Skeletal muscle metabolism and work capacity: a ^{31}P-NMR study of Andean natives and lowlanders

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MATHESON, GORDON O., PETER S. ALLEN, DAVID C. ELLINGER, CHRISTOPHER C. HANSTOCK, DANIEL GHEORGHIU, DONALD C. MCKENZIE, CAROLE STANLEY, WADE S. PARKHOUSE, AND PETER W. HOCHACHKA. *Skeletal muscle metabolism and work capacity: a ^{31}P-NMR study of Andean natives and lowlanders.* J. Appl. Physiol. 70(5): 1963–1976, 1991.—Two metabolic features of altitude-adapted humans are the maximal O_2 consumption ($\dot{V}O_{2\,max}$) paradox (higher work rates following acclimatization without increases in $\dot{V}O_{2\,max}$) and the lactate paradox (progressive reductions in muscle and blood lactate with exercise at increasing altitude). To assess underlying mechanisms, we studied six Andean Quechua Indians in La Raya, Peru (4,200 m) and at low altitude (<700 m) immediately upon arrival in Canada. The experimental strategy compared whole-body performance tests and single (calf) muscle work capacities in the Andeans with those in groups of sedentary, power-trained, and endurance-trained lowlanders. We used ^{31}P nuclear magnetic resonance spectroscopy to monitor noninvasively changes in concentrations of phosphocreatine ([PCr]), [P_i], [ATP], [PCr]/[PCr] + creatine ([Cr]), [P_i]/[PCr] + [Cr], and pH in the gastrocnemius muscle of subjects exercising to fatigue. Our results indicate that the Andeans *1*) are phenotypically unique with respect to measures of anaerobic and aerobic work capacity, *2*) despite significantly lower anaerobic capacities, are capable of calf muscle work rates equal to those of highly trained power- and endurance-trained athletes, and *3*) compared with endurance-trained athletes with significantly higher $\dot{V}O_{2\,max}$ values and power-trained athletes with similar $\dot{V}O_{2\,max}$ values, display, respectively, similar and reduced perturbation of all parameters related to the phosphorylation potential and to measurements of [P_i], [PCr], [ATP], and muscle pH derivable from nuclear magnetic resonance. Because the lactate paradox may be explained on the basis of tighter ATP demand-supply coupling, we postulate that a similar mechanism may explain *1*) the high calf muscle work capacities in the Andeans relative to measures of whole-body work capacity, *2*) the $\dot{V}O_{2\,max}$ paradox, and *3*) anecdotal reports of exceptional work capacities in indigenous altitude natives.

altitude adaptation; lactate paradox; maximal oxygen uptake paradox

TWO METABOLIC CHARACTERISTICS of high-altitude-adapted humans set the stage for the present study: the maximal O_2 consumption ($\dot{V}O_{2\,max}$) paradox and the lactate paradox. The former arises from the observation that a human's capacity to perform sustained muscular work improves as a result of endurance training at sea level as well as after a period of acclimatization to moderate altitude. Exercise performance improvements resulting from endurance training at sea level are associated with increases in $\dot{V}O_{2\,max}$ capacities (24), whereas those seen in altitude adaptation (27, 30) occur with little or no change in $\dot{V}O_{2\,max}$ capacities (13, 39, 42, 45). Improved muscle work capacity with no change in $\dot{V}O_{2\,max}$ capacity (the $\dot{V}O_{2\,max}$ paradox) has not been appreciated or properly explained by earlier studies in this field.

Because our goal in this study was to assess or expose altitude-related adaptations at the peripheral (muscle metabolic) level in Andean natives, our experimental strategy focused on the functional properties of a single muscle (the gastrocnemius) in an aerobic exercise protocol to fatigue. To this point, our efforts to identify sites of adaptive adjustments in Andean natives have relied on measurement of whole-organism exercise performance (especially $\dot{V}O_{2\,max}$) under normoxic and hypoxic conditions (23). In whole-body aerobic exercise tests, the maximal sustainable power output requires a maximal metabolic power input of ~30 μmol ATP · g muscle^{-1} · min^{-1}. In contrast, maximal power output during exercise protocols involving smaller muscle masses in humans can reach values some three to four times higher. For example, metabolic rates of 350 ml O_2 · kg^{-1} · min^{-1} have been reported for the human quadriceps muscle (2).

Generally, it is believed that the peripheral metabolic adaptations (increased capillary and mitochondrial volume densities plus elevated activities of oxidative enzymes) that accompany improvements in work capacity allow greater overall O_2 fluxes per gram of muscle even if individual mitochondria in muscle may operate at reduced O_2 utilization rates (25). These types of adaptations are found in the skeletal muscle of endurance-trained athletes, where increases in [ADP] and [P_i] and concomitant decreases in phosphocreatine concentration ([PCr]) and [ATP] at any given work rate are less than in the untrained state (25). If these types of adaptations were to underlie the improved work capacities of

altitude-adapted individuals, then similar morphometric and enzyme activity changes would be expected in muscles of altitude-acclimatized lowlanders or indigenous highlanders. The problem is that this is not observed (8, 17, 18, 26, 28, 33, 46).

If we cannot appeal to the "classical" molecular adaptations of endurance-trained athletes (which increase $\dot{V}O_{2\,max}$ capacities), how are we to explain the findings of Maher et al. (30) and Horstman et al. (27) as well as anecdotal reports of notably improved work capacities of indigenous highlanders (29, 40)? One possibility may lie in adaptations that improve the efficiency of energy flux at the level of working muscle. Although there may be several biochemical strategies for upscaling energetic efficiency, the largest advantages arise from maximizing the ratio of work achievable to amount of ATP utilized (22). In muscles designed this way, it is expected that large changes in work rate would be accompanied by smaller than usual changes in the concentrations of the adenylates, [PCr], [P_i], and pH in muscle (22); i.e., the muscles would display relatively tight ATP demand-supply coupling. In most skeletal muscles, a change in phosphorylation potential correlates with change in O_2 consumption ($\dot{V}O_2$) because the former drives the latter (11); we refer to this situation as a loosely coupled energy demand-supply system, simply because the concentrations of ATP and other key metabolites (including PCr, P_i, H^+, and lactate) change as the rate of ATP cycling changes (22). Possible mechanisms that characterize tightly vs. loosely coupled energy demand-supply muscles are discussed elsewhere (3, 22). For the purposes of this study, muscles maximizing the ratio of work to amount of ATP utilized (muscles maximizing energetic efficiencies) would behave as if energy demand-supply coupling were tighter than usual and may account for the $\dot{V}O_{2\,max}$ paradox.

If this were the case, reductions in the magnitude of Δ[ADP], Δ[P_i], Δ[PCr], and Δ[H^+] (i.e., reductions in the degree of change in the phosphorylation potential or all regulatory parameters related to it during exercise at altitude) could also serve to explain the second major metabolic characteristic of altitude-adapted individuals, the so-called lactate paradox. First described over 50 years ago (10, 14) and more recently analyzed by several authors (7, 18, 21, 41), the lactate paradox refers to the effects of altitude acclimatization on muscle lactate formation (18) and on blood lactate accumulation (10, 14, 39, 41) during incremental $\dot{V}O_{2\,max}$ tests: the higher the altitude of acclimatization, the lower the lactate formation rates and the lower the lactate concentrations observed. It is termed a paradox because acute hypoxia in unacclimatized individuals serves to increase muscle and blood lactate levels at any given work load (6, 31) and because at first glance one would expect the Pasteur effect to come into play (glycolysis increasingly activated with progressive hypobaric hypoxia to meet the ATP shortfall due to tissue hypoxemia). Thus, just as the concept of a more tightly coupled energy demand-supply regulation would help explain the $\dot{V}O_{2\,max}$ paradox above, it could also explain the lactate paradox in muscles of altitude-adapted individuals on the basis of less adenylate perturbation and consequently less stimulation of glycolysis.

To test these concepts experimentally, we selected as subjects six high-altitude-adapted Andean natives (Quechua Indians) who had lived all their lives at moderate altitude (~4,000 m). Our research strategy was to compare whole-body and single-limb calf muscle exercise capacities of the indigenous highlanders with those of three other groups of lowlanders separated by distinct differences in their physical conditioning: *1*) completely sedentary, *2*) power-trained athletes, and *3*) endurance-trained athletes. Whole-body comparisons of strength and aerobic and anaerobic capacity were performed using standard human performance measurement techniques. To obtain measurements that would shed light on the nature of the energetic adaptations that occur in exercising skeletal muscle, ^{31}P nuclear magnetic resonance (NMR) spectroscopy was used, because this type of data collection enabled repeated measures of key muscle metabolites to be obtained more frequently than could be realistically or ethically obtained by needle biopsy. This technique allowed us to monitor relative [ATP], [P_i], [PCr], and pH during rest, exercise to fatigue, and recovery in the gastrocnemius muscle.

In this study we were able to show that acclimatized Andean natives are able to sustain single-limb work rates equal to those of elite endurance- and power-trained athletes with equal or reduced perturbation in high-energy phosphate metabolites and pH.

