td>
<td>0.77 ± 0.1</td>
<td>3.92 ± 0.05*</td>
<td>0.66 ± 0.07</td>
</tr>
<tr>
<td>Single-leg blood flow, l/min</td>
<td>0.53 ± 0.02</td>
<td>3.38 ± 0.20*‡</td>
<td>0.54 ± 0.03‡</td>
</tr>
<tr>
<td>Control</td>
<td>0.00 ± 0.05</td>
<td>0.66 ± 0.24</td>
<td>0.02 ± 0.05</td>
</tr>
<tr>
<td>Blocked</td>
<td>0.15 ± 0.07</td>
<td>-0.04 ± 0.17</td>
<td>0.05 ± 0.04</td>
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</table>

Values are means ± SE; n = 5 control and 6 blocked. Refer to Ref. 24 for previously published values. Statistical significance *different from rest, P < 0.05; †different from sea level, P < 0.05; ‡different from control, P < 0.05; §different from acute altitude, P < 0.05.
ing exercise at altitude leg \( \dot{V}O_2 \) rose in blocked subjects as at SL, but \( \beta \)-blockade did not affect leg \( \dot{V}O_2 \) during exercise at altitude (26).

Arterial [lactate] was low and stable at rest in control subjects (Fig. 1A and Table 2). On the initiation of exercise [lactate] rose and stabilized within 5 to 15 min of exercise under all environmental conditions. During exercise the initial rise in arterial [lactate] showed an ordering effect, with acute altitude exposure eliciting the greatest values and chronic exposure an intermediate response (Fig. 1A). As in the unblocked condition, in \( \beta \)-blocked subjects arterial lactate rose during exercise but then declined at SL and on acute altitude exposure. Additionally, compared with controls, \( \beta \)-blocked subjects had lower arterial lactate response to exercise regardless of environmental condition but not rest (Fig. 1B and Table 2).

Effects of exercise, altitude, and \( \beta \)-blockade on limb blood flow are presented in detail elsewhere (26, 33) and are summarized in Table 1. Briefly, exercise increased limb blood flow, whereas \( \beta \)-blockade tended to decrease it; altitude exposure did not have a consistent effect on limb blood flow, with a decrease after acclimatization in control subjects. Therefore, in terms of exercise, altitude, and \( \beta \)-blockade effects on limb net lactate release rate, changes in \( L \dot{v} \) over time were dominated by changes in limb lactate \([v-a]\).

In control subjects, limb blood flow and lactate \([v-a]\) were low at rest under all three experimental conditions (Table 1 and Fig. 2A). As a consequence of both large increases in limb blood flow and lactate \([v-a]\), exercise onset at SL produced a significant increase in \( L \) (Fig. 2C). Despite the initial elevation, at exercise onset, over the duration of exercise at SL \( L \) declined to near resting values (Fig. 2C) because lactate \([v-a]\) declined (Fig. 2A).

In resting control subjects acute altitude exposure did not produce significant changes in either limb blood flow (Table 1) or in lactate \([v-a]\) (Fig. 2A) compared with SL. Therefore, acute altitude exposure did not affect \( L \) (Fig. 2C) in resting controls. However, in control subjects exercise onset at A1 produced the greatest increase in lactate \([v-a]\) (Fig. 2A) and consequently \( L \) (Fig. 2C and Table 1). However, despite a constant elevation in limb blood flow, on acute exposure, leg \([v-a]\) decreased over time in unblocked subjects (Fig. 2A) so that after 30 min of exercise \( L \) was not different from zero (Fig. 2C).

After acclimatization exercise onset also resulted in an increase in limb blood flow and lactate \([v-a]\), but lactate \([v-a]\) was intermediate between SL and acute altitude exposure (Table 1 and Fig. 2A). As in the case of acute altitude exposure, during exercise after acclimatization lactate \([v-a]\) declined to zero (Fig. 2A) and as a consequence so did \( L \) (Fig. 2C). Because limb blood flow values decreased during exercise as the result of chronic altitude exposure (Table 1), the response pattern of \( L \) during exercise after chronic altitude exposure was more like that at SL than on acute exposure (Fig. 2C).

