Lactate and epinephrine during exercise in altitude natives

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Methods

Subjects. Ten healthy male natives from La Paz, Bolivia (3,500–4,000 m, altitude of the measurements 3,600 m), naive with regard to the scientific rationale behind the study, agreed to participate in the experiment. Genetically, the subjects ranged from Amerindian to European with the majority being mestizos. Two subjects dropped out after the first experiment; the data presented are from the eight who remained (age 24.4 ± 0.9 (SE) yr, body mass 62.1 ± 2.7 kg, height 166.5 ± 1.6 cm). After the subjects were screened by a physician, they were informed about the risks of the experi-

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METHODS

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IN UNACCLIMATIZED HUMANS exercising in acute hypoxia, the relationship between blood lactate levels ([La]) and power output (W) is shifted so that [La] is higher at any given W, whereas peak [La] ([La]_{peak}) is similar to (6, 9) or higher than (18) that in normoxia. In contrast, in chronic hypoxia (CH), the relationship between [La] and W is similar to that in normoxia, whereas [La]_{peak} is lower (2, 6, 9, 14, 20, 35). Such a reduction of [La]_{peak} after exhausting exercise, associated with the lower [La] at the same absolute O2 uptake (VO2) compared with in acute hypoxia, has been considered “paradoxi-

Cayser, Bengt, Roland Favier, Guido Ferretti, Dominique Desplanches, Hilde Spielvogel, Harry Koubi, Brigitte Sempore, and Hans Hoppeler. Lactate and epinephrine during exercise in altitude natives. J. Appl. Physiol. 81(6): 2488–2494, 1996. —We tested the hypothesis that the reported low blood lactate accumulation ([La]) during exercise in altitude-native humans is refractory to hypoxi-

Based on observations on Andean Amerindians, it was recently proposed that altitude natives may have fundamentally different features with regard to the energetics of exercise compared with lowlanders (16). A higher-than-normal mechanical efficiency was accompanied by lower-than-normal blood [La]. These low [La] values at any W appeared refractory to hypoxi-

altitude acclimatization (5, 15, 25, 28, 37). Indeed, in acute hypoxia at any given W, [Epi] is initially increased compared with normoxia; however, with accli-
matization it returns toward normoxic values, whereas the relationship between [Epi] and [La] remains largely unchanged (5, 25, 28). The reduction in [La]_{peak} would occur with acclimatization because at altitude, peak W (W_{peak}) is reduced (3, 19, 21).

LaPaz,Bolivia(3,600m)performed
ments and signed a consent form. The experiments were approved by the local ethical committee. For another study, the subjects had previously engaged in an endurance training protocol in ambient air (i.e., hypobaric hypoxia) as described elsewhere (10). The below-described experiments were conducted during the week after the end of the training protocol.

Exercise protocols. The subjects performed one- and two-leg cycling tests in hypoxia and normoxia on different occasions in a random balanced order. After 5 min of rest from sitting on an electrically braked cycle ergometer (model STS-3, Cardio-line), the subjects began cycling. One-leg cycling was performed with the nondominant leg, and the foot was firmly attached to the pedal by means of a special cycling shoe. The other leg rested on a support next to the ergometer. Cycling pace was kept between 60 and 80 revolutions/min and the cycle automatically adjusted to changes in revolutions per minute to maintain power constant. The ergometer used had sufficient inertia to prevent slowdown during the upstroke of the active leg. One-leg cycling started from 40 W, and the intensity was increased by 20-W steps every 4 min until voluntary exhaustion. Two-leg cycling started from 60 W and increased by 30-W steps. In the event that the subject could not sustain the last step for the full 4 min, Wpeak was defined as the highest intensity achieved by prior application of a hyperemia-inducing ointment (Trafuril, Ciba-Geigy). Arterial O2 saturation (Sao2) was continuously measured at rest and during the exercise tests oximetry (Biox, Ohmeda). Arterial O2 concentration (CaO2) was calculated as Hb × SaO2 × 1.34.

Before the one-leg exercise tests, a catheter was positioned in an antecubital vein of an arm and connected to a three-way valve. Samples (5 ml) were drawn with a syringe. Samples were drawn during exercise at the end of each load as well as at exhaustion. The first portion of blood present in the catheter and valve was discarded. The samples were immediately transferred into tubes containing EDTA and put on ice until the end of the experiment. Subsequently, they were centrifuged at 800 g for 10 min and the plasma was stored at −80°C. At the completion of the study, the samples were flown to France on dry ice for catecholamine analysis (23).

