Metabolic and work efficiencies during exercise in Andean natives

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HOCHACHKA, P. W., C. STANLEY, G. O. MATHESON, D. C. McKENZIE, P. S. ALLEN, AND W. S. PARKHOUSE. *Metabolic and work efficiencies during exercise in Andean natives.* J. Appl. Physiol. 70(4): 1720–1730, 1991.—Maximum O_2 and CO_2 fluxes during exercise were less perturbed by hypoxia in Quechua natives from the Andes than in lowlanders. In exploring how this was achieved, we found that, for a given work rate, Quechua highlanders at 4,200 m accumulated substantially less lactate than lowlanders at sea level normoxia (~5–7 vs. 10–14 mM) despite hypobaric hypoxia. This phenomenon, known as the lactate paradox, was entirely refractory to normoxia-hypoxia transitions. In lowlanders, the lactate paradox is an acclimation; however, in Quechuas, the lactate paradox is an expression of metabolic organization that did not deacclimate, at least over the 6-wk period of our study. Thus it was concluded that this metabolic organization is a developmentally or genetically fixed characteristic selected because of the efficiency advantage of aerobic metabolism (high ATP yield per mol of substrate metabolized) compared with anaerobic glycolysis. Measurements of respiratory quotient indicated preferential use of carbohydrate as fuel for muscle work, which is also advantageous in hypoxia because it maximizes the yield of ATP per mol of O_2 consumed. Finally, minimizing the cost of muscle work was also reflected in energetic efficiency as classically defined (power output per metabolic power input); this was evident at all work rates but was most pronounced at submaximal work rates (efficiency ~1.5 times higher than in lowlander athletes). Because plots of power output vs. metabolic power input did not extrapolate to the origin, it was concluded *1*) that exercise in both groups sustained a significant ATP expenditure not convertible to mechanical work but *2*) that this expenditure was downregulated in Andean natives by thus far unexplained mechanisms.

lactate paradox; muscle efficiency; altitude adaptation

FROM NUMEROUS previous studies (4, 17, 21, 25, 32, 35, 37), it is evident that indigenous Quechuas of the high Andes in South America display a number of functional and structural adaptations allowing them to at least partially circumvent the main metabolic problem they face: maintaining an acceptably high scope for sustained aerobic metabolism despite reduced availability of O_2 in the inspired air. As a result of adaptations at various levels of organization (14, 23, 25, 37), maximal O_2 uptake ($\dot{V}O_{2\,max}$) values at altitudes in the 4,200-m range are reduced only modestly (17, 37–39), in our studies to 89–95% of nor-

moxic values (Table 1). This represents a metabolic inhibition of only one-half to one-fifth of that experienced by most lowlanders under similar hypoxic stress (17, 23, 37). How this is achieved at the metabolic level is not well understood and is the issue we wish to address in this paper.

As a framework, it is useful to recall that many hypoxia-tolerant species behave as if selected for minimizing the cost (or for maximizing the efficiency) of cell metabolic and work functions, and earlier studies suggested similar adaptations in Andean natives (14). With potentially limiting O_2 availability, increasing efficiency, in principle, can be achieved in at least three ways (10, 12, 14, 30): *1*) maximizing the moles of ATP obtained per mole of fuel substrate metabolized; *2*) maximizing the moles of ATP obtained per mole of O_2 consumed; and *3*) maximizing work achieved per mole ATP utilized. In *1*, decreasing the contributions of anaerobic pathways (low ATP yield) relative to aerobic ones (high ATP yield) is favored. In *2*, glycogen (glucose) oxidation is favored over the oxidation of fats because it leads to fractionally more ATP per mole of O_2 consumed during complete oxidation (10, 15). In *3*, increasing efficiency classically defined as ratio of mechanical power output to metabolic power input is favored. To determine whether Andean natives display any of these adaptive strategies we needed indexes of aerobic vs. anaerobic contributions to exercise, indexes of carbohydrate vs. fat contributions to energy metabolism, and estimates of efficiency of conversion of metabolic energy into mechanical work, all under both normoxic and hypoxic conditions.

A common approach to addressing these kinds of problems involves the use of isotopically labeled intermediates to quantify the turnover rates of key carbon fuels (33, 34). However, for sociocultural reasons, we were unable to utilize this approach in this study of Quechua natives, so we used an alternate strategy. We reasoned that the status of each of the above key parameters would be reflected in the concentration profiles of key substrates and end products and in the fluxes of O_2 and CO_2. Low or modest lactate accumulations for a given work rate would indicate reliance on *strategy 1* above: taking advantage of high ATP yield efficiency of aerobic metabolism (13). Ratios of CO_2 flux to O_2 flux near unity, indicative of carbohydrate oxidation (3, 15), would imply

reliance on *strategy 2* during exercise: taking advantage of a high ATP yield per mole of O_2 used. Finally, high ratios of mechanical power output to metabolic power input would indicate reliance on *strategy 3*: maximizing work per mole ATP used. We reasoned that this approach would be particularly instructive when used in a comparative mode; hence, the study emphasizes comparisons between highlanders under hypoxic and normoxic conditions, between lowlanders under hypoxic and normoxic conditions and, where appropriate, between highlanders and lowlanders adapted to sea level conditions. We found that all three strategies for maximizing efficiency are utilized by Andean natives during exercise to fatigue. Interestingly, the underlying metabolic adaptations behave like (genetically or developmentally) fixed characteristics, because they are expressed even after 6 wk of deacclimation at sea level.

MATERIALS AND METHODS

Subjects. Six male healthy Andean Quechuas [average mass 62.8 ± 4.1 kg; average age 34.3 ± 1.1 yr (means $\pm$ SE)] who were born and raised in the La Raya region of Peru (3,300–4,500 m) and who currently live in Siquani (3,700 m) volunteered to participate in our study. The subjects were familiarized with the testing procedures on the cycle ergometer at the La Raya Veterinary Research Station ($\sim$4,200 m) 2 days before the initiation of these experiments. For comparative purposes, five lowlander athletes associated with the Sports Medicine Division at the University of British Columbia volunteered to participate. Their average age was 26.2 ± 1.3 yr, average body mass was 82 ± 2 kg.