In \( \beta \)-blocked subjects, the patterns of net release from legs were different from those in control subjects. At SL lactate \([v-a]\) and therefore \( L \) remained at zero during exercise (Figs. 2, B and D). On acute altitude exposure, exercise resulted in only transient increases in lactate \([v-a]\) (Fig. 2B) and \( L \) (Fig. 2D). Chronic altitude exposure with \( \beta \)-blockade produced the most...
notable effects on \(^{13}\)C-lactate observed. As in control subjects and under other environmental conditions, during rest after acclimatization the limbs of \(\beta\)-blocked subjects showed minimal L\(^{-}\) (Fig. 2D). However, working limbs of acclimatized \(\beta\)-blocked subjects showed high, but variable L (Fig. 2D), despite a limb blood flow that tended to be less than those in control subjects (Table 1).

Notwithstanding large effects of limb blood flow (Table 1) (20, 26) as well as initial increments in lactate [v-a] at exercise onset (Fig. 2, A and B), L for the final 15 min of exercise was little affected by exercise, altitude, and blockade, with ANOVA not yielding any significant differences in L among trials (Table 1).

Vastus lateralis lactate contents are given in dry weight units. Water contents of muscle biopsy samples averaged 76.2 and 76.6% in unblocked and blocked subjects, and no effects of exercise or environmental condition on water content of biopsy samples was observed. Vastus lateralis lactate contents in unblocked subjects (Table 2) were similar to values reported previously (14). Lactate was significantly greater in post- than preexercise samples, with the greatest muscle [lactate] observed after exercise on acute altitude exposure. After acclimatization, muscle [lactate] during exercise regressed to SL values. However, there were no significant differences in muscle lactate contents at rest, and there was no significant effect of \(\beta\)-blockade on muscle [lactate] under any altitude or exercise condition (Table 2).

DISCUSSION

Our results corroborate those of others (1, 6, 29, 30) showing that continuous, submaximal exercise, which results in elevated but stable circulating lactate levels, is accomplished with only a transient net lactate release from the working muscle bed. The initial surge in limb lactate release is followed by a return to baseline or, in some cases, a switch to net uptake because the lactate [v-a] becomes zero or negative. Furthermore, we confirm previous results (6) that exercise at high altitude, which is accompanied by elevated systemic lactate levels compared with SL, is also characterized by transient net lactate release from working limbs. Therefore, our results contribute to the growing body of evidence that working skeletal muscle is not the sole source of circulating lactate during sustained exercise at SL or altitude. Moreover, because \(\beta\)-blockade had inconsistent effects on L and no effect on muscle [lactate], the hypotheses are rejected that \(\beta\)-adrenergic stimulation of glycogenolysis in working muscle is primarily responsible for elevating blood [lactate] during exercise at altitude or blunting of the blood lactate response during exercise after acclimatization.

As in previous studies on Pikes Peak (5–7, 32), circulatory adjustments to hypoxemia were sufficient to maintain whole body and working muscle rates of \(^{13}\)O\(_2\) even though arterial \(^{13}\)O\(_2\) transport was reduced (Table 1). Moreover, after a rise in arterial \(^{13}\)O\(_2\) saturation with acclimatization (21, 33), values for whole body and limb \(^{13}\)O\(_2\) were not different between acute and chronic exposure. Thus we are unable to associate changes in arterial \(^{13}\)O\(_2\) content or transport with the observed changes in blood or muscle lactate concentrations or limb net release during steady-rate exercise. Although \(^{13}\)O\(_2\) lack can stimulate glycolysis leading to lactate production in muscle and other tissues (8), hypoxemia associated with hypobaric hypoxia at high altitude is more likely to result in decreased maximal rates of glycogenolysis, glycolysis, lactate production, and accumulation due to decreased muscle power output (23). Thus, in our experiments, a Pasteur-like effect of hypoxemia at high altitude is unlikely to explain the responses in arterial lactate and muscle net lactate release rate we observed.