MATERIALS AND METHODS

Subjects. Four separate groups of volunteers were tested: one group of altitude-adapted Andean natives and three groups (n = 6 in each group) of lowlanders distinguished by their level of training: sedentary, power trained, and endurance trained. The highlanders were Quechua Andean natives, lifetime residents of the La Raya region of Peru (3,700–4,500 m) and workers at the La Raya Veterinary Research Station (4,200 m). These subjects were relatively active in their home environment but did not train regularly or intensively. The 18 Caucasian lowlander subjects were lifetime residents below 700 m, and none had previously lived at altitudes exceeding their current residence. The sedentary group had occupations that involved sitting at a desk and did not actively train outside their work place. The power-trained group consisted of athletes in sports that required strength but not aerobic fitness (e.g., sprinting) and who engaged in regular weight training. The endurance-trained group was comprised of marathoners and ultramarathoners, all record holders in 26-, 50-, and 100-mile road races and all capable of marathon race times <2 h 30 min.

Performance measurements. Each subject received an incremental cycle ergometer test to fatigue to measure $\dot{V}O_{2\,max}$, a modified Wingate test to measure anaerobic power, and a maximal isokinetic torque test of plantar flexion of the foot to measure maximal voluntary contraction (MVC) of the calf muscle. The Andean natives were tested within 48 h of arrival at sea level. Each of the

lowlander subjects received the same battery of whole-body performance measurements. For the measurement of maximal aerobic capacity, after a 4-min warm-up, subjects cycled at 50 rpm with resistance set at 1.0 kg. The resistance was increased by 1.0 kg every 2 min until the respiratory exchange ratio was ~1.0 and then by 0.5 kg each minute until fatigue. Anaerobic power was measured using a modified cycle ergometer Wingate test (36) in which resistance was set at 0.095 kg/kg body wt. By use of a photoelectric cell to count pedal revolutions, work output (W) was calculated for each 5-s period during the 30-s test. Measurements of maximal calf strength were made at 60°/s by use of a Cybex II isokinetic dynamometer fitted with a foot pedal. Care was taken to ensure that positioning of the subject for this test was identical to that for the NMR test described below; i.e., the position of the knee and ankle, the angular velocity, and the axis of rotation were similar in the two tests.

NMR exercise protocol. The six Andean natives were tested within 48 h of leaving altitude, whereas the lowlanders were tested at their convenience. The right calf muscle (dominant limb) was exercised to fatigue aerobically in a specially fabricated nonferromagnetic ergometer. The ergometer bed consisted of a 2-m-long sheet of aluminum machined to conform to the shape of the NMR patient bed and secured in place by the weight of the subject, rubberized backing, and two straps running from each end of the NMR machine. On one end of the ergometer a foot pedal was mounted that allowed plantar flexion of the ankle from neutral (0°) to +15°. The right foot was strapped into the foot pedal device so that the axis of rotation of the foot pedal occurred in the same plane as the anatomic axis of plantar flexion of the ankle. One end of a nylon rope was attached to the base of the foot pedal and the other passed through a wall-mounted pulley system to a plastic container into which weight was incrementally added. Eccentric muscle work was eliminated because the weight attached to the base of the foot pedal served to return it immediately to the neutral position during relaxation.

The exercise protocol was designed as an aerobic test to fatigue. Duty cycle was fixed at 1:1 by the subjects depressing the foot pedal for 1 s and relaxing for 1 s (30 contractions/min). Cadence was maintained by the use of an audible beep and a visible light triggered by the pulse program of the data acquisition system. Each minute, 2 kg of weight were added while an infrared optical switch monitored pedal excursion to ensure complete depression with each contraction. Initial work rate was 42.3 J/min (0.71 W), and this was incremented by 23.5 J/min (0.39 W). Absolute work, work rates, and integrated (total) work were calculated directly from the mass being lifted. Because whole-body anaerobic and aerobic power measurements are standardly expressed relative to body mass, relative calf work rates were also calculated as a ratio of calf work (J) to body mass (J/kg). In addition, calf work rates at fatigue were expressed relative to the MVC of the calf muscle (%MVC).

Fatigue was taken as the inability to maintain rhythm or displacement despite verbal encouragement. With the Caucasian lowlanders, determining the point of fatigue was straightforward. With the Spanish-speaking Andean natives, an interpreter facilitated communication throughout the test.

Hypoxia. Each subject performed the NMR test twice, once breathing room air and once breathing a hypoxic gas mixture to simulate the hypobaric conditions in the subjects' native environment (inspiratory O_2 fraction 14.5 ± 0.5%). The subjects received 1 h of rest between the two tests, and the order of the tests was systematically varied to avoid a confounding effect from condition order. A gas cylinder of the hypoxic mixture was connected to a mouthpiece through which the subject breathed during the NMR experiments. Expired gases from the mouthpiece were delivered to a CO_2 sensor (P-61B) and CO_2 analyzer (CD-3A) by a flow control pump (R-1, Applied Electrochemistry AMETEK), allowing continuous monitoring of expired CO_2. This measurement allowed the titration of additional CO_2 from a separate gas cylinder to minimize hypocapnia and alkalosis induced by breathing the hypoxic mixture. Subjects were allowed to breathe the reduced-O_2 mixture for 20 min before starting the exercise, and after this adjustment period in most cases the addition of CO_2 to the inspired gas was negligible. An in-line O_2 sensor continuously monitored the concentration of O_2 delivered to the subject, and percent oxyhemoglobin saturation (range 90–92%) was monitored from the index finger by means of a pulsed oximeter (N-100 Nellcor). These experiments were conducted in Edmonton, Alberta (barometric pressure 704 Torr).

NMR data acquisition. ^{31}P spectra were acquired at 1.5 T from the gastrocnemius muscle of the right leg of each subject by means of a Philips Gyroscan NMR machine. The subject was positioned supine with the belly of the right calf resting centrally on a 4-cm-diam surface coil antenna, the knee comfortably positioned in 30° flexion with foam supports, and both the upper and lower legs firmly secured with Velcro strapping.

The spectral volume of ≈20 ml centered 2 cm into the calf was localized using a simple depth pulse sequence (4) that included $\theta/5$ and $\theta/3$ high-flux signal suppression to remove signals from the surface region. Typical resting spectra had a signal-to-noise ratio of 8:1 for β-ATP and displayed a clear resolution of the J coupling within the three ATP peaks. Phase cycling and signal averaging were accommodated within 60 averages of the free induction decays using a repetition interval of 1 s. The raw time domain data were processed using Fourier transformation, spline baseline correction, two orders of phase correction, and a convolution difference procedure with line broadenings of 5 and 15 Hz. The processed spectra were curve fitted using simplex optimization routines to give peak areas (relative $[P_i]$, [PCr], and [ATP]) and chemical shift differences (allowing calculation of intracellular pH). The curve-fitting routines employed could use Lorentzian, Gaussian, or a mixture of the two for the chosen line shapes. The line shape could be chosen independently for each peak, and the choice made minimized the subtraction error between the data and the fitted spectrum. The initial guess for each resonance was made by the operator before simplex optimization. The relative

TABLE 1. *Measurements of whole-body work capacity*

	AHL	SED	PWR	AER
Age, yr	34.0±1.1	27.0±1.2	24.3±1.3	29.5±0.4
Height, cm	159.5±2.1	181.6±3.1	181.2±2.8	176.3±2.0
Weight, kg	60.5±1.6	94.3±7.5	89.8±3.6	63.9±2.2
HR_{max}	182.7±3.5	182.3±5.1	188.0±2.5	171.0±4.2
$RER_{fatigue}$	1.25±0.04	1.09±0.04	1.17±0.06	1.11±0.03
$\dot{V}O_{2\,max}$, l/min	3.05±0.18	3.32±0.34	4.07±0.30	4.05±0.08
$\dot{V}O_{2\,max}$, $ml \cdot kg^{-1} \cdot min^{-1}$	50.3±2.0	35.4±2.9	45.3±2.9	63.3±1.3
Absolute anaerobic capacity, W	341.2±17.5	598.9±44.7	796.7±70.4	539.3±47.0
Relative anaerobic capacity, W/kg	5.65±0.28	6.47±0.54	8.79±0.48	8.22±0.59
Δanaerobic capacity, %	62.8±1.9	49.2±2.4	50.2±1.6	71.3±4.6

Values are means ± SE. HR_{max}, maximum heart rate; $RER_{fatigue}$, respiratory exchange ratio at fatigue; $\dot{V}O_{2\,max}$, absolute (l/min) and relative ($l \cdot min^{-1} \cdot kg^{-1}$) maximal O_2 uptake (graded cycle ergometer exercise); Δanaerobic capacity, power output in last 5 s of Wingate test divided by power output in first 5 s, expressed as percentage. AHL, Andean natives; SED, sedentary; PWR, power trained; AER, endurance trained. Results of Bonferroni post hoc tests are summarized in Table 3.

peak areas were subsequently corrected for relaxation time differences.

