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Physiology

^{31}P magnetic resonance spectroscopy of the Sherpa heart: A phosphocreatine/adenosine triphosphate signature of metabolic defense against hypobaric hypoxia

(hypoxia adaptation/heart hypoxia/heart ATP)

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ABSTRACT **Of all humans thus far studied, Sherpas are considered by many high-altitude biomedical scientists as most exquisitely adapted for life under continuous hypobaric hypoxia. However, little is known about how the heart is protected in hypoxia. Hypoxia defense mechanisms in the Sherpa heart were explored by *in vivo*, noninvasive ^{31}P magnetic resonance spectroscopy. Six Sherpas were examined under two experimental conditions [normoxic (21% F_iO_2) and hypoxic (11% F_iO_2)] and in two adaptational states—the acclimated state (on arrival at low-altitude study sites) and the deacclimating state (4 weeks of ongoing exposure to low altitude). Four lowland subjects were used for comparison. We found that the concentration ratios of phosphocreatine (PCr)/adenosine triphosphate (ATP) were maintained at steady-state normoxic values (0.96, SEM = 0.22) that were about half those found in normoxic lowlanders (1.76, SEM = 0.03) monitored the same way at the same time. These differences in heart energetic status between Sherpas and lowlanders compared under normoxic conditions remained highly significant ($P < 0.02$) even after 4 weeks of deacclimation at low altitudes. In Sherpas under acute hypoxia, the heart rate increased by 20 beats per min from resting values of about 70 beats per min, and the percent saturation of hemoglobin decreased to about 75%. However, these perturbations did not alter the PCr/ATP concentration ratios, which remained at about 50% of the values expected in healthy lowlanders. Because the creatine phosphokinase reaction functions close to equilibrium, these steady-state PCr/ATP ratios presumably coincided with about 3-fold higher free adenosine diphosphate (ADP) concentrations. Higher ADP concentrations (i.e., lower [PCr]/[ATP] ratios) were interpreted to correlate with the K_m values for ADP-requiring kinases of glycolysis and to reflect elevated carbohydrate contributions to heart energy needs. This metabolic organization is postulated as advantageous in hypobaria because the ATP yield per O_2 molecule is 25–60% higher with glucose than with free fatty acids (the usual fuels utilized in the human heart in postfasting conditions).**

Heart disease does not develop instantaneously. During early stages in disease development, it therefore is probable that the biochemical responses of the heart are initially "protective" or adaptive, designed to sustain normal organ function in the face of increasingly serious O_2 limitation. That certainly is the case in many animal species adapted through phylogenetic time for surviving hypoxic conditions (1–4), and there is no reason to believe that the fundamental processes would not be similar in humans. What then is the nature of such defensive adaptations in the human species and when do the biochemical responses of the heart stop being adaptive or protective and start becoming pathological? We think that an absence of naturally evolved models of defense against hypoxia in the human species (relative to which intervention concepts and strategies could be compared and evaluated) has hindered examination of these questions. We consider that humans indigenous to high altitude environments and thus adapted for many generations for sustaining normal functions under conditions of hypobaric hypoxia (4, 5) could provide the kind of framework needed to evaluate metabolic defense responses against hypoxia in the healthy human heart.

To this end, we organized an international interdisciplinary team and began a series of pilot studies with Himalayan natives, Sherpa volunteer subjects, born to families who have lived for generations in Nepal at altitudes between about 3000 and 5000 m. Of human groups that have been studied so far, the Sherpas are considered by many biomedical scientists as perhaps best of all adapted to chronic hypobaric hypoxia, although the data base on Andean natives is probably larger (5). Earlier physiological studies have shown that cardiac output in high-altitude natives is adjusted according to the acclimation state (6) and especially according to the O_2-carrying capacity of the blood. Earlier biochemical studies of the metabolic properties of the heart in hypoxia-adapted natives found evidence for elevated glucose preference of the heart (7, 8). With these studies as our points of departure, our aim was to take advantage of developments along many different conceptual and technological fronts (9–36) making it now possible to address these issues noninvasively and to interpret the results in relatively precise terms. In the present study, we used ^{31}P magnetic resonance spectroscopy (MRS) for real-time monitoring of the energetic status of the Sherpa heart. We found that the steady-state concentration ratio of phosphocreatine (PCr) over adenosine triphosphate (ATP) was maintained at about half that in hearts of lowlanders.