Like results of our previous investigation (6), our present results show an association between the rise in arterial [lactate] and L at the onset of exercise. Also, as in our previous investigation, L declined over time, whereas arterial [lactate] remained elevated. One explanation could be that muscle lactate production accounted for a mass release of lactate into the vasculature at exercise onset and then the elevated arterial [lactate] persisted because of lack of clearance. Muscle lactate accumulation under all altitude conditions supports the conclusion of increased muscle lactate production during exercise (Table 2). However, by means of \(^{13}\)C-lactate tracer in our previous study we established that lactate undergoes a very rapid turnover in the

Table 2. Pre- and postexercise arterial and vastus lateralis lactate concentrations in control and \(\beta\)-blocked male subjects during rest and exercise at sea level and after acute and chronic exposure to 4,300 m altitude

<table>
<thead>
<tr>
<th></th>
<th>Rest Level</th>
<th>Exercise</th>
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<th>Rest Level</th>
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<tbody>
<tr>
<td>Arterial [lactate], mM</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.9±0.1</td>
<td>1.5±0.3*</td>
<td>0.8±0.1</td>
<td>4.4±0.8†</td>
<td>0.6±0.1†</td>
<td>2.1±0.6§</td>
<td></td>
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</tr>
<tr>
<td>Blocked</td>
<td>0.7±0.1</td>
<td>0.8±0.2‡</td>
<td>0.7±0.1</td>
<td>2.4±1.1†‡</td>
<td>0.7±0.1</td>
<td>1.2±0.2‡§</td>
<td></td>
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</tr>
<tr>
<td>Muscle [lactate], mmol/kg dry wt</td>
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<td></td>
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<tr>
<td>Control</td>
<td>4.9±1.1</td>
<td>11.1±2.5*</td>
<td>5.5±0.9</td>
<td>22.6±3.3†</td>
<td>4.3±0.7</td>
<td>15.1±3.9§</td>
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<tr>
<td>Blocked</td>
<td>5.6±3.5</td>
<td>13.8±0.8*</td>
<td>5.6±3.2</td>
<td>25.4±1.9†</td>
<td>8.7±3.0</td>
<td>15.5±1.2§</td>
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</table>

Values are means ± SE; n = no. of successful measurements. *Different from rest, P < 0.05; †different from sea level, P < 0.05; ‡different from control, P < 0.05; §different from acute altitude, P < 0.05.
blood, especially during exercise on acute altitude exposure (5). Thus, whereas elevated L at altitude could account for the greater rise in arterial [lactate] during the onset of exercise, elevated limb L could not account for persistent elevation in circulating [lactate] during exercise as limb declined to zero over time in all conditions (Table 1 and Fig. 2).

The transient nature of net lactate release from working muscle in the face of elevated, but constant arterial lactate levels during steady-rate submaximal exercise, is interpreted to mean that tissues other than working skeletal muscle contribute to the circulating lactate load during sustained submaximal exercise. Wasserman and associates (31) have produced several
reports to indicate significant hepatic lactate release in exercising dogs. However, hepatic lactate release has, to our knowledge, not been observed in exercising humans (1, 30). In humans, lactate release has been demonstrated from cutaneous and adipose tissues (3). In addition, erythrocytes (22) can be expected to produce lactate. In contrast, other tissues, such as heart (12) and red skeletal muscle (3, 29), can be net consumers of lactate. Therefore, the source of blood lactate observed during submaximal exercise at SL and high altitude is unknown but, based on results of this investigation, a β-adrenergic stimulation of muscle glycogenolysis is not likely to be necessary for elevation in blood lactate during exercise at altitude.

Although β-adrenergic blockade has been seldom used to study L from working human muscle, results from our SL trials are largely consistent with those of Juhlin-Dannfelt and Åström (16). As in their study, β-blockade significantly reduced arterial [lactate] and did not effect whole body or leg V O₂ during leg cycling, eliciting 50% of V O₂max at SL. Additionally, in our study, β-blockade significantly reduced leg blood flow, whereas in the report of Juhlin-Dannfelt and Åström, the tendency for a reduction in blood flow was not significant. This latter discrepancy may be attributable to differences in the mode of propranolol administration, which in our study was oral and chronic, whereas in their study it was acute and local via infusion into the femoral artery.