Metabolism and work assessments. The Andean subjects performed weekly tests of incremental exercise to fatigue (30 W every 2 min at 60 rpm) on a Monark bicycle ergometer. Initial tests were performed at La Raya at 4,200 m altitude and subsequently at weekly intervals at sea level in Vancouver, British Columbia, under normoxic conditions and under hypoxic conditions (inspired O_2 tensions reduced to 14%). O_2 and CO_2 fluxes were determined with O_2 and CO_2 sensors built into a Medical Graphics 2001 metabolic cart (Minneapolis, MN) and monitored continuously through an initial rest period before exercise and during the incremental exercise tests. Data on each exercise protocol were presented essentially in real time, individually as well as in graphical form relating various parameters. O_2 and CO_2 fluxes, expressed initially in milliliters or millimoles per kilogram per second, were converted to watts per kilogram with the use of standard equivalence assumptions (27). Resting metabolic rates were subtracted from metabolic rates at various work rates for calculating net metabolic power input. On the basis of a vast amount of previous work (29), this value of metabolic power input was taken to represent the metabolic demands of muscle work; any anaerobic contributions at submaximal exercise intensities were considered minimal (13, 21, 22, 29, 33, 34) and were not included in our calculations. At exercise intensities approaching $\dot{V}O_{2\,max}$, it is appreciated that anaerobic contributions to muscle metabolism increase. However, on the basis of data on lactate fluxes and lactate accumulation (Refs. 33 and 35; data below), we concluded that even at $\dot{V}O_{2\,max}$, the errors introduced into power input calculations by ignoring anaerobic contributions were probably no more than 10%. Nevertheless, because of this potential uncertainty, most of our conclusions on energetic efficiencies were derived from differences between Andean natives and lowlanders rather than from absolute values. Net energetic efficiency was operationally defined as the ratio of total power output to total net energy expenditure (metabolic power output in watts per kilogram body weight/power input in watts per kilogram). Gross energetic efficiency was defined as ratio of total power output to total energy expenditure with no subtraction of resting metabolic rate; i.e., power output in watts per kilogram/gross metabolic input in watts per kilogram. In addition, the intercepts of plots of metabolic input vs. power output were used to assess the fraction of metabolism that was required for exercise but was not directly convertible to mechanical work (see discussion below). These efficiency parameters were calculated for the Andean natives at 2 and 6 wk of deacclimation and were compared with the lowlander athletes under both hypoxic and normoxic conditions.

Blood sampling. Small ($\sim$1-ml) samples of blood were obtained (for the assessment of various metabolites, ions, hormones, and osmotic pressure) at rest, during the last 10 s of each incremental (30-W) work bout, and during recovery. Samples were drawn from an indwelling catheter in the cephalic vein, introduced 25–30 min before exercise. Blood samples were placed in centrifuge tubes immediately after collection; blood cells were spun down and the plasma fraction was frozen in liquid nitrogen. Plasma samples were stored at $-80°$C until required for metabolite, hormone, or ion assays. Because of limited plasma volumes, some of our measurements could not be made on all of our samples; in most cases, however, enough measurements were usually possible to identify the presence or absence of any trends as a result of deacclimation.

Metabolites, ions, osmotic pressure, and hormones. Most of the assays required for this study are routinely performed in our laboratories. Osmotic pressure was determined with a Wescor (model 550) vapor pressure osmometer. K^+ and Na^+ concentrations in plasma samples were determined using a Techtron atomic absorption spectrophotometer (AA12) in transmission mode. Glucose and lactate were assayed using standard enzymatic techniques (13). Thyroxine (T_4) was quantified using a fluorescence polarization immunoassay that includes both protein bound and unbound forms of T_4; triiodothyronine (T_3) was quantified using a Tri-TAB (Organon Teknika, Durham, NC) radioimmunoassay procedure; both procedures are widely used (24) and are the techniques used at the University Hospital in Vancouver, British Columbia.

Reagents and gases. Coupling enzymes and metabolites for the quantitative determination of plasma glucose and lactate concentrations were obtained from Sigma Chemical, St. Louis, MO. Other chemicals used were in all cases reagent grade. Gases of specified composition were obtained from local dealers.

TABLE 1. *Maximal aerobic performance features in Andean natives under normoxic and hypoxic conditions during 6 wk of deacclimation from altitude to sea level*

Condition	Maximum Power Output, W	$\dot{V}O_{2max}$, $ml \cdot kg^{-1} \cdot min^{-1}$	Maximum Heart Rate, beats/min
Quechuas			
Initial			
La Raya	225±10	43±2	181±4
Normoxia	275±16	50±2	184±4
Deacclimation			
3 wks			
Hypoxia	240±11	48±2	176±3
Normoxia	280±17	53±2	183±2
6 wks			
Hypoxia	250±6	45±3	183±3
Normoxia	270±11	47±2	186±5
Lowlanders			
Hypoxia	345+9	53+0.5	177+6
Normoxia	408±7	64±2.3	181±3

Values are means ± SE of 6 Quechuas and 5 lowlanders.

RESULTS AND DISCUSSION

Effect of hypoxia on maximum metabolism and work. Maximum O_2 consumption rates, maximum power output, and maximum heart rates under hypoxic and normoxic conditions during the 6-wk study are summarized and compared with trained lowlanders in Table 1. Although a small deacclimation effect was observed [discussed in another paper (23)], the point of emphasis is how refractory these parameters were to reduced O_2 availability in the inspired air; a 5–11% effect of hypoxia covered the range of responses by the Andean natives from the beginning to the end of the study or about one-half the sensitivity of our trained lowlander subjects (Table 1). These data confirmed measurements of earlier workers and imply that the aerobic performance capacities of altitude-adapted natives, compared with lowlanders, are at least two to five times more resistant to hypoxia, with untrained lowlanders being the most sensitive (14, 17, 20, 22, 32, 37–39). Most of the rest of this study was designed to better understand this fundamental adaptation.

Plasma water, K^+, and Na^+. Water is an end product of oxidative metabolism and at $\dot{V}O_{2\,max}$ is produced at about $3\,mmol \cdot kg^{-1} \cdot min^{-1}$ (Table 1). Because it is freely permeable and rapidly equilibrates throughout all aqueous compartments, the metabolic production of water during incremental exercise to fatigue makes a minimal contribution to changes in metabolite concentrations. However, because of reported redistribution of ions and water between compartments during exercise (18) and because of relatively large changes in hematocrit during deacclimation (23), we begin our analysis with estimates of plasma osmotic pressures and of K^+ and Na^+ concentrations (Table 2). Plasma osmotic pressure was relatively stable during incremental aerobic exercise tests; values at fatigue in the Quechua subjects were only some 5% higher than at rest. There were coordinate increases in K^+ and Na^+ concentrations that could account for approximately half of the osmotic pressure change (Table

2). A point of emphasis is that in Andean Indians the observed osmotically driven water and ion movements are too modest to significantly contribute to either metabolite concentration changes to be discussed below or to the relatively large exercise-related increase in hematocrit that we characteristically observed (23). Therefore, at least a part of the hematocrit increase presumably represents an absolute increase in circulating erythrocyte numbers, presumably mobilized from either the venous side of the circulation or the spleen.

Plasma glucose concentrations. Glucose homeostasis was only marginally disrupted by exercise in the Andean subjects. Small increases were observed during exercise under both normoxic and hypoxic conditions (Table 3). There were essentially no effects of hypoxia on plasma glucose regulation either during exercise or during recovery (Table 3). These observations are in general agreement with previous measurements of both plasma glucose and plasma free fatty acids in Andean natives (see Ref. 28 for a review). Aside from glucose concentrations that are modestly lower than typically found in lowlanders (compare Table 3 with data in Ref. 28 for example), these data imply stable glucose regulation during exercise under both normoxic and hypoxic conditions in Andean natives, and this pattern does not change in any major way during 6 wk of deacclimation at sea level. We tentatively make the same conclusions for fat mobilization because plasma glycerol concentrations were not seriously perturbed by exercise under either normoxic or hypoxic conditions (28) (C. Stanley, unpublished data). After these studies were completed, changes in glucose appearance and clearance rates were reported for lowlanders acclimated to altitude (G. A. Brooks, personal communication). However, if similar adjustments occurred in our subjects, our data would not have observed them.