^{31}P spectra were acquired over 1-min intervals during rest, during exercise to fatigue, and for 20 min in recovery. Each free induction decay acquisition was made in intervals between muscle contractions, while the limb was stationary. The relative peak areas were subsequently corrected for relaxation time differences. Data so acquired permitted the dynamic changes in energy metabolism to be monitored with a 1-min time resolution and with excellent reproducibility.

The chemical shift difference between cellular P_i and PCr was used to calculate the median cellular pH according to the following equation

$$pH = pK - \log (\delta obs - \delta HPO_4^{-2})/(\delta H_2PO_4^- - \delta obs)$$

where δobs is the exchange-averaged chemical shift of P_i and δHPO_4^{-2} and $\delta H_2PO_4^-$ are the limiting chemical shifts at high (pH 10) and low (pH 4) pH. For these experiments, the values for the acidic and basic end points and the pK are $\delta HPO_4^{-2} = 3.19$ ppm, $\delta H_2PO_4^- = 5.72$ ppm, and $pK = 6.80$ respectively.

Data analysis. Comparisons of the four subject groups were made using simple descriptive statistics and analysis of variance (ANOVA). Demographic measures, whole-body measures of work capacity, and calf muscle work capacities were compared using a one-way ANOVA design (4 groups). NMR measures were contrasted using a mixed-model-design [4 (groups) × 7 (time)] ANOVA. Alpha was set a priori at $P \leq 0.05$, and post hoc Bonferroni testing was used to identify group differences. Post hoc analyses were hypothesis driven, with the number of comparisons multiplied by the α per comparison ≤0.05.

RESULTS

Post hoc results of one-way ANOVA group comparisons of work capacity and results of two-way mixed-model ANOVA (group × time) comparisons of NMR data are presented in Table 3. Significant main effects for time were ignored, main effects for condition (normoxia vs. hypoxia) were not significant ($P \geq 0.05$), and there were no significant trends in the interactions to warrant further discussion.

Demographics and whole-body exercise capacity. Table 1 lists the demographic data and results of whole-body work capacity tests in the four subject groups. Single-

TABLE 2. *Measurements of calf muscle work capacity*

	AHL	SED	PWR	AER
MVC, J	86.5±11.1	94.5±15.3	125.8±11.6	71.0±9.2
Work, J				
Normoxia	12.7±1.1	9.3±0.5	13.9±1.0	11.2±0.8
Hypoxia	12.7±1.1	9.1±0.7	13.0±0.7	10.0±1.1
Integrated work, J				
Normoxia	3,365.0±537	1,802.0±168	3,965.0±510	2,633.0±346
Hypoxia	3,365.0±537	1,783.0±276	3,504.0±372	2,189.0±483
%MVC				
Normoxia	15.4±1.8	11.2±1.8	11.3±1.2	17.3±2.9
Hypoxia	15.4±1.8	10.8±1.6	10.8±1.1	14.8±1.6
Integrated work/MVC				
Normoxia	40.6±7.3	21.2±3.4	32.3±4.6	40.6±8.3
Hypoxia	40.6±7.3	20.1±2.7	28.7±3.6	31.0±5.3

Values are means ± SE. MVC, maximum voluntary contraction of right calf muscle measured isokinetically at 60°/s plantar flexion; Work, maximum work performed with each gastrocnemius contraction at fatigue; Integrated work, total work performed by gastrocnemius muscle at fatigue; %MVC, ratio of work per contraction at fatigue to MVC of calf muscle. Results of Bonferroni post hoc tests are summarized in Table 3.

TABLE 3. *Results of Bonferroni pairwise comparisons if univariate group statistic results are $P \leq 0.05$*

Dependent Variable	P (Univariate F)	AHL vs. AER	AHL vs. PWR	AHL vs. SED	AER vs. PWR	AER vs. SED	PWR vs. SED
		Table 1					
$\dot{V}O_{2\,max}$	<0.001	✓		✓	✓	✓	✓
Absolute anaerobic capacity	<0.001	✓	✓	✓	✓		✓
Relative anaerobic capacity	0.001	✓	✓			✓	✓
Δanaerobic capacity	<0.001		✓	✓	✓	✓	
		Table 2					
MVC calf muscle	0.029				✓		
Work, J							
Normoxia	0.009				✓		✓
Hypoxia	0.016				✓		✓
Integrated work							
Normoxia	0.009				✓		✓
Hypoxia	0.023				✓		✓
% MVC							
Normoxia	0.109						
Hypoxia	0.077						
Integrated work/MVC							
Normoxia	0.121						
Hypoxia	0.066						
		Fig. 1					
Mass-specific calf work at fatigue							
Normoxia	<0.001		✓	✓		✓	✓
Hypoxia	<0.001	✓	✓	✓		✓	
		Fig. 2					
Mass-specific %MVC at fatigue							
Normoxia	0.002		✓	✓	✓	✓	
Hypoxia	0.003		✓	✓	✓	✓	
		Fig. 3					
Mass-specific integrated work							
Normoxia	0.006			✓		✓	✓
Hypoxia	0.007			✓			
		Fig. 4					
Gastrocnemius muscle pH							
Normoxia	<0.001		✓	✓	✓	✓	
Hypoxia	<0.001		✓	✓	✓	✓	✓
		Fig. 6					
Gastrocnemius muscle $[P_i]/[PCr]$							
Normoxia	0.025		✓	✓	✓	✓	✓
Hypoxia	0.029				✓	✓	
		Fig. 9					
Gastrocnemius muscle {PCr}							
Normoxia	0.004		✓	✓	✓	✓	
Hypoxia	0.003		✓	✓	✓	✓	
		Fig. 10					
Gastrocnemius muscle $\{P_i\}$							
Normoxia	0.004			✓	✓	✓	
Hypoxia	0.006			✓	✓	✓	

✓, Significant differences between groups.

factor univariate ANOVA results and post hoc Bonferroni results for each of the variables are presented in Table 3. In general, the Andean natives and the endurance-trained group were slightly older and shorter and had lower body mass than the sedentary and power-trained groups.

Significant differences were found in $\dot{V}O_{2\,max}$ among the four groups (Table 3). The sedentary group had the lowest aerobic capacity, the Andean natives and power-trained group were intermediate, and the endurance-trained group had the highest aerobic capacity.

Significant between-group differences were also found in the absolute and relative anaerobic capacities of the four subject groups (Tables 1 and 3). The Andean natives produced the least amount of absolute anaerobic power, ~60% of the sedentary and endurance-trained values and only 40% of the power-trained values. The absolute power output was the same in the endurance-trained and

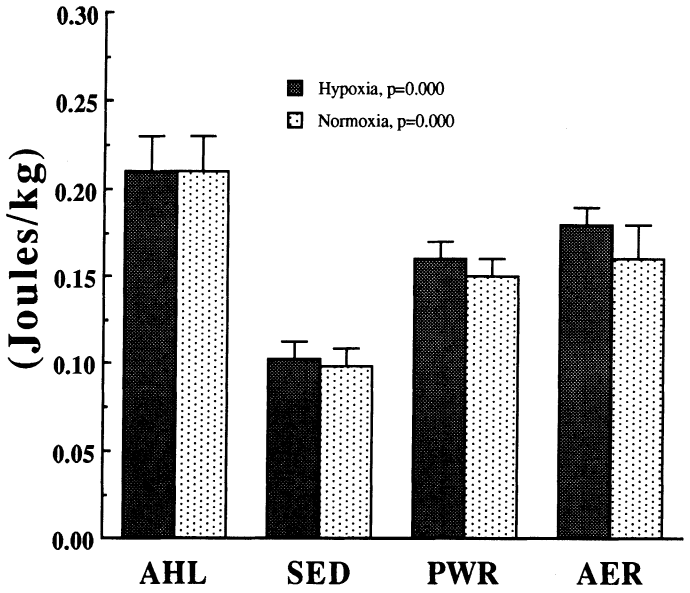

FIG. 1. Mass-specific calf work at fatigue (calculated as work at fatigue divided by body mass) in normoxia and hypoxia. AHL, Andean natives; SED, sedentary; PWR, power trained; AER, endurance trained. Values are means ± SE. Univariate *F* test results indicate overall significance values for group main effect. Results of Bonferroni post hoc tests are summarized in Table 3.