Perhaps the most notable difference between our report and that of Juhlin-Dannfelt and Åström (16) was absence of a significant difference in working leg L in our study, whereas in their report L was reduced 50% by β-blockade. This distinction may also be attributable to differences in experimental design because they made measurements only at 15 min of exercise, whereas we report data during 45 min of exercise (Table 1). Consistent with them, lactate [v-a] was greatest at exercise onset (Fig. 2), but we observed lactate [v-a] to decline over time. Given the transient nature of leg L at exercise onset, our results on control (Fig. 2A) vs. blocked subjects (Fig. 2B) are not dissimilar from those of Juhlin-Dannfelt and Åström at 15 min of exercise.

That working mammalian muscle first releases lactate when contractions start, but then switches to zero net release or consumption was first observed by Stainsby and Welch (28) who studied canine muscles contracting in situ. Likely, there exists a temporal aspect of the phenomenon that is related to the differential rates of activation of glycolysis and oxidative phosphorylation (8), but clearly there also exists a concentration effect where net lactate uptake by working skeletal muscle depends on the presence of an arterial lactate load as demonstrated by Gladden (13) on canine muscle contracting in situ, and by Richter et al. (24) on human muscle in vivo.

As always, our results and interpretations are limited by methodological considerations. For instance, recognizing limitations of measuring limb blood flow by thermodilution, we present data on limb blood flow (Table 1) and lactate [v-a] (Fig. 2, A and B), as well as the magnitude and direction of net limb lactate exchange (Table 2 and Fig. 2, B and D). Furthermore, we acknowledge that our reported values for L underestimate the magnitude of intra-muscular lactate production because lactate extraction by muscle occurs during net release (6, 29). Furthermore, there are intra- and intercellular lactate exchange, oxidation, and other pathways of lactate metabolism (6, 8). From our previous work using continuous infusion of [13C]lactate we know that while the fractional extraction of lactate across a working muscle bed approximates 50%, tracer lactate taken up is essentially removed by oxidation (6). Even though muscle lactate flux can be very high on acute altitude exposure, oxidative metabolism represents the entirety of the energy flux as lactate produced in or taken up by myocytes is oxidized. Thus during sustained submaximal exercise at SL or altitude, working skeletal muscle is a site of simultaneous lactate production and oxidation, with the balance of uptake and release often summing to zero (5, 6).

β-Adrenergic blockade did not eliminate the transient elevations in limb lactate net release during exercise at altitude (Fig. 2). Similarly, Kien et al. (18) observed significant L from small but well-perfused rectus femoris muscle groups in the absence of significant elevations in circulating epinephrine. Therefore, we conclude that cAMP-independent mechanisms of muscle glycogenolysis, such as increased cytosolic Ca²⁺ flux, must be primarily responsible for the transient glycogenolysis and lactate release from working muscle during exercise at SL and high altitude.

Least expected among our results was persistence of elevations in L during exercise after chronic altitude exposure in the face of dense β-blockade (Fig. 2D). We attribute this result in part to the mode of computation and in part to the physiology. From the computation standpoint, we reiterate that muscle [lactate] during exercise was unaffected by β-blockade at altitude (Table 2) and that arterial [lactate] was decreased (Fig. 1B and Table 2). Because femoral venous [lactate] was related to muscle [lactate] (33), the increases in lactate [v-a] and L in blocked subjects after acclimatization (Fig. 2, B and D) were due in part to the reduction in arterial [lactate] and not an increase in femoral venous [lactate]. However, from the physiological standpoint, the results are interpreted to mean that muscle lactate production was increased under β-blockade. Given that after acclimatization in the blocked condition vascular conductance to working muscle was less (i.e., arterial [lactate] and flow were less), there needed to be greater muscle lactate production to maintain the equivalent muscle [lactate]. Persistence of glycogenolysis in muscle after acclimatization under dense β-blockade is attributable to elevated muscle glucose (26) and decreased fatty acid uptake (25).