Statistics. Values are means ± SE. Comparisons between means were done with Student’s paired t-test. In case of repeated measures, in-time comparisons were performed with analysis of variance and analysis of covariance. Linear regression analysis was used on individual and group [La] vs. [Epi]. P < 0.05 was considered significant.

RESULTS

Gas exchange. The VO2 vs. W relationships in the four experimental conditions are shown in Fig. 1A. VO2peak during two-leg cycling was significantly higher in AN compared with CH (3.18 ± 0.39 vs. 2.90 ± 0.37 l/min, respectively; P < 0.05). This higher VO2peak was attained at a significantly higher Wpeak (242 ± 25 vs. 226 ± 26 W, respectively; P < 0.05). In contrast, Wpeak was the same for both one-leg exercise tests (119 ± 5 vs. 118 ± 6 W, respectively; not significant), whereas VO2peak during one-leg cycling was lower in AN compared with hypoxia (2.10 ± 0.12 vs. 2.26 ± 0.10 l/min, respectively; P < 0.05). AN did not change the linear relationship between VO2 and submaximal W during either one- or two-leg exercise (see Fig. 1A). At the highest intensity during one-leg exercise in hypoxia, VO2 and W were shifted up. During the one-leg exercise, the slopes of the lines were steeper than during two-leg cycling exercise. Calculated net mechanical efficiency at submaximum amounted to ~20% during one-leg cycling and ~27% during two-leg cycling.

[La] vs. W. During two-leg cycling in AN, the relationship between [La] and W was shifted down and to the right and [La]peak was reduced from 9.0 ± 1.4 to 8.3 ± 1.6 (P < 0.05) and was attained at a significantly higher Wpeak (Fig. 1B). During one-leg cycling, a similar shift in [La] vs. W relationship occurred compared with during two-leg cycling, and [La]peak decreased significantly from 5.1 ± 0.2 mM in hypoxia to 4.3 ± 0.2 mM in AN (P < 0.05). During one-leg exercise, higher [La]
levels were found at any submaximum W compared with during two-leg exercise.

[Hb], SaO2, and blood gases. Both one- and two-leg exercise caused hemocoenustration. During one-leg exercise, [Hb] increased during hypoxic exercise (from 167 ± 3 to 182 ± 4 g/l; P < 0.05), but no significant difference was reached during normoxic exercise (from 172 ± 2 to 176 ± 2 g/l; not significant). Both at rest and at exhaustion, SaO2 was significantly higher in AN compared with hypoxia (Fit. 1C). No significant desaturation compared with resting values occurred during the exercise in both conditions. CaO2 increased from 230 ± 10 to 237 ± 9 ml/dl in normoxia and from 210 ± 10 to 228 ± 16 ml/dl in hypoxia during the exercise due to the increased [Hb] In hypoxia, arterial PO2 (P(O2)) increased from 56.8 ± 0.7 to 63.9 ± 1.6 Torr, whereas arterial PCO2 (P(CO2)) decreased from 28.9 ± 1.0 to 24.3 ± 0.8 Torr. The pH decreased from 7.41 ± 0.01 to 7.31 ± 0.01. In normoxia, P(O2) increased from 84.2 ± 3.6 to 102.3 ± 3.0 Torr, whereas P(CO2) decreased from 30.5 ± 1.3 to 26.0 ± 1.1 Torr. The pH decreased from 7.40 ± 0.01 to 7.32 ± 0.01.

During two-leg exercise, [Hb] increased from 171 ± 3 to 181 ± 4 g/l in hypoxia and 173 ± 4 to 190 ± 3 g/l in normoxia. SaO2 did not decrease significantly during two-leg exercise in normoxia but dropped significantly from 90 ± 1 to 84 ± 1 during hypoxic exercise (Fit. 1). CaO2 increased from 229 ± 16 to 246 ± 20 ml/dl in normoxia and from 214 ± 11 to 212 ± 18 ml/dl in hypoxia. In hypoxia, P(O2) decreased from 57.4 ± 1.6 to 55.3 ± 1.5 Torr, whereas P(CO2) decreased from 27.6 ± 1.6 to 24.1 ± 1.2 Torr. The pH decreased from 7.41 ± 0.01 to 7.25 ± 0.02. In normoxia, P(O2) increased from 83.1 ± 3.0 to 90.0 ± 2.1 Torr, whereas P(CO2) decreased from 29.1 ± 1.3 to 27.1 ± 0.8 Torr. The pH decreased from 7.40 ± 0.01 to 7.25 ± 0.02.