Plasma lactate concentrations. One of the most useful sources of information about metabolic homeostasis during exercise in humans is the plasma lactate concentration profile during the exercise test and during recovery from it. Large perturbations in plasma lactate pools are clearly indicative of a serious mismatch between muscle energy demands and O_2 fluxes, i.e., between muscle ATP demands and the capacity to supply ATP through aerobic metabolic pathways. The usual situation seen during incremental $\dot{V}O_{2\,max}$ tests for lowlanders under normoxia and hypoxia is shown in Fig. 1 (*top; curves B and C, respectively*). During early phases of exercise, plasma lactate concentrations remain stable but begin to rise when work rates reach about 50% of maximum; at fatigue in such lowlanders, plasma concentrations in excess of 10–12 mM are not at all uncommon (Fig. 1, *top*). In well-trained athletes, plasma lactate concentrations can increase into the 20 mM range (9). When such lowlanders exercise under hypoxic conditions, for any given power output, they generate and accumulate more lactate in the plasma than in normoxia (Fig. 1, *top;* cf. *curves C and B*). This metabolic response is common in many animals and tissues under O_2 limiting conditions; usually, it is an attempt to make up for the energy deficit caused by O_2 insufficiency and is a special version of the Pasteur effect (12). Alternatively, it could represent a regulatory mis-

TABLE 2. *Osmotic pressure, Na^+, and K^+ in plasma of Quechua natives during rest, at the end of incremental $\dot{V}O_{2\,max}$ exercise, and at the end of an anaerobic exercise protocol*

| Condition | Osmotic Pressure, mmol/kg | | [Na$^+$], μeq/ml | | [K$^+$], μeq/ml | |
	Rest	End	Rest	End	Rest	End
			Aerobic			
La Raya	278.8±2.5	298.6±2.5	157.2±2.4	165.1±1.6	3.6±0.1	4.9±0.3
6 wk DA	282.6±2.6	291.5±2.5	158.9±2.2	166.9±2.8	4.2±0.2	5.5±0.3
			Anaerobic			
La Raya	280.3±4.6	298.6±4.6	165.8±2.8	166.1±3.1	4.0±0.1	4.8±0.2
6 wk DA	282.6±2.6	292.0±3.1	158.9±2.2	162.7±1.7	4.2±0.2	4.6±0.1

Values are means ± SE of 6 subjs. Plasma of Andean volunteers was measured before and after maximal exercise as described in MATERIALS AND METHODS. Parameters were tested at hypobaric hypoxia (4,200 m) in La Raya and after 6 wk of deacclimation (DA) at sea level.

match between the glycolytic path and mitochondrial metabolism.

We found that the behavior of our Andean subjects, when tested at La Raya (4,200 m), differed strikingly from this standard metabolic pattern. At all exercise intensities to fatigue, plasma lactate concentrations were notably lower than in lowlanders. Curves of plasma lactate concentration vs. power output in watts in effect are strikingly rightward shifted, so that at fatigue maximum plasma lactate values are in the 5 mM range, or less than half that commonly seen in lowlanders (Fig. 1, *top, curve A*). Although these data are consistent with the concept that O_2 fluxes to working muscles are measurably more closely balanced with energy demands in Andeans than in lowlanders, they are perplexing for an obvious reason: despite the hypobaric hypoxia, Quechua natives produce less, rather than more, lactate for a given amount of muscle work. This kind of response has become known in the literature as the lactate paradox (11, 35), and it has been frequently analyzed in lowlanders during sojourns to high altitude (7, 35). Although it was first reported for Andean natives by Edwards (4) over 50 years ago, the underlying mechanism accounting for the lactate paradox has eluded science to this day. We analyze our current interpretations elsewhere (11, 21); suffice to mention at this point that the lactate paradox seems to be an expression of unusually close regulation of skeletal muscle energy demand-energy supply coupling and

hence in the regulatory interactions between glycolysis and mitochondrial metabolism.

The expression of the lactate paradox in Andean highlanders differs in another striking way from that in lowlanders. In lowlanders, the lactate paradox is expressed only after a period of acclimation to high altitude (7, 35) and it deacclimates over a similar time course (usually 2-3 wk). In Andean native highlanders, in contrast, the expression of this metabolic trait does not deacclimate. Under all conditions tested, at 3 and 6 wk of deacclimation at sea level under hypoxic conditions simulating the indigenous environment (Fig. 1, *middle* and *bottom*) and at 3 and 6 wk at sea level under normoxia (Fig. 2, *middle* and *bottom*), plasma lactate concentration curves remain rightward shifted compared with those for lowlanders. Because the power achieved at fatigue varied between individuals, the sampling times were standardized as fractions of the time taken to fatigue (% fatigue time on the x-axis of Figs. 1 and 2). Peak concentrations at fatigue remained in the 5 mM range and typically increased only slightly during the first 2 min of recovery to values in the 7-8 mM range. Thus, despite other adjustments that were occurring with deacclimation, such as changing hematocrit values (23), these data imply that, even on descent to sea level, Andean natives maintain a closer matching of energy demand and supply functions than do lowlanders under both normoxic and hypoxic conditions. Because this characteristic does not deacclimate, we assume that it is either a developmentally or a genetically fixed characteristic of metabolic organization presumably selected in Andean natives because efficiency (in terms of ATP yield per mole of substrate metabolized) is far higher in aerobic pathways than in anaerobic ones (10-12). In view of this behavior, we anticipated that Andean natives would display relatively stable CO_2-to-O_2 flux ratios as well as CO_2 and O_2 concentrations (end-tidal PO_2 and PCO_2).

End-tidal gas tensions. End-tidal PCO_2 and PO_2 values are shown in Fig. 3. Under all conditions that we studied, we observed that end-tidal gas tensions were regulated at fairly steady levels until work rates were about 70% of maximum, i.e., fairly close to the fatigue. Generally end-tidal PCO_2 seemed to be more stable than end-tidal PO_2. In these characteristics, the Andean natives displayed the anticipated responses; the main difference between them and lowlander subjects was in the lesser response to exercise under hypoxia (Fig. 3). On the basis of the lac-

TABLE 3. *Plasma glucose in Andean natives before and after aerobic exercise*

	Rest	End	30 min Recovery
	Normoxia		
La Raya Deacclimation			
1 wk	4.93±0.26	6.83±0.28	5.95±0.38
3 wk	4.45±0.30	4.97±0.28	4.98±0.15
6 wk	4.96±0.08	5.88±0.13	4.98±0.18
	Hypoxia		
La Raya Deacclimation			
1 wk	4.98±0.47	5.63±0.30	5.50±0.34
3 wk	4.60±0.20	4.91±0.18	4.73±0.29
6 wk	5.29±0.30	5.25±0.36	4.87±0.16