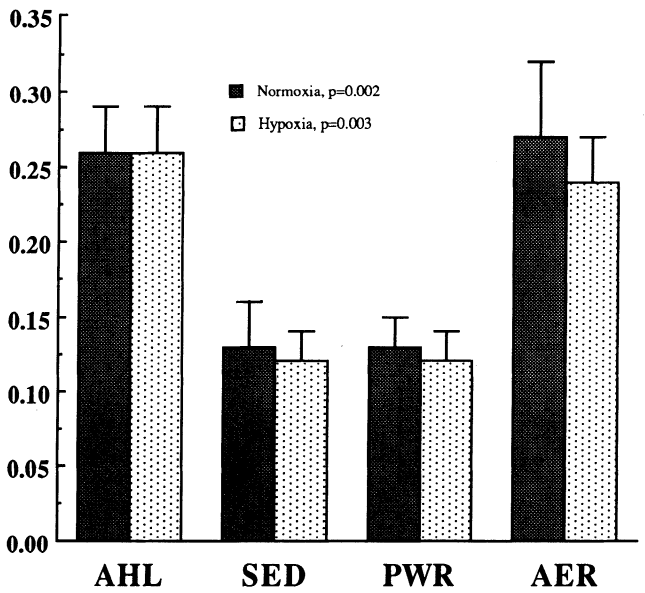

FIG. 2. Calf work at fatigue as a function of maximum voluntary contraction of calf muscle and body mass in normoxia and hypoxia. Values are means ± SE. Univariate *F* test results indicate overall significance values for group main effect. Results of Bonferroni post hoc tests are summarized in Table 3.

sedentary groups. When relative anaerobic power outputs were calculated, the Andean natives still had the lowest values, 15% lower than the sedentary group and 30–35% lower than the endurance- and power-trained groups, respectively (Tables 1 and 3). The relative power outputs of the endurance-trained group were the same as those of the power-trained group.

The percent drop in anaerobic power output (Δanaerobic capacity calculated as a percent ratio of work output in the first 5 s divided by work output in the last 5 s) is shown in Tables 1 and 3. Significant group differences were found, with the sedentary and power-trained groups

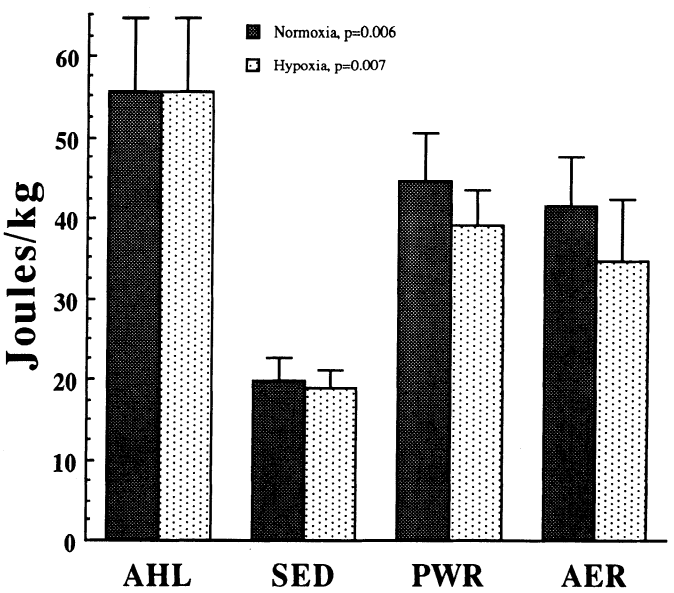

FIG. 3. Mass-specific integrated (total) calf work at fatigue in normoxia and hypoxia. Values are means ± SE. Univariate *F* test results indicate overall significance values for group main effect. Results of Bonferroni post hoc tests are summarized in Table 3.

having the largest drop and the endurance-trained group and the Andean natives having the smallest drop.

Isokinetic calf MVC values are shown in Table 2. Post hoc testing showed the power-trained group to be significantly stronger than the endurance-trained group (Table 3).

Calf muscle work capacity in normoxia and hypoxia. Table 2 shows calf muscle work capacities in the four subject groups in conditions of normoxia and hypoxia. Single-factor univariate ANOVA results for each of the variables and post hoc test results are presented in Table 3.

Between-group differences in the absolute work capacities of the calf muscle at fatigue are shown in Table 2. The most consistent finding was a significantly greater amount of calf work at fatigue in the power-trained group than in the endurance-trained group (Table 3).

Relative (mass-specific) work capacities were calculated as ratios of work output to body weight and MVC of the calf (Figs. 1–3). By these comparisons, the Andean natives and the endurance-trained group were similar and generally performed more work at fatigue than the power-trained group (Table 3). In turn, the power-trained group performed more work at fatigue than the sedentary group. Although normoxia vs. hypoxia comparisons were not significant, it is notable that the Andean natives performed the same amount of work at fatigue in both conditions while all the other groups performed less work in the hypoxic condition.

^{31}P-NMR spectroscopy. Two-factor (group × time) univariate ANOVA results for each of the NMR variables in Figs. 4, 6, 9, and 10 are presented in Table 3 together with the results of Bonferroni post hoc testing.

Gastrocnemius muscle pH values at rest, at fatigue, and at selected points in recovery in the four groups were compared and contrasted in normoxia (Fig. 4*A*) and hypoxia (Fig. 4*B*). Significant overall group differences were found in both conditions (Table 3). The Andean natives and the endurance-trained group had similar decrements

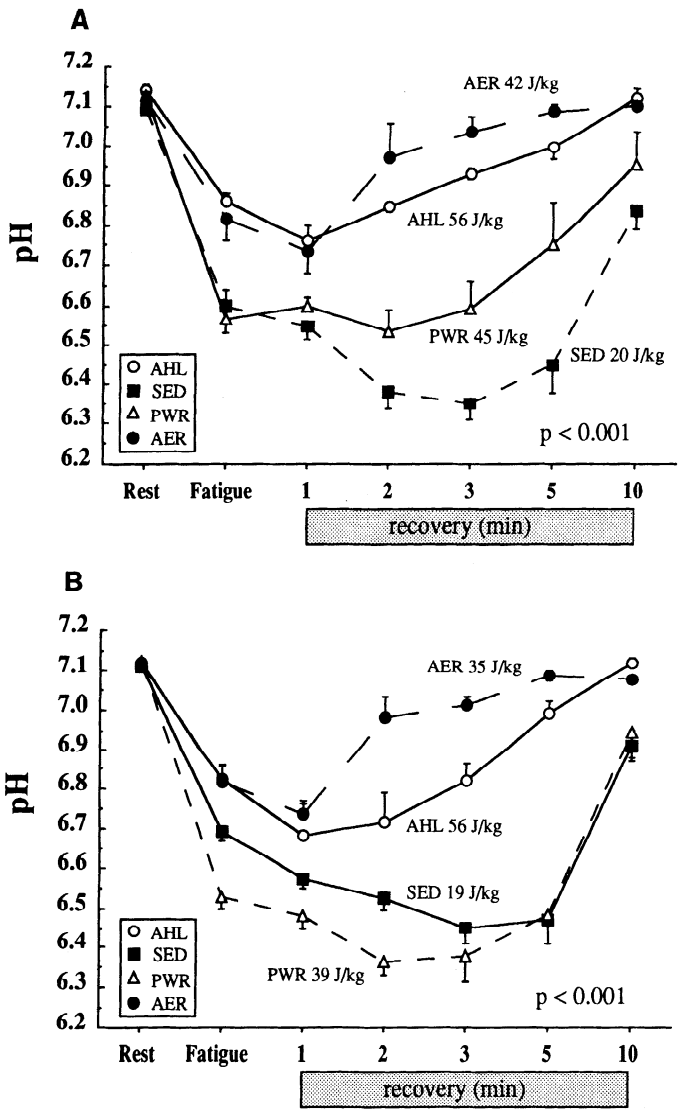

FIG. 4. Gastrocnemius muscle pH at rest, at fatigue, and during recovery from exercise in normoxia (*A*) and hypoxia (*B*). Values for mass-specific integrated work at fatigue are included. Values are means ± SE. Univariate *F* test results indicate overall significance values for group main effect. Results of Bonferroni post hoc tests are summarized in Table 3.

in gastrocnemius muscle pH at fatigue and similar rates of recovery through the first 10 min, and these values were significantly higher than those of the power-trained and sedentary groups (Table 3). The condition main effect (normoxia vs. hypoxia) was not significant across the groups (Fig. 5). The ^{31}P-NMR spectra showed no appreciable widening during the approach to fatigue or in recovery.

$[P_i]/[PCr]$ values at rest, at fatigue, and through the first 5 min of recovery are shown in Fig. 6, *A* (normoxia) and *B* (hypoxia). Again, overall significant group main effects were found in both conditions (Table 3), although the condition main effect (normoxia vs. hypoxia) was not significant (Fig. 7). The power-trained group had the greatest increase in $[P_i]/[PCr]$ at fatigue, followed by the sedentary group, the Andean natives, and the endurance-trained group (Table 3).

[ATP] values fell in all groups after aerobic exercise to fatigue (Fig. 8), but significant differences between groups and conditions were not found.