METHODS

Subjects. All of the studies to follow were reviewed by Human Ethics Committees at our universities. All Sherpa subjects were volunteers and were carefully briefed on procedures prior to initiating the study. In studies performed in the 2-week interval before arrival of the Sherpas, identical tech-

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Abbreviations: MRS, magnetic resonance spectroscopy; PCr, phosphocreatine; 1-D and 3-D, one and three dimensional; FSW, Fourier Series Window; 2,3DPG, 2,3-diphosphoglycerate; CPK, creatine phosphokinase; PGK, phosphoglycerate kinase; PK, pyruvate kinase; FFA, free fatty acid; F_iO_2, inspired O_2 fraction.

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niques to those of this study were used for comparative data on four lowland volunteers; all four subjects (three males, one female) were in good health and acclimatized to low altitudes (Minneapolis altitude is about 300 m). The mean age of the lowlander subjects was 30 years (SEM = 2). No gender differences were noted in the MRS data collected.

The six Sherpa volunteers, native to the Yilajun region of Nepal at about 3400 m, were professional guides and trekkers, conditioned for operations at variable altitudes, from Kathmandu at ≈1600 m to well over 6000 m. One of our subjects (CT) had participated in an expedition to over 8000 m about 3 weeks prior to our study. The average age of the subjects was 23.8 years (range 20–30); the average body weight was 58.5 kg (range 47–65). $\dot{V}O_2$(max), the maximum flow of oxygen determined by bicycle ergometry, was 50.3 (± 1.0 SEM) $ml \cdot kg^{-1} \cdot min^{-1}$, in the same range as previously found for other highland natives (14–17).

Monitoring Different Acclimation States. ^{31}P MRS was used to quantify phosphate metabolites in the heart muscle of Sherpas by using previously described methods (18, 19) and the protocols given below. Heart phosphorus spectra were acquired for two adaptational states: (*i*) the initial or "acclimated" state, assessed as soon as possible [4 days, including travel and time for other experiments (8)] after leaving altitude, and (*ii*) a deacclimating state, assessed after deacclimation at low altitude. Exactly 27 days separated the two (MRS1 and MRS2) data acquisition times. In lowlanders, altitude acclimation–deacclimation cycles are easily monitored by quite striking changes in hematocrit and in hemoglobin concentrations (17). In Sherpas, these changes were much more modest. Hematocrit on arrival at low altitude was 42.8% (1.8 SEM); after 3 weeks of deacclimation, it dropped to 37.9% (1.0 SEM). The respective hemoglobin concentrations were 14.6 (0.6 SEM) and 13.2 (0.4 SEM) g/dl (100 ml). Plasma metabolite concentrations were determined by standard clinical chemistry laboratory methods. Interestingly, plasma glucose concentrations on arrival were the same as after deacclimation, 5.13 (0.21 SEM) and 5.03 (0.15 SEM) $\mu mol \cdot ml^{-1}$, respectively. Plasma free fatty acid (FFA) concentrations were 0.32 (0.03 SEM) and 0.63 (0.09 SEM) $\mu mol \cdot ml^{-1}$ at the two data acquisition times.

MRS Protocols. Our ^{31}P MRS studies were performed on a SIS (Sunnyvale, CA) imaging spectrometer console, interfaced to a Siemens (Erlangen, Germany) 4-T 1.25-m horizontal bore magnet equipped with actively shielded gradients of 1.0 G/cm. Magnetic resonance imaging (MRI) and MRS were carried out with a double-tuned (^1H, ^{31}P) balanced-match, quadrature surface coil. Details of the patient cradle and the gated rapid-imaging protocol have been reported (18, 19).