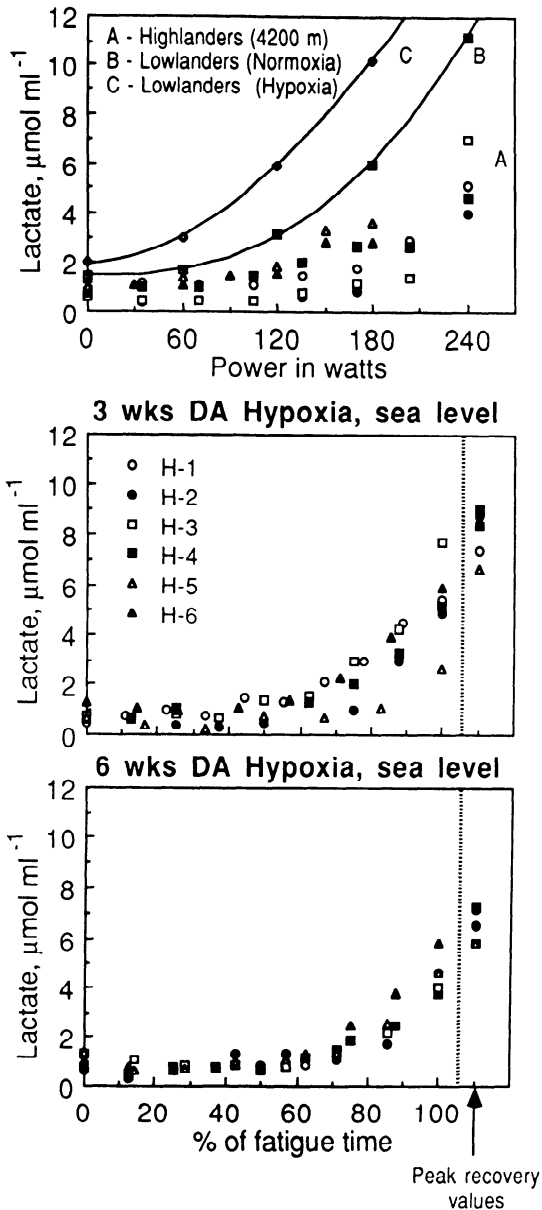Values are means ± SE of 6 subjs, expressed in μmol/ml.

FIG. 1. Accumulation of lactate in plasma during incremental exercise to fatigue. *Top: curve A,* data for 6 volunteer Quechua native highlanders obtained at La Raya, Peru; *curve B,* data for lowlanders under sea level conditions; *curve C,* data for lowlanders acutely exposed to hypoxia in a hypobaric chamber [*curves B* and *C* replotted from West (35)]. *Middle* and *bottom:* similar data after 3 and 6 wk of deacclimation (DA) for Andean highlanders (*H-1–H-6*) at sea level but performing under hypoxic conditions (breathing 14% O_2). Because watts achieved at fatigue varied between individuals, x-axis (*middle* and *bottom*) is standardized as a fraction of time taken to reach fatigue. Peak plasma lactate values (at ~2 min of recovery after fatigue) are also shown. Low lactate level in Quechuas at fatigue, despite exercising under hypoxic conditions, is termed lactate paradox (11, 35). In *middle* and *bottom,* lactate paradox is shown as an expression of metabolism in Quechuas that does not deacclimate at least over the 6-wk period of this study.

tate data, we would have expected end-tidal values to be either better regulated than in lowlanders, or at least as well regulated; thus, these results and theoretical expectations are considered to be in harmony.

CO₂ and O₂ fluxes: the apparent respiratory quotient (RQ). CO_2-to-O_2 flux ratios representative of all experimental conditions that we studied are summarized in Fig. 4. At the cell level this ratio, termed the RQ, is an accu-

rate reflection of which fuels are preferentially oxidized (15). At the whole-organism level, CO_2 fluxes can be influenced by other factors (such as pH shifts and CO_2 or bicarbonate movement into or out of tissues), which is why the whole-body CO_2-to-O_2 flux ratio is termed the apparent RQ (RQ_{app}). Nevertheless, at steady state the RQ_{app} yields useful information on fuel utilization (3). For work rates less than ~60% of maximum, Andean natives showed RQ_{app} values close to 1.0; although fractionally higher than in lowlanders at similar work rates, we conclude that in both groups carbohydrate is the main fuel being utilized in support of muscle work (3). We assume that this metabolic organization has been selected in both groups in part at least because of an efficiency
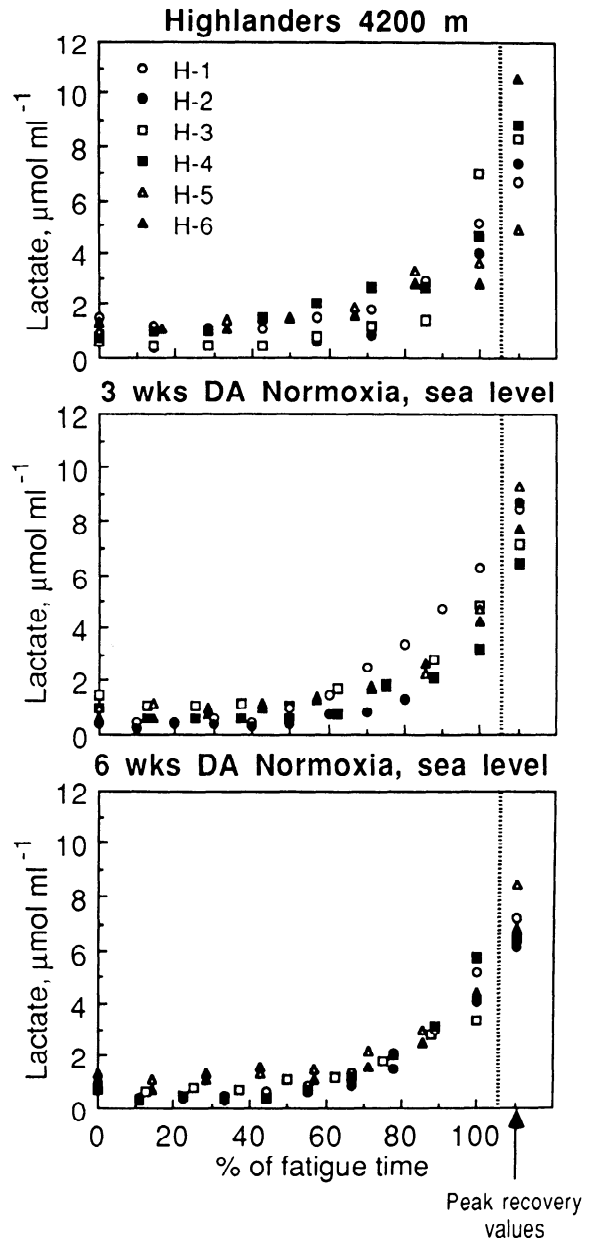