HR and DP. During one-leg exercise, HR was significantly lower throughout the normoxic test compared with hypoxia, reaching maximum values of 164 ± 5 vs. 173 ± 5 beats/min (P < 0.05), respectively. DP was higher at submaximum W in hypoxia than in normoxia and reached significantly higher peak values in hypoxia in normoxia (28,324 ± 1,745 vs. 25,903 ± 1,901 Torr/min, respectively; P < 0.05; Fig. 1D). During two-leg exercise, HR was also significantly lower throughout the normoxic test compared with hypoxia but reached the same maximum value of 188 ± 4 beats/min. DP was higher at submaximum W in hypoxia than in normoxia but reached similar peak values in hypoxia compared with normoxia (29,832 ± 1,062 vs. 29,643 ± 1,083 Torr/min, respectively; not significant).

[La] vs. [Epi]. During one-leg exercise in normoxia, both the [La] and [Epi] vs. W relationships were significantly shifted down compared with hypoxia (P < 0.001 and P < 0.05, respectively) (Figs. 1A and 2B). There was no significant difference between the norepinephrine concentration vs. W relationships in the two conditions (Fig. 2B). Individual [Epi] and [La] were significantly correlated (average r = 0.81). Analysis of covariance (independent variable [La]; dependent variable [Epi]; covariate W) indicated no effect of inspired O2 fraction (FIO2) on the [Epi] vs. [La] relationship. Regression analysis showed no significant differences in slope and intercept of the [Epi] vs. [La] relationship in the two conditions. In Fig. 3A, the average values of the two parameters measured at each W are related to each other, showing the similarity of the relationship in the two conditions, except for the fact that at equivalent
both [Epi] and [La] attained significantly lower values in AN compared with CH.

**DISCUSSION**

[La] vs. W during two-leg exercise. The primary aim of the present study was to test the hypothesis that the [La] vs. W relationship in altitude natives is refractory to changes in FIO2. During two-leg cycling, the present lifetime-acclimatized subjects had significantly lower [La] levels at any given W in AN than in CH (Fig. 1B). The [La] vs. W relationship in CH was similar to that of unacclimatized lowlanders acutely exposed to the same PiO2 as our subjects (18). The [La]peak levels in our subjects were similar to those reported in unacclimatized lowlanders (14, 18, 35) and higher than reported in altitude native Quechua Amerindians from the Andes plateau (17). The latter were reported to exhibit a [La] vs. W relationship refractory to changes in FIO2, and it was argued that this may be due to a constraint tighter linkage between glycolysis and oxidative phosphorylation in altitude natives (17). If this hypothesis were correct, then the relationship between [La] and W should not have changed in AN compared with CH and [La]peak levels should have been lower compared with those observed in lowlanders. This was not the case, and the hypothesis, therefore, does not seem to hold for our altitude native subjects (10). However, because genetically these subjects ranged from Amerindian to European with the majority being Mestizos, our results may not be fully comparable with those obtained on the Quechas in the above-cited studies. Nevertheless, as discussed in detail below, our study is the first that clearly indicates that altitude natives seem not to be fundamentally different with regard to [La] during exercise compared with acclimatized lowlanders.

What could be the reason for the shift in the relationship between [La] and W on acute exposure to normoxia? The classic answer to this question is that hypoxia reduces mass O2 transport, which leads to tissue disoxia and, therefore, increased reliance on anaerobic metabolism. However, the concept of O2-limited metabolism during exercise is currently much debated (4, 8, 13). Several investigators have used the decrease in VO2peak and the increase in [La] at any W in hypoxia as proof for the cellular disoxia hypothesis. However, increased [La] per se is not proof of cellular disoxia. There is now persuasive evidence suggesting that lactate production in healthy subjects during exercise does occur under aerobic conditions and that lactate is not a waste product but an important and useful substrate (4). In lowlanders, it was found that acute hypoxia not only decreased VO2peak but also decreased VO2 at submaximum W, a finding that is in agreement with the disoxia hypothesis (18). In hypoxia, [La] was higher at submaximum W and reached a higher [La]peak than in normoxia. On the other hand, there was a tight relationship between [La] and circulating catecholamines that was independent of FIO2. Although one must be careful about implying cause and effect simply from correlational studies, Hughson et al. (18) concluded that [La] might increase in hypoxia in part as a direct consequence of stimulation of skeletal muscle glycogenolysis by the increase in circulating catecholamines. Even though our subjects did not show any significant effect of FIO2 on submaximum VO2, we propose that the mechanism for their lower [La] levels
in AN could be similar to that of the higher [La] levels in lowlanders exposed to acute hypoxia. Because our subjects did not consent to additional catheters, we have no data on blood catecholamine concentration during two-leg cycling in the two conditions, but the analysis of the blood samples obtained during one-leg cycling discussed below supports this hypothesis.