The phosphorylation potential in our experiments was difficult to estimate because its calculation requires knowledge of $[Mg^{2+}]$ and $[K^+]$ changes as well as $[H^+]$ and [adenylates] per se; however, this problem does not arise for the calculation of the creatine energy charge, [PCr]/([PCr] + [Cr]), a value termed {PCr} by Connett and Honig (11, 12) and considered the main determinant of $\dot{V}O_2$ in mammalian skeletal muscles. Because the relative size of the total creatine pool (PCr + Cr) is constant in resting mammalian muscles from various species [assuming 25 μmol/g wet wt muscle for skeletal muscles in humans (12)], it was possible to calculate {PCr} under various conditions (Fig. 9). The calculations showed that [PCr]/([PCr] + [Cr]) qualitatively followed the pattern observed for $[P_i]/[PCr]$. Comparing rest with fatigue, the greatest change was observed for the sedentary and power-trained subjects; the least change was observed for the Andean natives and the endurance-trained subjects (Table 3). However, for the same change in {PCr}, the integrated work per kilogram achieved by the Andean natives exceeded that by the endurance-trained athletes (Table 2, Fig. 4).

Another regulatory parameter correlating with $\dot{V}O_2$ in skeletal muscles is $[P_i]/([PCr] + [Cr])$, termed $\{P_i\}$ (12). Because at steady state [PCr] and $[P_i]$ are stoichiometrically related, in principle the regulatory parameter $\{P_i\}$ should be a kind of mirror image of {PCr}. The expected result is in fact observed, with $\{P_i\}$ changing the most during exercise to fatigue in sedentary and power-trained subjects and the least in the Andean natives and endurance-trained subjects (Fig. 10, Table 3). As in the {PCr} analysis, it is worth emphasizing that, for the same change in $[P_i]/([PCr] + [Cr])$, the calf muscle sustained 1.3–1.4 times more work per kilogram in Andean natives than in endurance-trained lowlanders (Table 2, Fig. 4).

DISCUSSION

Quechuas: unique physiological phenotype. These results indicate that, with respect to whole-body measures of work capacity, the Andean natives are not typical of any of the three groups of lowlanders tested. In particular, their absolute and relative anaerobic capacities are very low while their aerobic capacities are intermediate compared with trained and untrained lowlanders. Similar findings have previously been reported (19, 29, 40), and investigators have concluded that altitude-adapted indigenous natives do not appear to have enhanced whole-body work capacities, at least on the basis of anaerobic and aerobic power outputs. Thus, whole-body measures of work capacity in the Andean natives in this study defy categorization in terms of the three groups of lowlanders tested, and these findings serve to indicate that adaptations that accrue from power or endurance training are not uniformly or even representatively embodied in the physiological profile of the Andean native.

Absolute calf work results are significantly different for the power-trained group compared with the endurance-trained and sedentary groups. However, relative calf work results show the Andean natives and the endur-

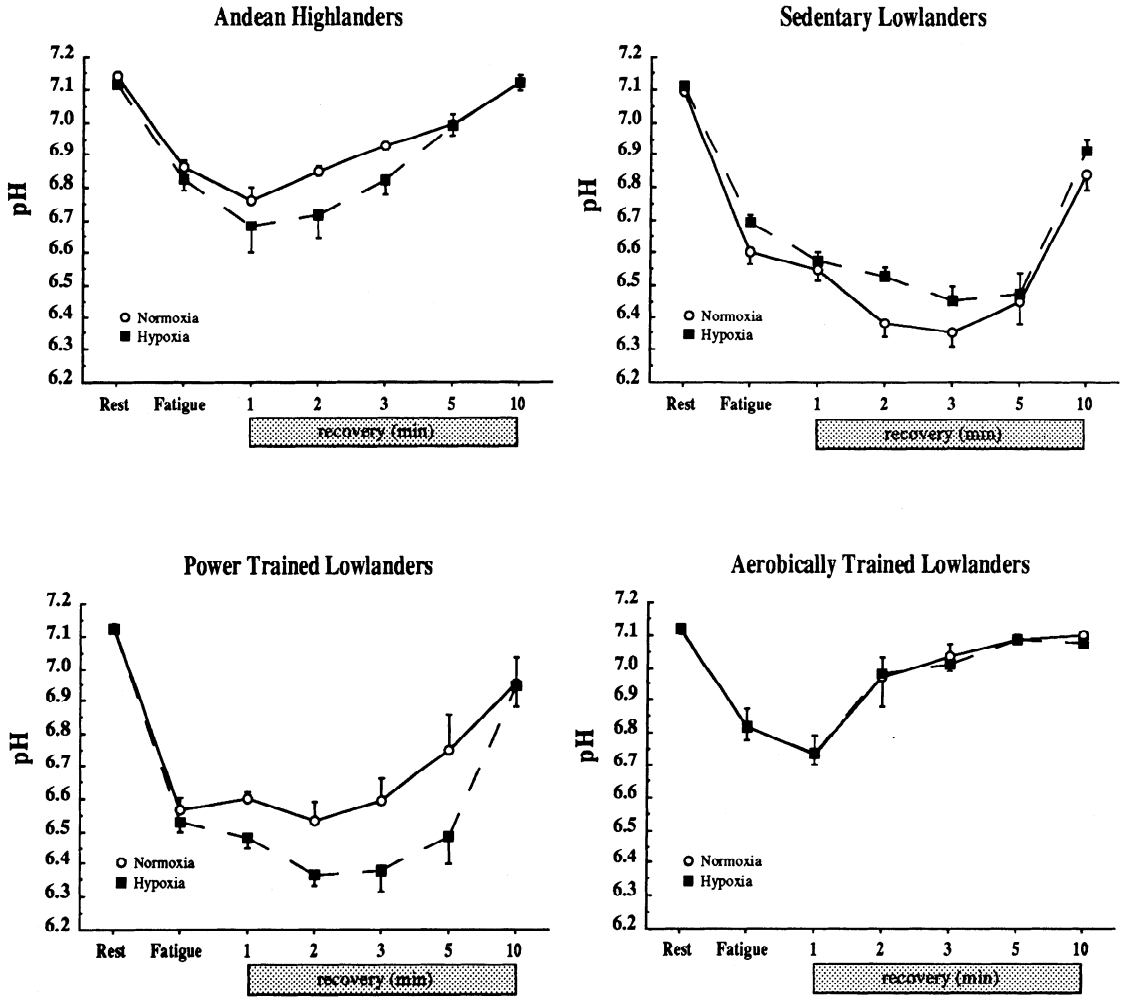

FIG. 5. Gastrocnemius muscle pH during normoxia (FI_{O_2} 0.21) and hypoxia (FI_{O_2} 0.15) at rest, at fatigue, and during recovery from exercise. Values are means ± SE. Normoxia vs. hypoxia contrasts are not significant ($P > 0.05$).

ance-trained group to be similar, with higher values than those for the power-trained and sedentary groups. Most importantly, the Andean natives' work capacities are associated with equivalent perturbation in muscle pH, [PCr], and [P_i] at fatigue compared with endurance-trained athletes, who possess significantly greater aerobic and anaerobic work capacities. Similarly, the calf work capacities are associated with significantly less metabolic perturbation in the Andean natives than in the power-trained group with similar $\dot{V}O_{2\,max}$ values and the sedentary group with similar anaerobic work capacities. In short, in comparative terms, the single-muscle work capacity of the Andean natives does not appear to be related to whole-body measures of their work capacity, whereas their skeletal muscle metabolic profile most closely resembles that of the endurance-trained group.

Skeletal muscle metabolic capacity with acclimation. At altitude, the overall metabolic scope for activity is compressed [$\dot{V}O_{2\,max}$ drops ≈11%/1,000-m altitude (15)]; yet acclimatory adjustments provide significant (40–60%) improvements in cycling (30) and treadmill (27) time to exhaustion in the absence of appreciable increase in $\dot{V}O_{2\,max}$. Maher et al. (30) found a 45% increase in cycle ergometer endurance time to fatigue at 75% $\dot{V}O_{2\,max}$ after 12 days of acclimatization to 4,300 m, and Horstman et al. (27) reported a 60% increase in time to exhaustion on treadmill running at 85% $\dot{V}O_{2\,max}$ after 16 days of acclimatization to 4,300 m. In addition to these data, anecdotal reports of physical feats of Himalayan Sherpa and Andean Quechua have been known for years (29, 40, 43). However, whole-body measurements of aerobic and anaerobic capacity in indigenous highlanders in this study and in other studies (43) fail to show unusual ("superhuman") work capacities. Given that the quadriceps muscle in humans is capable of a metabolic rate on the order of 350 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ when central cardiac limiting factors are accounted for (2), additional adaptive changes within the skeletal muscle (peripheral adaptations) may result from prolonged hypobaric hypoxia and may be exposed in single-limb exercise where competitive demands for cardiac output are minimized.

One adaptive strategy would see an increase in skeletal fiber capillarity, mitochondrial volume density, and oxidative enzyme capacity. These changes would allow ATP synthesis to occur at lower [O_2] and would require less increase in [ADP] and [P_i] for any given respiratory chain by using a smaller fraction of the oxidative capacity of the mitochondrial respiratory chain. In effect, these adaptations would allow the muscle to operate at greater O_2 flux rates without excessive demands for high substrate concentrations (11, 12).