Our results indicating that β-adrenergic mechanisms cannot explain the blood lactate responses we observed during exercise at SL or high altitude may be interpreted within the context of data obtained recently by Faintrenie and Géloën (11), indicating a major role of α-1 signaling of glycolysis and lactate production in
white adipocytes. Previously, we (6) reported that β-blockade resulted in elevated norepinephrine concentrations. It could have been that α-adrenergic stimulation was partially responsible for mobilization of glycogen reserves and increased glycolysis in adipose during exercise at altitude as norepinephrine rose during rest and exercise after acclimatization (21). Failure to observe significant differences in lactate [v-a] or L in blocked versus control subjects (Fig. 2) may be because the mass of adipose tissue in legs was insignificant in comparison with whole body adipose mass. The possibility of an α-adrenergic role in determining the acute and chronic metabolic responses during exercise at high altitude is essentially unexplored.

The limited data available on muscle net lactate release rates from working human muscles (Table 1 and Fig. 2, C and D) offer some comparisons and contrasts with more extensive data sets available on canine muscles studied in situ (27, 28). As in human muscle (Fig. 2C), Stainsby et al. (27) showed that β-blockade did not prevent the surge in lactate release from canine muscle contracting in situ (their Fig. 3B). Moreover, epinephrine infusion did augment lactate release from canine muscle, an effect that was blocked by propranolol. However, Stainsby et al. did not study lactate release from muscles of altitude-acclimatized dogs, and they did not investigate effects of hypoxia on lactate release rate from working canine muscle. However, they did determine that norepinephrine infusion had no significant net lactate release from canine muscle contracting in situ. This absence of an effect of norepinephrine on lactate release from canine muscle is consistent with our hypothesis of an α-adrenergic effect on lactate production and release by nonmuscle tissues in altitude-acclimatized humans.

Because of the limited sampling frequency, lactate contents of biopsy samples offer limited information on muscle lactate exchange transients. For this reason, muscle lactate values are best compared with resting and end-exercise values (Table 2). Muscle lactate contents in unblocked control subjects were remarkably similar to those observed in our previous experiment on Pikes Peak (14). The new results are that β-adrenergic blockade did not prevent accumulation of working muscle lactate (Table 2). The sources of working muscle lactate are difficult to know under the conditions studied as muscle glycolysis, vasculature delivery, and other possible factors, all likely affected intramuscular lactate concentrations (3).

Although subject number in this 1991 Pikes Peak study was almost double that in the 1988 effort (5–7), and housing capacity of the Maher Laboratory as well as effort on part of the research team was close to maximal, sample size and ensuing statistical power may not have been adequate for some statistical comparisons. Based on previous experience (5) the 1991 design possessed sufficient power to demonstrate significant exercise, altitude, acclimatization, and β-blockade effects on several parameters of interest [e.g., blood glucose flux (26)]. In the present report, ANOVA followed by Scheffé post hoc comparisons resulted in significant differences in several parameters (e.g., arterial [lactate]) (Table 2), which were also visually apparent (Fig. 1). With regard to other parameters, e.g., L in β-blocked subjects (Table 1 and Fig. 2D), ANOVA and visual assessments appear to yield different results, as the assumption of homoscedasticity is probably not justified due to the fact that four subjects demonstrated L, one subject demonstrated 0 net lactate exchange, and another net uptake after 45 min of exercise at altitude after acclimatization. Thus concern for a Type II statistical error emerges. In this case the data are best left to the reader for interpretation. Despite vagaries of statistical analysis, as already discussed, it is our opinion that the finding of a tendency for increased limb L during exercise after acclimatization in β-blocked subjects is probably physiologically significant. To reiterate, the result is opposite that expected and is most likely attributable to an effect of β-blockade on increasing muscle glucose uptake (26), while suppressing free fatty acid uptake (25).