FIG. 2. Effect of deacclimation on accumulation of lactate in plasma during incremental exercise to fatigue. *Top:* initial conditions at La Raya, Peru. *Middle* and *bottom:* normoxic conditions at sea level in Quechua natives after 3 and 6 wk of deacclimation. Except for normoxia, conditions were the same as in Fig. 1. In all panels, x-axis is standardized as a fraction of exercise time taken to reach fatigue.
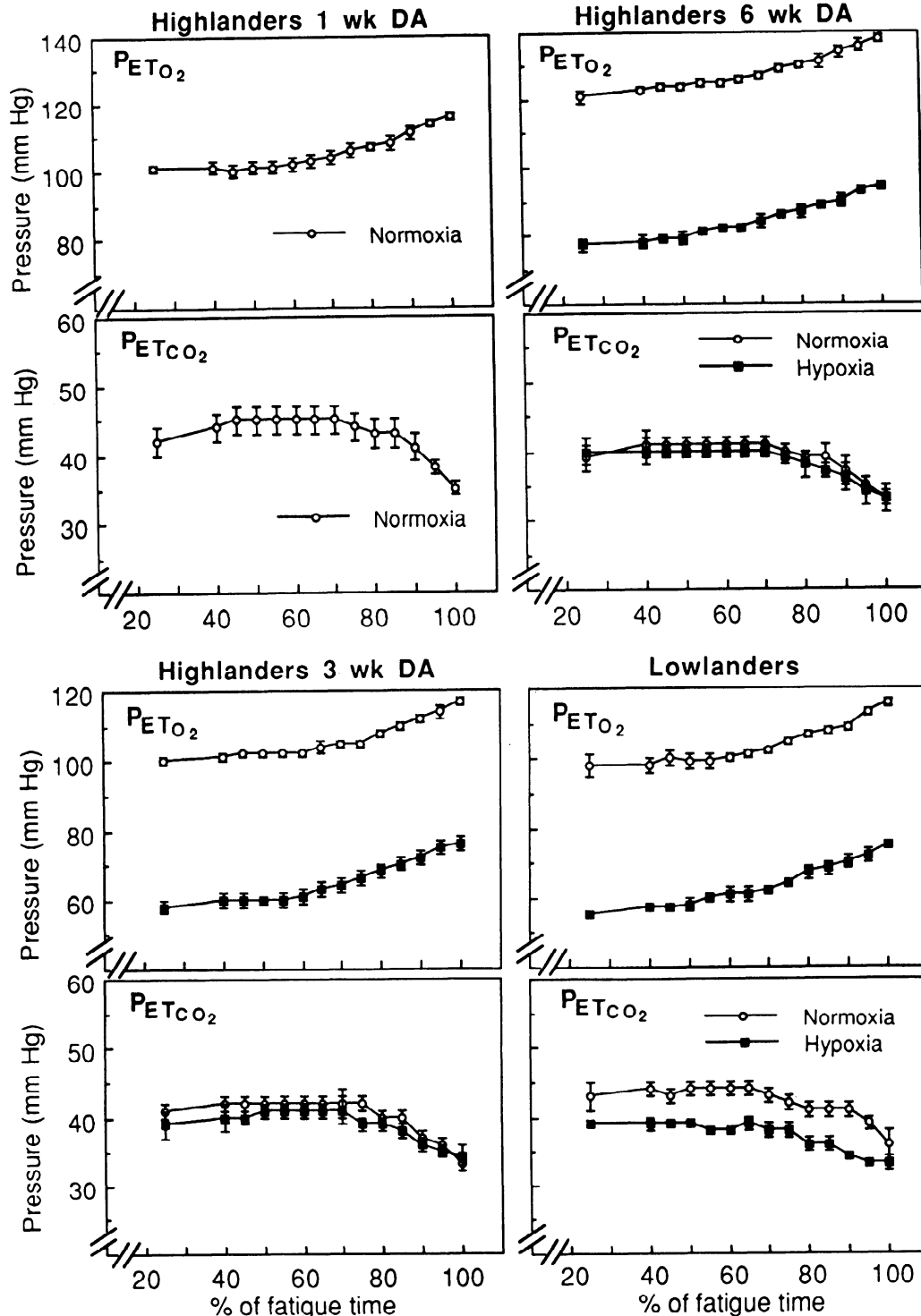
FIG. 3. End-tidal O_2 and CO_2 pressures (PET_{O_2} and PET_{CO_2}) during incremental exercise to fatigue in Quechua highlanders at various deacclimation periods after arrival at sea level compared with lowlanders (*lower right*). Except during the 1st wk of deacclimation, end-tidal values are given for exercise protocols under normoxic and hypoxic conditions. In the 1st wk of deacclimation, too many other experimental demands were being made on the subjects to allow these measurements to be made under both normoxic and hypoxic conditions. Error bars, SE; $n = 6$ for highlanders and 5 for lowlanders.

advantage: the complete oxidation of glycogen yields about 11% more ATP per mole of O_2 than for the complete oxidation of fat. In some tissues, such as cardiac muscle, the O_2 wasting effects of fatty acids can extend this difference two- to threefold (10, 15). Thus, when O_2 is at a premium, using glycogen as the dominant (if not only) carbon source is a biochemically efficient strategy because it maximizes the ATP yield per mole of O_2 consumed. Like the lactate paradox, this characteristic does not deacclimate in highlanders at sea level and is not altered during exercise under acute hypoxia.

Work efficiency during submaximal and maximal perfor-

mance. Energetic efficiency of muscle work in this paper is operationally defined as the ratio of mechanical power output to metabolic power input, both expressed in watts per kilogram and determined from whole body measurements of maximal and submaximal performance. By this definition, Andean natives exercising at maximum rates in normoxia displayed an energetic efficiency of ~30%.