However, the available literature has not provided

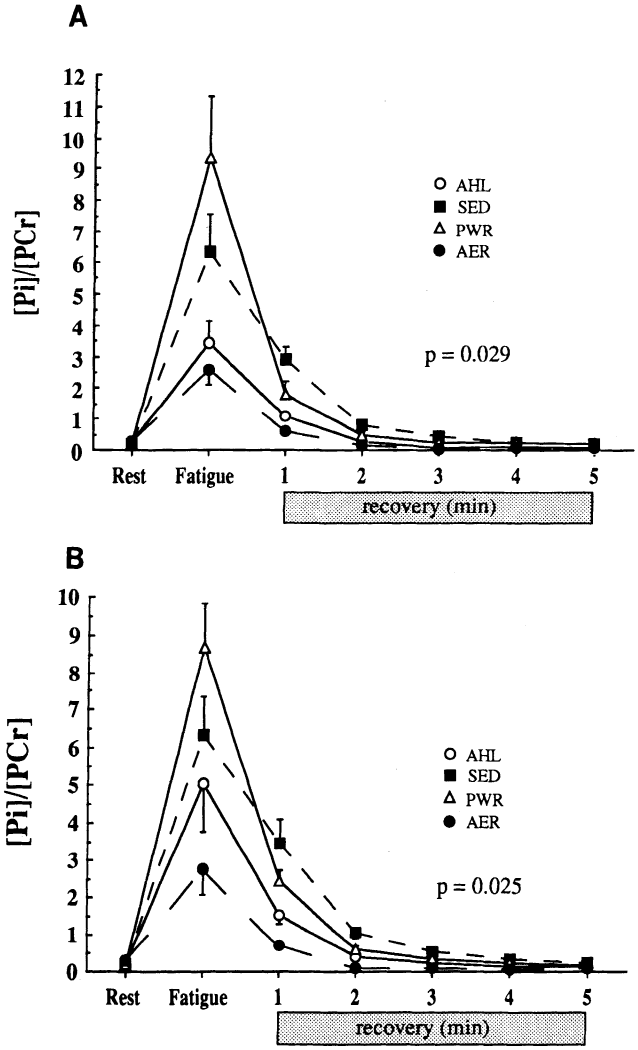

FIG. 6. P_i-to-phosphocreatine concentration ratio ($[P_i]/[PCr]$) in gastrocnemius muscle at rest, at fatigue, and during recovery from exercise in normoxia (*A*) and hypoxia (*B*). Values are means ± SE. Univariate *F* test results indicate overall significance values for group main effect. Results of Bonferroni post hoc tests are summarized in Table 3.

many examples of this strategy in lowlanders acclimatized to altitude or in altitude-adapted indigenous highlanders. For example, the total contractile pool of skeletal muscle is reduced in lowlanders returning from long periods at altitudes reaching or surpassing 8,500 m: cross-sectional area of the thigh is reduced by 10% and mean fiber cross-sectional area of the vastus lateralis muscle by 20% (26). Similar findings are found in elite high-altitude climbers who have previously scaled peaks above 8,500 m without supplemental O_2 (33) and in Himalayan Sherpas who reside at 3,000–5,000 m (8). In addition, reductions are seen in the capillary-to-fiber ratio and the volume density of total mitochondria (both interfibrillar and subsarcolemmal) in these three groups. The volume density of total mitochondria is reported to be reduced by 25% in postexpedition climbers (26) and was found to be equal in elite climbers and sedentary individuals but considerably lower than endurance-trained orienteers (33). The capillary-to-fiber ratio is slightly greater in elite climbers than in sedentary lowlanders but significantly less than in endurance-trained runners, and the same is true for the volume density of mitochondria (26, 33). In Nepalese Sherpas, similar morphometric measures are found (8). Finally, Green et al. (17) also report similar changes in the acclimation Operation Everest II study.

These morphometric findings are reconcilable if the absolute oxidative capacity of the muscle or at least the relative oxidative capacity (oxidative-to-glycolytic ratio) is increased. Unfortunately, from the studies to date, it would appear that altitude-adapted individuals also are unable to appeal to this mechanism. Although studies in guinea pigs (34) and rats (35) do not show decrements in oxidative capacities, in lowlanders returning from great altitudes, activities of the oxidative enzymes succinate dehydrogenase, citrate synthase, malate dehydrogenase, cytochrome oxidase, 3-hydroxyl-CoA dehydrogenase, and hydroxybutyrate dehydrogenase are reduced 10–30% (28). These changes (impairment of oxidative capacity) are secondary to loss of mitochondrial structure rather than a qualitative reduction in enzymatic activity, because the reduction in enzymatic activity can be accounted for by reductions in mitochondrial volume density. Green et al. (17) found similar reductions in oxidative capacity in Operation Everest II. Young et al. (46) showed no effects on oxidative enzyme activities in the vastus lateralis of five subjects exposed for 18 days to 4,300 m. Finally, the activities of the glycolytic enzymes phosphofructokinase and lactate dehydrogenase are reported to be unchanged or reduced after chronic exposure to hypobaric hypoxia (17, 46).

Improved work capacity-energy coupling and the $\dot{V}O_{2\,max}$ paradox. If $\dot{V}O_{2\,max}$ does not increase after residence at altitude and if muscle fiber diameter, capillarity, mitochondrial volume, and absolute or relative oxidative capacities are not upscaled (in fact, appear to be unchanged or downscaled), we are left to explain the improvements in muscular work rate that occur with altitude and are found in indigenous highlanders anecdotally and in our study. The present study demonstrates less perturbation in $\{PCr\}$, $\{P_i\}$, and $[P_i]/[PCr]$ and perhaps, most notably, significantly less drop in pH in gastrocnemius muscle at fatigue compared with subjects having equal aerobic (power-trained group) and greater anaerobic (sedentary group) capacities. Because all these parameters, especially $\{PCr\}$ and $\{P_i\}$, either reflect the phosphorylation potential or are stoichiometrically related to the phosphorylation potential (11, 12), we conclude that the latter parameter is also less perturbed during skeletal muscle work in Andean natives relative to their aerobic and anaerobic capacities. These findings reflect closer ATP supply-demand coupling in skeletal muscle during sustained work in Andean natives than in all other groups studied. The mechanisms that are postulated to explain this are reviewed elsewhere (3, 22, 23). Briefly, in loosely coupled energy demand-supply systems [dog gracilis is an excellent example (11, 12)], the phosphorylation potential, $\{PCr\}$, $\{P_i\}$, [PCr], $[P_i]$, [ADP], [ATP], and muscle pH all change in step with work rate increases, thus favoring both increased oxidative phosphorylation rates and increased rates of glycolysis and lactate production.