One-leg cycling performance. The rationale for one-leg exercise was based on the observation that at least part of the difference between maximum [La] accumulation during normoxic and hypoxic two-leg exercise in acclimatized subjects is due to a lower maximum W and \( \dot{V}O_2 \) in hypoxia (14, 19). Because the major limiting factors are located in the periphery during one-leg exercise, we argued that during one-leg exercise peak W and \( \dot{V}O_2 \) would be quite similar in the two conditions allowing direct comparison of the data obtained at equal absolute and relative levels. One-leg exercise was performed at a slightly lower mechanical efficiency compared with two-leg exercise, as previously reported by Fulco et al. (11). Submaximum one-leg \( \dot{V}O_2 \) vs. W relationships were indeed the same in CH and AN, but the subjects attained a slightly but statistically significantly higher \( \dot{V}O_2 \) peak in hypoxia (Fig. 1A). We attribute this paradoxical rise to a further reduction in mechanical efficiency at high W during the hypoxic exercise test. We observed that the subjects moved about more at the end of the hypoxic exercise than during the normoxic trial, indicating additional but less economical muscle recruitment. Alternatively, because the end point of exercise was volitional and the usual criteria to ascertain \( \dot{V}O_2 \) peak could not always be met, the possibility of some subject not reaching the "true" maximum cannot be excluded. In any case, in the absence of invasive data of one-leg muscle \( \dot{V}O_2 \) peak, only circumstantial evidence supports the contention of similar \( \dot{V}O_2 \) peak in the two conditions. First, \( W_{\text{peak}} \) was the same for a constant O\(_2\) cost of mechanical work implying equal \( \dot{V}O_2 \) peak. Second, during hypoxic compared with normoxic two-leg exercise, maximum cardiovascular capacity was reached at lower W, as evidenced by the plateau in DP vs. W (Fig. 1D). In contrast, during one-leg exercise DP never reached its maximum. In addition, \( \text{SaO}_2 \) did not drop significantly during one-leg exercise (Fig. 1C). Therefore, during one-leg exercise mass O\(_2\) transport may not have reached the same (maximum) levels as during two-leg exercise. In other invasive studies on submaxim\( \dot{V}O_2_{\text{peak}} \) two-leg exercise in hypoxia, the O\(_2\) flow to the legs remained remarkably constant despite increases in \( \text{CaO}_2 \) caused by acclimatization (1, 36). During one-leg kicking exercise, changes in \( \text{CaO}_2 \) were offset by changes of leg blood flow of opposite sign, thereby maintaining mass O\(_2\) transport to the leg constant (30). On the other hand, recent experiments in lowlanders during maximum one-leg kicking exercise suggest that peripheral O\(_2\) transfer may be diffusion limited and may lead to a lower \( \dot{V}O_2 \) peak in hypoxia (33). We speculate that during one-leg exercise in both AN and CH, the cardiopulmonary determinants of O\(_2\) transport were not outstripped and maximum mechanical W and \( \dot{V}O_2 \) were mainly set by the periphery, although the conclusive argument awaits invasive measurements.