Highlanders 1 wk DA

Highlanders 3 wk DA

Highlanders 6 wks DA

Lowlanders

FIG. 4. Ratios of CO_2 flux to O_2 flux [or apparent respiratory quotient (RQ) value] during incremental exercise to fatigue for Quechua highlanders compared with lowlanders under normoxic and hypoxic conditions. As in Fig. 3, hypoxic runs were not possible during the 1st week of deacclimation. Error bars, SE; $n = 6$ for highlanders and 5 for lowlanders. Fractionally higher apparent RQ values for Andean natives are assumed to arise from an exercise-based hyperventilation relative to lowlander athletes; comparatively low lactate levels observed (Figs. 1 and 2) and comparatively stable intracellular muscle pH (21) imply that these differences between the 2 subject groups cannot be ascribed to a higher degree of metabolic acidosis in Andean natives.
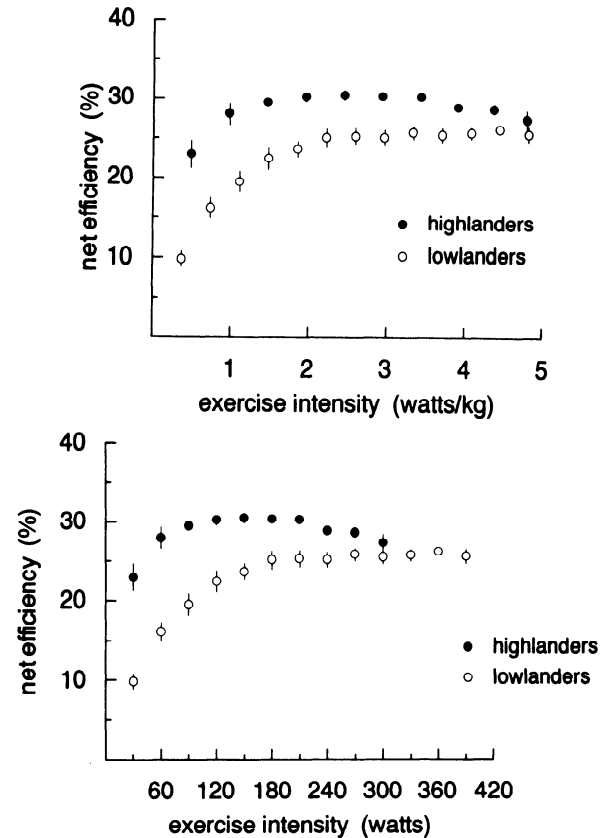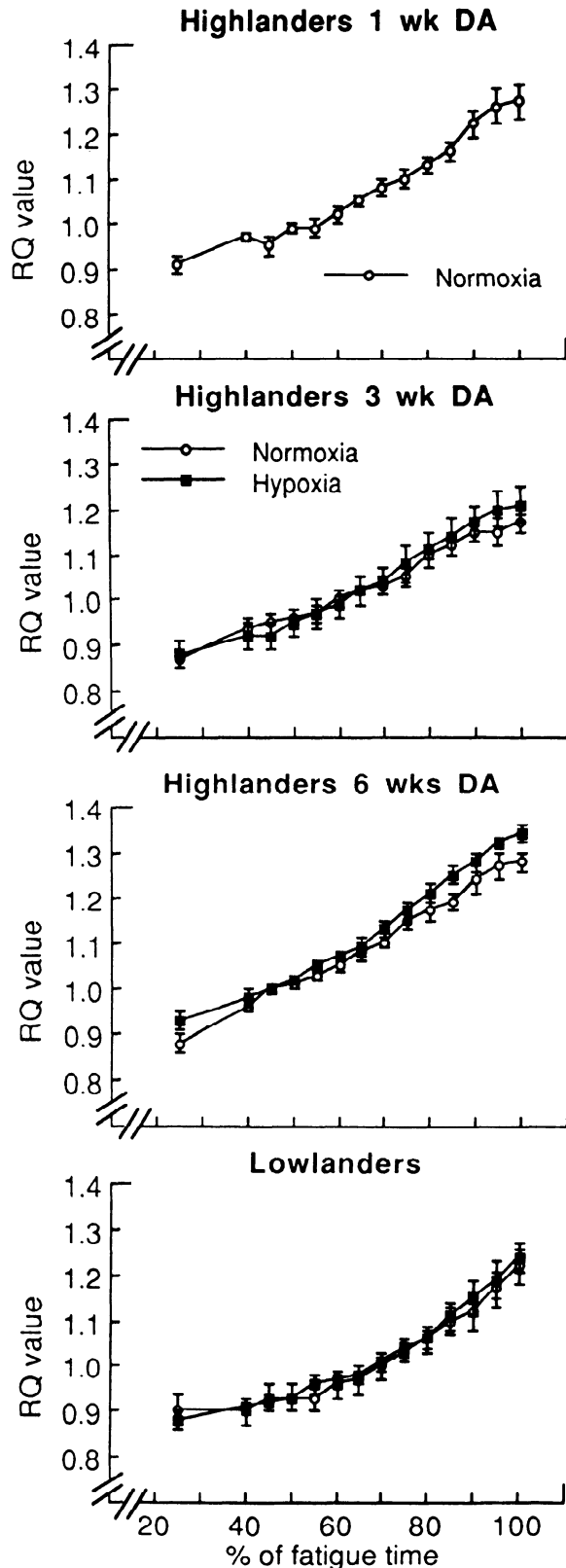

FIG. 5. Net efficiency of exercise during incremental exercise to fatigue as a function of exercise intensity in Quechua natives compared with lowlanders. For purposes of comparison, data under normoxic and hypoxic conditions are combined in both subject groups. *Top*: exercise intensity expressed in mass-specific terms; *bottom*: exercise intensity not adjusted for body mass. Error bars, SE, which in some cases are within symbols. See text for details.

These values were essentially the same at 2 and 6 wk of deacclimation and, for this reason, were combined for comparison with lowlanders. Both normoxic and hypoxic values are slightly higher than the 25–26% efficiency values found for lowlander athletes; although this difference was slightly exaggerated under hypoxia, the (normoxia + hypoxia) data are combined for ease of discussion (Fig. 5). For both our subject groups (highlanders and lowlander athletes) these efficiencies are somewhat higher than those frequently reported in the literature for maximum work on cycle ergometers by more sedentary or less well-trained individuals (22, 38). The differences between the two subject groups remained clearly evident even in comparisons of gross efficiencies (Fig. 6).

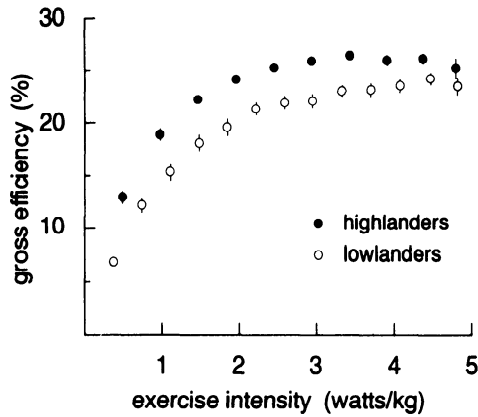The largest difference between Quechuas and low-

FIG. 6. Gross efficiency of exercise during incremental bicycle ergometer tests to fatigue as a function of exercise intensity in Quechua natives compared with lowlanders. As in Fig. 5, data under hypoxia and normoxia are combined for purposes of comparison. In some cases, SE bars are within symbol.

landers appears when the comparison in normoxia and hypoxia is made for submaximal exercise, where the efficiency estimates for Quechuas approach values that are 1.5- to 2-fold higher than in lowlanders (Fig. 5). Such large differences in energetic efficiencies of the two groups imply that a significant energetic advantage is enjoyed by Andean natives during submaximal exercise (although not shown, this is even more pronounced under hypoxic conditions). Compared with lowlanders under these conditions, the Andean natives are behaving as if they are able to get some 1.5 times as much work out of a given amount of O_2 and carbon fuel. We conclude that this characteristic would be particularly advantageous in high-altitude environments, which may explain why the characteristic appears to be either genetically or developmentally fixed in the Andean natives.

The energetic advantages of being able to get about 1.5 times more work out of a given amount of O_2 and carbon fuel (and ultimately out of a given amount of ATP) may immediately account for why Andean natives generate and accumulate less lactate for any given work rate than do lowlanders; however, they do not yield insight into underlying mechanisms.