In summary, we observed the following: the blood lactate response to submaximal exercise is only partially and transiently related to net lactate release from contracting muscle; a blood lactate paradox of decreased lactate accumulation during a given submaximal exercise task can occur in men after acclimatization to high altitude independent of β-adrenergic influence; a muscle lactate paradox of decreased lactate accumulation during submaximal exercise after altitude acclimatization can occur independent of β-adrenergic influence; lower circulating lactate levels during exercise in altitude-acclimatized men are not due to lesser muscle lactate accumulation; and factors in addition to oxygen transport, muscle oxygen consumption, β-adrenergic stimulation of muscle glycogenolysis, and muscle lactate net release determine the arterial [lactate] during exercise at high altitude. As a consequence of observations that during exercise at altitude arterial blood [lactate] is elevated (compared with rest) and stable, while net lactate release from working muscle ceases, we conclude that tissues other than working skeletal muscle are normally responsible for maintaining the elevation in arterial [lactate] during exercise at altitude and that β-adrenergic stimulation is not requisite for participation by all those tissues. The possibility exists that while β-adrenergic stimulation is normally important in terms of mitigating stresses of exercise and altitude, because of redundancies in physiological controls, compensatory mechanisms such as α-adrenergic stimulation mollify the impediments brought by β-blockade.

Perspectives

Results of the present investigation contribute to the growing body of evidence that conditions that limit oxygen availability, such as iron deficiency anemia and altitude exposure, result in a shift to glycolytic metabolism (4). In the past, investigators have attempted to understand changes in blood [lactate] in terms of the apparently paradoxical observations that altitude exposure results in decreased circulating lactate levels.
Despite persistence of hypoxemia (9, 15, 17, 19, 23). However, positing of a lactate paradox is attributable to the supposition that the lactate response to altitude exposure results from a Pasteur effect. In contrast, it may be that increased glucose and lactate fluxes at altitude (5, 6) reflect the overall shift toward carbohydrate utilization and that altitude acclimatization results in more efficient distribution and utilization of lactate, thus optimizing the energy available for a given oxygen consumption (4).

In the present, as well as in companion reports describing responses to 3 wk of acclimatization to 4,300 m altitude (14, 32, 33), it is apparent that peripheral oxygen transport and use are maintained during altitude exposure. Thus, despite hypoxemia of altitude, there is no evidence of muscle oxygen lack during submaximal exercise. Importantly, we failed to observe an increase in muscle mitochondrial content in men after a 3-wk altitude exposure (14).

Absence of muscle mitochondrial proliferation in response to short-term (3-wk) high-altitude exposure (14) is consistent with the observation that muscle mitochondrial content of Andean natives is the same or less than that of persons of European extraction (9). That neither short-term nor adaptation over generations of altitude exposure result in skeletal muscle mitochondrial proliferation makes the response to altitude different from that of endurance training, which is associated with proliferation of the mitochondrial reticulum (4, 8).

Long-standing debate whether circulatory oxygen transport or peripheral mitochondrial capacity limit \( V_{O_2 \max} \) at SL is ongoing. One view is that once a "critical muscle mass" is recruited during exercise, tissue respiratory capacity exceeds arterial oxygen transport (\( T_{O_2} \)) (4) and \( V_{O_2 \max} \) is limited by \( T_{O_2} \). Because at altitude pulmonary \( O_2 \) uptake and \( T_{O_2} \) are limited (23), then even an average muscle mitochondrial volume density results in tissue respiratory capacity in excess of \( T_{O_2} \). Thus failure of hypobaric hypoxia to provide a stimulus for mitochondrial adaptation can be understood; there is no stimulus to expand capacity of an organelle system that is not limiting. However, necessity to utilize carbohydrate energy sources (glycogen, glucose, lactate) remains a priority at altitude because of the energetic advantages in the presence of a limited \( T_{O_2} \).

Our previous results (5, 6, 23) suggest prominent roles for catecholamines in regulating carbohydrate energy flux during exercise at altitude. Our more recent results contained in the present and companion reports (20, 21, 25, 26) show that \( \beta \)-adrenergic signaling is not obligatory to determining the shift to carbohydrate energy sources at altitude. Participation of mechanisms intrinsic to muscle as well as endocrine signaling indicate the presence of complex and redundant mechanisms regulating acute and chronic metabolic responses to altitude.

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