[\( \text{Epi} \)] vs. [\( \text{La} \)] relationship during one-leg exercise. In lowlanders, the changes in the [\( \text{La} \)] vs. W relationship during acclimatization have been attributed, at least in part, to changes in the adrenergic drive of glycolysis (5, 15, 19, 25, 28, 37). The present study is the first to report data on [\( \text{Epi} \)] vs. [\( \text{La} \)] in exercising altitude natives. If, for the same \( \dot{V}O_2 \) vs. W relationships, any differences in [\( \text{La} \)] vs. W in these subjects are tightly related to changes in [\( \text{Epi} \)] vs. W, then the argument in favor of the catecholamine hypothesis would be strengthened. As in the two-leg exercise test, during one-leg cycling [\( \text{La} \)] at any given W was lower in AN compared with \( \text{CH} \). The shape of the [\( \text{Epi} \)] vs. W curve was similar to that of the [\( \text{La} \)] vs. W curve in both conditions (Fig. 2). Individual [\( \text{Epi} \)] and [\( \text{La} \)] were tightly correlated (mean r = 0.81), and this relationship was independent of \( F_{\text{IO}_2} \). This finding, besides confirming the findings of Hughson et al. (18), who also found a tight relationship between lactate and catecholamines independent of \( F_{\text{IO}_2} \), in nonacclimatized lowlanders, is compatible with several other observations carried out during altitude exposure. During sustained submaximal cycle exercise at altitude, glycolyse use is increased during the initial phase when [\( \text{Epi} \)] is high and returns toward control levels after acclimatization (15). Both at sea level and at high altitude, the rates of lactate appearance in blood as well as arterial [\( \text{La} \)] are closely related to [\( \text{Epi} \)], suggesting a relationship between adrenergic drive and [\( \text{La} \)] (5, 15, 25, 28). In view of the above-discussed findings on similar submaximum and maximum one-leg \( \dot{V}O_2 \), the argument of disoxia as a cause for the different [\( \text{La} \)] vs. W relationships appears weakened. In any case, even if the one-leg \( \dot{V}O_2_{\text{peak}} \) had been lower in hypoxia than in normoxia, the argument that there is a tight association between [\( \text{La} \)] and [\( \text{Epi} \)] in acclimatized natives, like in unacclimatized and acclimatizing lowlanders (5, 18), that is independent of \( F_{\text{IO}_2} \), would still hold true. Whether such an association is the result of a cause-effect relationship remains to be proven.

Because the glycogenolytic effect of [\( \text{Epi} \)] leading to higher [\( \text{La} \)] is claimed to be mediated through muscle \( \beta_{2} \)-receptors (6, 22, 29, 34) via a second-messenger system initiating a cascade of events eventually increasing glycolysis and [\( \text{La} \)], one could roughly expect a ligand-receptor type of relationship. Thus a sigmoid curve was fitted to the present data in Fig. 3A. For comparison in Fig. 3B, we have replotted the average data points [obtained via a digitizing procedure by using a scanned image of a graph of Podolin et al. (27)] that were originally fitted through a straight line. Podolin et al. looked at the effects of glycogen depletion on [\( \text{Epi} \)] and [\( \text{La} \)] during normoxic exercise. In both studies, it appears as if beyond a given [\( \text{Epi} \)], [\( \text{La} \)] approaches an asymptote, which would be in agreement with the saturation hypothesis. Close inspection of the data in the study by Hughson et al. (18) also showed that in several subjects the [\( \text{La} \)] vs. [\( \text{Epi} \)] relationship seemed to approach a plateau. Of course,
should not be overlooked that we are looking at blood [La] values that result from production, uptake, and utilization (4). The observed saturating effect must therefore be interpreted with caution until further evidence has been gathered, preferably with tracer techniques allowing measurement of lactate appearance rates instead of [La] values. Contrary to the findings of Hughson et al., which were obtained in acute hypoxia, we did not find that norepinephrine concentration was different at any given W on changes of FIO2. The effect of CH on catecholamines is known to have a different time course for epinephrine and norepinephrine (25). [Epi] during exercise is initially higher than at sea level and then drops as acclimatization progresses, whereas norepinephrine concentration is initially not much different from that found at sea level and then progressively increases. If at altitude epinephrine seems more related to lactate, norepinephrine seems more related to systemic vascular resistance (25).

Contrary to the findings on acclimatized lowlanders (22, 31), the present subjects did not increase [La]peak during hypoxic one-leg exercise beyond the values obtained for two-leg exercise. We have no thorough explanation for this finding but speculate that it may be related to the hypothesis of an early central (nervous) limitation of exhaustive exercise with large muscle groups in lowlanders at very high altitude (3, 19, 21, 22). Therefore, this hypothesis does not seem to apply to the present subjects in their usual habitat at 3,600 m.

In conclusion, the new findings of this study are that, compared with unacclimatized lowlanders exercising in normoxia and hypoxia, endurance-trained high-altitude natives 1) have similar [La] vs. W curves; 2) have similar displacements of [La] vs. W curves on changes in FIO2; and 3) show a tight relationship between [Epi] and [La] during exercise that is independent of FIO2. Thus high-altitude natives appear not fundamentally different from lowlanders with regard to the effect of acute changes in FIO2 on [La] during exercise. The present findings are compatible with the contention of an increased adrenergic drive that reduces the apparent linkage between glycolysis and oxidative phosphorylation in humans exercising in hypoxia.

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