Mechanisms for adapting work efficiency of muscle. A clue to the origin or nature of increased efficiency of muscle work in Andean natives derives from plots of power output vs. metabolic power input (Fig. 7). Three features of these plots are particularly instructive. First, the slopes of such plots (which are the ratios of power output to metabolic power input) are fully analogous to the instantaneous efficiency estimates of Gaesser and Brooks (5), which are not based on mass-specific metabolic rates. They represent the efficiency with which energy generated by metabolism is convertible to mechanical work and are similar for Andean natives and lowlanders, particularly in the midrange of exercise intensities. The implication is that the efficiency with which metabolic energy is converted strictly into mechanical work is similar in Andean natives and lowlanders.

However, when such plots are extrapolated to zero exercise intensity (zero power output), they do not go through the origin, which represents resting metabolic rate. In similar plots of power output vs. gross metabolic input (Fig. 7) these curves are further rightward shifted and do not extrapolate to resting metabolic rates. Although this result, a second striking feature of these plots, in fact is commonly observed in exercise studies of both animals and humans (27, 29), it is also commonly overlooked and has not been properly explained previously. In essence, because such extrapolations do not extend through the origin they imply that a fraction of energy metabolism during exercise is not directly convertible to mechanical work but is nevertheless required for sustaining a given work rate.

A third striking feature of the data of output vs. input shown in Fig. 7 is that the plots for lowlanders are "rightward shifted" relative to those for Andean natives under all conditions tested. That is, compared with Andean natives, lowlanders are behaving as if even more energy-consuming processes not directly convertible to mechanical work are required in addition to that supporting mechanical work per se; because of such additional energy expenditure, a given power output requires a somewhat higher metabolic input. Although Ca^{2+} adenosinetriphosphatase (ATPase) and actomyosin ATPase represent the dominant ATP sinks during muscle work, we recognize that not all the energy of ATP hydrolysis
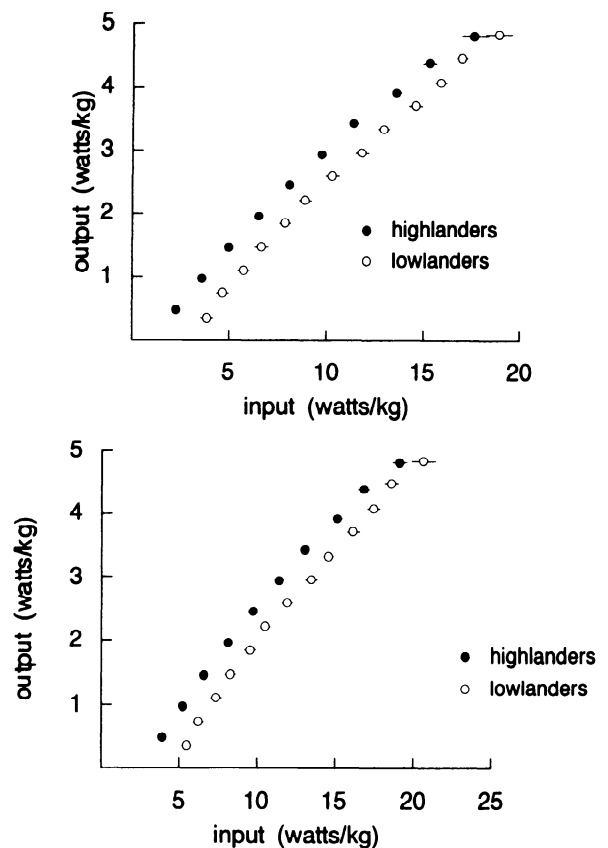

FIG. 7. *Top*: plots of combined data (hypoxia plus normoxia) of power output vs. net metabolic power input for Andean native highlanders compared with lowlanders. Error bars, SE, which in some cases are within symbols. *Bottom*: similar plots of power output vs. gross metabolic power input for Andean native highlanders compared with lowlanders. Despite rightward shift of curves compared with *top*, slopes for the 2 data sets remain similar. Error bars, SE, which in some cases fall within symbols. See text for details.

required for myofilament contraction and for Ca^{2+} pumping can appear as work (i.e., conversion of metabolic energy into muscle work is never 100% efficient). If for the moment we assume that myofilaments are conservative and functionally equivalent in highlanders and lowlanders (consistent with similar slopes in Fig. 7) and if we concentrate only on Ca^{2+} ATPase, then the less efficient the Ca^{2+} cycling processes, the larger the waste of energy in this kind of function, the more "rightward shifted" the output vs. input curves will be. Inefficiency of Ca^{2+} cycling in principle could be caused by either inefficient Ca^{2+} ATPases or inefficient regulation of sarcoplasmic Ca^{2+} release (leaky sarcoplasmic recticulum). If correct, this interpretation requires that muscles of Andean natives display more efficient Ca^{2+} cycling than do muscles of lowlanders. Because the efficiencies of Ca^{2+} ATPases vary by about twofold [from about 1 Ca^{2+}/ATP split to the theoretical maximum stoichiometry of 2 Ca^{2+}/ATP split (30)] and at least two kinds of Ca^{2+} pumps are known [two genes for Ca^{2+} ATPase have been sequenced (1)], one possibility suggests that muscles of lowlanders display higher proportions of inefficient Ca^{2+} ATPases than do muscles in Quechuas. Alternately, Ca^{2+} release could be less tightly regulated. In either event, muscles of lowlanders during exercise would have to sustain more energy-costly Ca^{2+} cycling than muscles in Andean natives during exercise. These ideas are diagrammatically summarized in Fig. 8.

Although at this time we have no direct evidence supporting or rejecting this model, we are confident enough to propose it because we are aware of another physiological condition in which an improved energetic efficiency of working skeletal and cardiac muscles is displayed: in hypothyroidy or in muscles with reduced thyroid sensitivity (2, 8, 19, 26, 30, 36). Both in hypothyroid humans and animal models, energetic efficiency as ultimately as-

TABLE 4. *Plasma T_4 and T_3 concentrations in Quechua natives*

Condition	T_4	T_3
La Raya	96.3 ± 5.8	1.78 ± 0.36
Deacclimation		
3 wk	89.3 ± 6.5	1.92 ± 0.09
6 wk	97.3 ± 7.5	$1.72+0.09$

Values are means $\pm$ SE, expressed in nM. Except for La Raya samples for subjects at rest, all hormonal analyses were done on blood samples drawn 30 min after $\dot{V}o_{2\,max}$ tests. Normal range for thyroxine (T_4) using the same assay procedures at the University of British Columbia Health Care Center are 58-154, with a mean of $\sim$108 nM. Meinhold (24) assumes 115 ± 2.5 (SE) nM for 112 healthy subjects analyzed. T_3, triiodothyronine.

sessed by the ratio of power output to metabolic power input is substantially higher than in euthyroid or hyperthyroid states. That is, muscle work in hypothyroidy is more efficient, and in animals (19) as well as humans (36) this effect is particularly large and easily measurable at submaximal work rates. Although the lactate paradox per se has not been described in this physiological state, it is instructive *1*) that the "anaerobic" threshold is rightward shifted in hypothyroidy (16) in a manner reminiscent of Figs. 1 and 2, *2*) that perfused hindlimb preparations in hypothyroid rats produce less lactate in response to a given stimulus than do muscles from euthyroid or hyperthyroid individuals (31), and *3*) that metabolic activation rate during cold exposure in Quechuas is notably blunted compared with lowlanders (20). Because additionally there is a well-established inverse relationship between hypobaric hypoxia and thyroid hormone status (6, 8), we are encouraged to hypothesize that muscle function in Andean natives behaves in a manner analogous to that of muscles with downregulated T_3 control (2, 26). If so, this condition could adequately account for the lactate paradox and the improved energetic efficiencies observed particularly at submaximal work rates.