Our NMR data suggest that any given muscle work

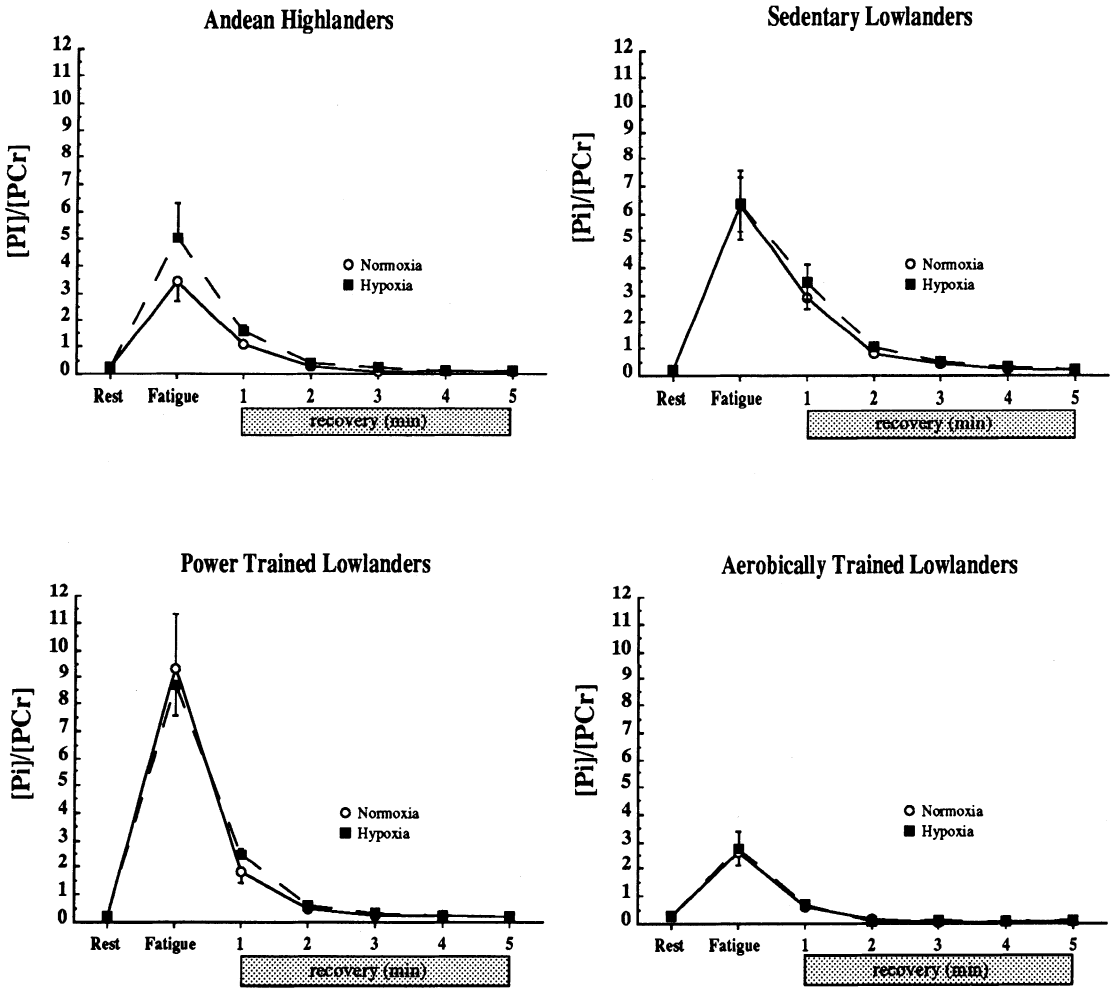

FIG. 7. $[P_i]/[PCr]$ in the gastrocnemius muscle during normoxia (FI_{O_2} 0.21) and hypoxia (FI_{O_2} 0.15) at rest, at fatigue, and during recovery from exercise. Values are means ± SE. Normoxia vs. hypoxia contrasts are not significant ($P > 0.05$).

rate is sustained by less change in these key controlling parameters and thus by less (kinetic and thermodynamic) activation of mitochondrial metabolism in Andean natives than in lowlanders. That is why improvements in muscle performance observed in high-altitude natives are not (indeed, need not be) reflected in $\dot{V}O_{2\,max}$ capacities (11, 12) and why calculations of conversion of metabolic power input to mechanical power output indicate improved efficiencies in Andean natives (23).

Energy coupling and the lactate paradox. If the above interpretation is valid, the lactate paradox also can be readily explained [on the basis of reduced changes in the phosphorylation potential and in all related regulatory parameters at equivalent work loads (21)] because of reduced activation of glycolysis. Indeed, in the most tightly coupled energy demand-energy supply coupled muscle currently described (heart), no net production of lactate or H^+ as a function of work rate is observed (3). In this regulatory characteristic, as in the aerobic ones above, skeletal muscles in Andean natives behave in a manner between classical skeletal muscle and cardiac muscle. In our view, the low lactate levels observed at fatigue in $\dot{V}O_{2\,max}$ tests likely reflect muscle metabolism with somewhat modified (and appropriately intermediate) regulatory properties.

Another way to assess the degree of imbalance between adenosinetriphosphatase (ATPase) fluxes and ATP synthase fluxes is based on ATP concentration changes. In human skeletal muscles (32), as in all vertebrates thus far examined (16), the drop in ATP at fatigue is essentially stoichiometrically accounted for by a rise in IMP; because the pool sizes of ADP and AMP are so small relative to ATP, changes in their concentrations hardly influence the relationship between ATP and IMP. This means that changes in ATP or IMP concentrations at fatigue reflect the same information: the degree to which ATPase fluxes exceed the ATP synthesis rates through the exercise period. In our hypoxia protocol, for example, the four groups (Andean natives, endurance trained, power trained, and sedentary) at fatigue sustained 24.4, 20.4, 28.9, and 27.7% decreases in ATP, respectively (Fig. 8). Given ATP contents of ~5.5 μmol/g in nonworking human muscle, these values translate into changes of 1.32, 1.12, 1.59, and 1.52 μmol ATP/g, respectively. As would be expected from the pathways involved (16), these values are similar to the increases in IMP reported in human muscles worked to fatigue (16). What fraction of the overall ATP turnover rate do these values represent?

The relative ATP turnover rates can be calculated

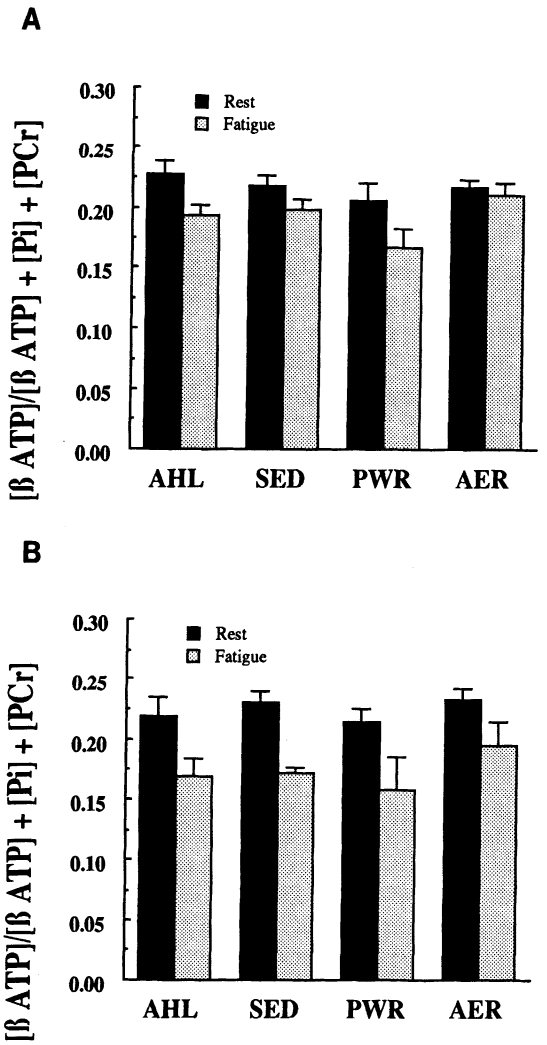

FIG. 8. [ATP] calculated with reference to total phosphate content in gastrocnemius muscle at rest and fatigue in normoxia (*A*) and hypoxia (*B*). Values are means ± SE. Group contrasts are not significant ($P > 0.05$).

from the relative amounts of work done in the protocol. This calculation is based on the empirical observation that the mass of the gastrocnemius-plantaris-soleus group is close to 1% of body weight (1, 44). Efficiency of conversion of metabolic energy to mechanical work for isolated muscle groups is usually quite low (20); we assumed 15% for our subjects, which yielded metabolic rates per gram of muscle similar to estimates based on whole-body measures of $\dot{V}O_{2\,max}$ (23). Using standard equivalence (joules to calories to O_2 fluxes to ATP fluxes), we could calculate that in the work protocol to fatigue the four subject groups turned over 553.3, 387.5, 392.5, and 189.4 μmol ATP/g muscle for Andean native, endurance trained, power trained, and sedentary, respectively. In the process, in the case of Andean natives, calf muscle ATP concentration dropped at fatigue by ~1.32 μmol/g; this means that the percent imbalance of fluxes (through ATPase and back through ATP synthases) was only 0.24%. The endurance-trained, power-trained, and sedentary groups sustained 0.29, 0.41, and 0.80% imbalances, respectively. In terms of comparative phosphate fluxes, in the case of Andean natives, one ATP was lost to IMP for each 417 spins of the ATP → ADP + P_i cycle; for the endurance-trained, power-trained, and sedentary groups, one ATP was lost for each 345, 244, and 125 turns of the ATP → ADP + P_i cycle, respectively. This means that the ATPase-ATP synthase fluxes are 3.30 times better balanced in calf muscles of Andean natives than in the sedentary lowlanders; they are 1.71 and 1.21 times better balanced than in the power- and endurance-trained groups, respectively.

These calculations are highly instructive for two reasons. First, they clearly indicate extremely precise regulation of energy demand-supply coupling in exercising muscles in all subject groups examined. Second, they imply that even modest loosening of energy coupling is crucial and impacts seriously on performance characteristics: Andean natives, for example, sustained 15.2 min of our protocol while the sedentary subjects fatigued in only 10.5 min.