Although functional tests of thyroid status (i.e., turnover rates and tissue clearance rates, tissue receptor site densities, and receptor site regulation) were not possible in this study, plasma T_4 and T_3 concentrations indicate that, at least by these criteria, Andean natives are assuredly not definable as systemically hypothyroid (Table 4). On the other hand, plasma T_4 and T_3 concentrations are modestly lower than in lowlanders [89–97 nM T_4 in Table 4 vs. 115 ± 2.5 (SE) nM given by Meinhold (24) for normal healthy humans]. The Clinical Chemistry Laboratory at the University Hospital in Vancouver considers 108 nM as an average T_4 concentration in plasma of healthy British Columbian lowlanders; i.e., values that are marginally higher than in the Quechua subjects. These results are in agreement with the reported inverse relationship between serum thyroid hormone concentrations in Andean natives and degree of polycythemia, an index of the degree of high-altitude adaptation attained (E. Pretell, personal communication), and with numerous animal studies (6, 8). Although these observations are consistent with our model, we do not take them as necessarily supportive of it. Because of the wide variety of critical roles played by thyroid hormones (30), we consider that the only way the energetic advantages of hy-
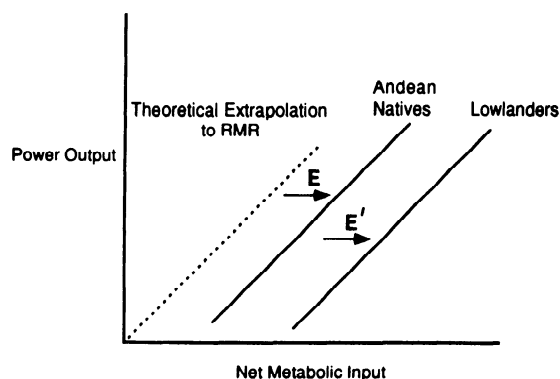

FIG. 8. Diagrammatic summary of relationship between power output and net metabolic power input in Andean natives and lowlanders. Because resting metabolic rate (RMR) is not included in calculations of metabolic input, dashed line suggests patterns that would be observed if essentially all metabolically generated energy was convertible to mechanical power output. "Rightward shift" of curve for Andean natives implies that some fraction of metabolically derived energy (E) is not convertible to mechanical work per se even if it is essential for the exercise. Because curve for lowlanders is shifted even farther to the right, an even greater fraction of metabolically derived energy (E') is required for essentially noncontractile functions. On the other hand, slopes of both plots are essentially the same, implying that efficiency of contraction machinery per se is similar in Andean natives and lowlanders. See text for details.

pothyroidy could be reaped at the level of working muscles without sacrificing other thyroid functions would be through downregulation of muscle sensitivity to thyroid hormones; for example, through downregulation of functional hormone receptor abundance per gram of tissue. In this event, muscles of Andean natives could behave as if they were in a hypothyroid environment even if plasma supplies of T_4 and T_3 were in the normal or near-normal range.

Although a part of the observed efficiency adjustments also may be due to lower energy demands of nonmuscular functions during exercise, some interesting expectations arise, if, for heuristic reasons, we assume that muscle work in Andean natives is energetically more efficient because of different phenotypic expression of myosin and/or Ca^{2+} pump isoforms (T_3 regulation need not be assumed at all for this model). From earlier work (in vitro with isolated mitochondria or isolated perfused working muscle preparations as well as in vivo), it is well established that any given muscle metabolic rate (or any given muscle work rate) can be sustained with less perturbation of adenylate, phosphate, or creatine phosphate concentrations in efficient compared with less efficient muscles (11, 30, 36). Nuclear magnetic resonance spectroscopic analyses of calf muscles during incremental exercise to fatigue, described in detail in our companion paper (21), confirm this expectation for Andean natives and supply additional support for our basic model of biochemical adaptation in high-altitude humans.

Conclusions. During incremental exercise to fatigue in their normal (4,200 m) environment, Quechua natives accumulate plasma lactate to concentrations that are only one-third to one-half the values observed in lowlanders; low lactate accumulation despite hypobaric hypoxia is termed the "lactate paradox" in the literature (7, 11, 35).

In lowlanders, the lactate paradox is a metabolic acclimation requiring about 2-3 wk to be expressed; it deacclimates along a similar time course. In Andean natives, on the other hand, the lactate paradox does not deacclimate, at least over the 6-wk time course of our study. Similarly, it is not affected by acute exposure to experimental hypoxia (reduced O_2 in inspired air). Because of its apparent stability, we infer that the lactate paradox is either a developmentally or genetically fixed metabolic characteristic of Quechua people. In our view, the lactate paradox is merely an expression of a metabolic organization that maximizes the amount of ATP obtained per mole of carbon substrate catabolized.

The plasma metabolite data imply closer matching of O_2 and fuel fluxes with energy demands of working muscles in Quechuas than in lowlanders. Closer matching of these fluxes in turn is reflected in a substantial (nearly twofold) improvement in energetic efficiency of muscle work at submaximal rates. Being able to work more or to work longer on a given amount of O_2 and carbon fuel (ultimately on a given amount of ATP) helps explain the lactate paradox: improved efficiency minimizes the need for anaerobic sources of ATP.

Plots of power output vs. metabolic power input in lowlanders and highlanders do not extrapolate to the origin, implying that during exercise in both groups muscle work sustains a significant ATP expenditure that is not converted to mechanical work. This energy cost is greater in lowlanders than in highlanders, which presumably is why such plots for lowlanders are rightward shifted relative to those for Andean natives. It is postulated that this difference is due to the occurrence of more efficient Ca^{2+} ATPase and/or myosin ATPase isoforms in muscles of Andean natives than in lowlanders, a mechanism analogous to (but not necessarily homologous with) work efficiency adjustments in muscles with reduced T_3 sensitivity or downregulated T_3 control.

These new metabolic data and new interpretations strongly support the penetrating insights of Hurtado et al. (14), first gained some 35 years ago. They are also consistent with the conclusion that selectively significant biochemical and physiological adaptations underly the frequent, if anecdotal, claims that Andean natives perform more capably in their normal environment than do Caucasian lowlanders.

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