Parenthetically, we should add that these differences

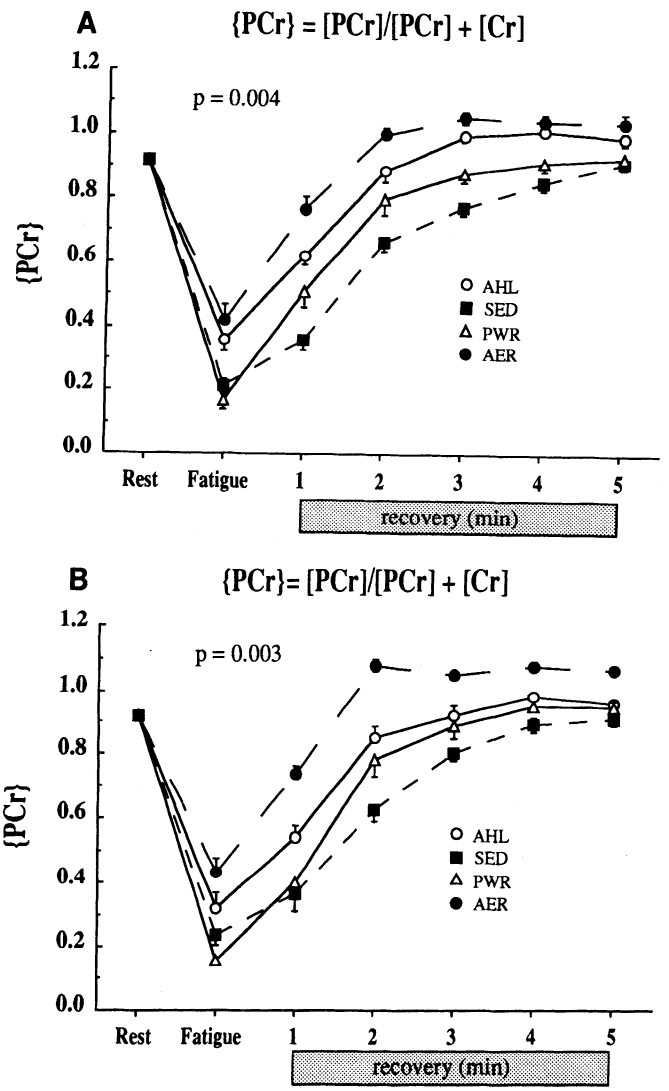

FIG. 9. Calf muscle {PCr} at rest, at fatigue, and during the first 5 min of recovery from exercise in normoxia (*A*) and hypoxia (*B*). Values are means ± SE. Univariate *F* test results indicate overall significance values for group main effect. {PCr} = [PCr]/([PCr] + [Cr]). [PCr]/([P_i] + [PCr]) + [β-ATP] = 23 μmol/g at rest; [PCr] + [Cr] = 25 μmol/g (Refs. 10 and 11). Results of Bonferroni post hoc tests are summarized in Table 3.

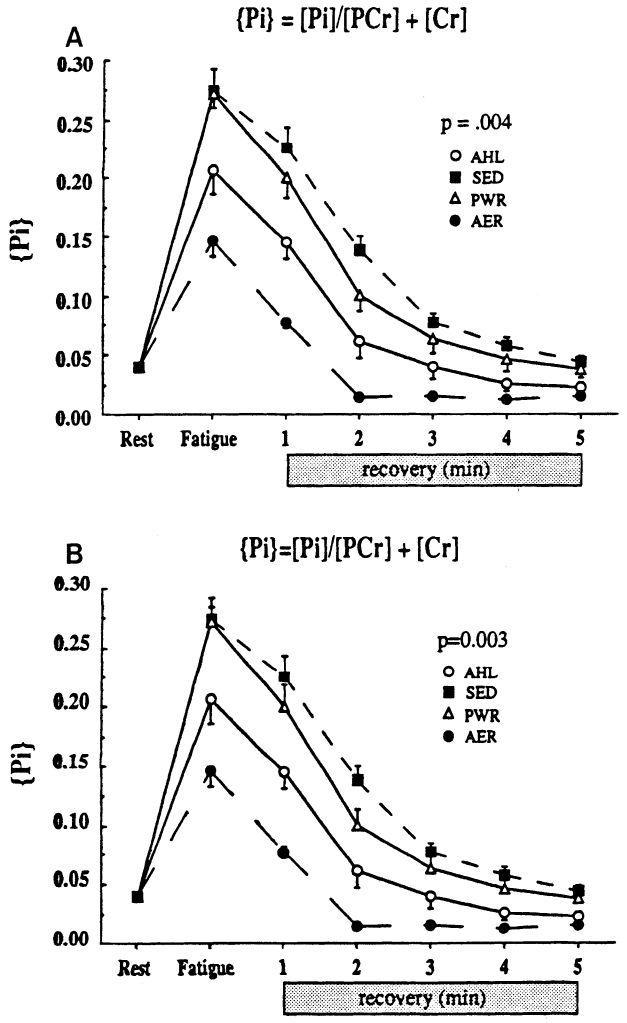

FIG. 10. Calf muscle $\{P_i\}$ at rest, at fatigue, and during the first 5 min of recovery from exercise in normoxia (*A*) and hypoxia (*B*). Values are means ± SE. Univariate *F* test results indicate overall significance values for group main effect. $\{P_i\} = [P_i]/([PCr] + [Cr])$. $[P_i]/[P_i] + [PCr] + [\beta\text{-ATP}] = 1$ μmol/g at rest; $\{P_i\} = 1/25 = 0.04$ at rest. Results of Bonferroni post hoc tests are summarized in Table 3.

between the groups are based on the assumption that the mass of the gastrocnemius-plantaris-soleus group is a constant fraction of body weight. Our observation is that Andean natives have small calf muscles, whereas power-trained individuals have inordinately large calf muscles. However, such adjustments in calf muscle mass would expand the differences we have noted, whereas our assumptions minimize them. Thus, corrections for intergroup differences in relative size of calf muscles would strengthen, not weaken, our general conclusion that ATPase and ATP synthase fluxes are most closely coupled in Andean natives. In this regard, as in others, the Andean natives are most similar to the endurance-trained group and differ most from the sedentary lowlanders.

In addition to this theory (21), several other hypotheses have been put forward to explain the lactate paradox. Cerretelli et al. (9) have suggested that reduced buffering capacity during ascent to altitude (principally a reduction in plasma $[HCO_3^-]$ as a consequence of hyperventilation and associated reductions in arterial P_{CO_2}) contributes to greater increases in $[H^+]$ and consequent inhibition of glycolysis, most likely at the level of phosphofructokinase. In the present study, muscle pH at fatigue was high compared with lowlanders and certainly not sufficient to inhibit glycolysis. Moreover, the lactate paradox did not deacclimate in the Andean natives examined [no indication of reversal after 6 wk at sea level (23)]. In addition, after 14 days of acclimatization to 4,300 m, Young et al. (46) have measured muscle pH 0.15 units higher and venous blood lactate 30% lower after exhaustive exercise. Thus it would appear that this explanation can be discounted.

From the Operation Everest II study, on the basis of the finding that the integrity of the glycolytic pathway does not appear compromised, Green et al. (18) suggest that the lactate paradox may result from hypoxia-induced decreased activation of the skeletal muscle contractile mechanism either through a disturbance in activation (motoneuron pool) or reduced sensitivity to respond to a calcium stimulus. Although some evidence exists to suggest that central nervous system inhibition may result from peripherally generated inhibitory reflexes activated by hypoxia (5) (presumably on the basis of failed cerebral autoregulation), with this theory it is not possible to explain the lactate paradox at moderate altitudes where cerebral oxygenation is not seriously impaired; nor is this theory consistent with the observation that the lactate paradox does not deacclimate in Andean natives even after 6 wk at sea level (23). Thus the interpretation of Green et al. (18) at least tentatively can be dismissed.

Muscle glycogen depletion at altitude has also been suggested as a possible cause of the lactate paradox (9). However, Green et al. (18) have shown that muscle glycogen content is not reduced at fatigue in subjects who demonstrate the lactate paradox.

Finally, Sutton and Heigenhauser (38) suggest that the alkalemia associated with altitude, being the net effect of respiratory alkalosis (on the basis of alveolar hyperventilation and reduced arterial P_{CO_2}) and metabolic acidosis (on the basis of lowered plasma $[HCO_3^-]$ through renal excretion), may not effect increases in lactate efflux of the same magnitude as changes in strong ion difference or permeability. To our knowledge, in studies in which the extracellular pH has been artificially manipulated through means such as induced respiratory alkalosis, metabolic acidosis, and metabolic alkalosis, the controlling factor for lactate efflux is the absolute $[H^+]$ (37). Thus the alkalemia of altitude would favor lactate efflux at any given cytosol concentration and serve to increase plasma lactate. In any case, this explanation would not hold for the Andean natives whose resting arterial pH and $[HCO_3^-]$ measures were normal but whose plasma [lactate] at the end of exhaustive exercise was significantly lower than in trained lowlanders (23).

Conclusions. Although the Andean natives in the present study display very low anaerobic capacities and intermediate aerobic capacities, they demonstrate very high calf muscle work capacities compared with power-trained and sedentary lowlanders. These findings are not explained on the basis of whole-body measures of anaerobic and aerobic capacities but may be explained by ^{31}P-NMR measurements. Because it is well established that

{PCr} and {P_i} are linear transformations of the phosphorylation potential in vivo over a broad range of muscle pH values (11, 12), the data from the present study imply that, for any given work rate, the calf muscle phosphorylation potential in Andean natives is less perturbed than in other subject groups with similar $\dot{V}O_{2\,max}$ values and equally perturbed compared with trained subjects with significantly higher $\dot{V}O_{2\,max}$ values. Presumably, this metabolic regulatory transition is an adaptive response to chronic hypobaric hypoxia and occurs in addition to the central (cardiopulmonary) and erythropoietic adjustments known to result from altitude acclimatization.

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