This ^{31}P spectroscopy study, done under two oxygenation states, required high-quality spectra to be acquired in a short time period. Therefore, we implemented a three-dimensional (3-D) spectroscopic imaging version of the one-dimensional (1-D) "Fourier Series Window" (FSW), which in all aspects (including voxel size, repetition time, and data analysis) was directly comparable to our earlier (18) study. Briefly, cardiac gated [using a Nonin fiber optic pulse oximeter (Nonin, Plymouth, MN)] 3-D phase-encoding for ^{31}P was performed over a 20 × 10 × 12 cm field of view (*x, y, z*) by using seven, nine, and three phase-coding steps in each direction, respectively, and utilizing a total of 347 transients, which took ≈13 min (every second or third heart beat, depending upon heart rate). In our particular implementation of the 3-D FSW experiment (18), the number of acquisitions at each of the linearly incremented phase-encoding gradient values is determined by the Fourier coefficients of the desired voxel shape in exact analogy to that previously described for the 1-D FSW approach (19).

In the FSW approach, the 3-D window function has a constrained width, which in this case allows us to delineate 40 virtually unique, nonoverlapping voxels over the chosen field of view, with little of the intravoxel smearing seen in the standard 3-D implementation of spectroscopic imaging. Exponential filters of between 10 and 25 Hz were applied in the chemical-shift dimension. No other postprocessing or baseline manipulation was employed. When using the 3-D FSW approach with a surface coil, we need only one radio-frequency pulse, in this case an adiabatic pulse of 90-degree excitation pulse, known (20) as BIR-4.

In comparing our ^{31}P heart data to earlier ISIS (18)-column studies plus 1-D FSW studies (19), which utilize up to three adiabatic pulses before detection of the signal, we noticed an improvement in the off-resonance characteristics of the spectra (carrier is between PCr and γ-ATP peaks). Additionally, we found a more prominent phosphomonoester peak in the heart using the 3-D FSW experiment, suggesting a short transverse relaxation time (T_2) for this phosphate. Comparisons of the 3-D FSW vs. 1-D FSW approaches showed that the 3-D FSW saturation-corrected PCr/γ-ATP metabolite ratios in lowlanders (1.76) were the same as those found in our earlier work—1.8 (18, 19)—and similar to other studies (36). Saturation correction was carried out by using nonlocalized ^{31}P spectra from the chest wall as described (19, 20). Previous work found that ATP and other adenylates in blood do not contribute significantly to the ^{31}P signals from the heart at 4 T (19). With our FSW techniques, chest wall metabolites can be excluded in the voxels overlapping the heart, giving us confidence in the assignment of these spectra to heart muscle. The amplitude of the PCr and γ-ATP peaks were integrated both manually and by using the Varian line-fitting routines assuming Lorentzian lineshapes. No significant differences were found between the two techniques.

Heart ^{31}P MRS spectra were obtained for each Sherpa subject breathing normal air (≈21% O_2) and breathing a gas mixture which was 11% O_2 and 89% N_2. MRS data acquisition (Fig. 1) did not begin until new steady-state conditions were realized.

RESULTS

Representative ^{31}P MRS spectra of the heart of an individual Sherpa in acclimated normoxic (CT3) and hypoxic (CT5)

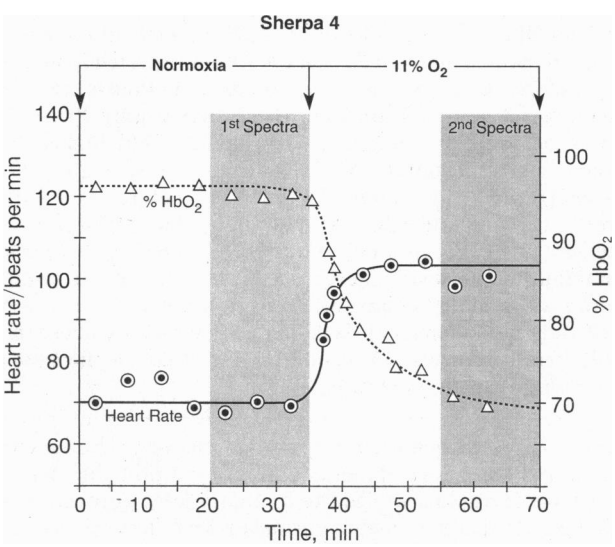

FIG. 1. Heart rate (⊙) and % HbO_2 (△ in an individual Sherpa under normoxic (≈21% O_2) and hypoxic (11% O_2) F_iO_2 conditions. Heart rate was monitored with a Siemens electrocardiographic unit, and the percent HbO_2 in arterial blood was measured with a pulse-gated finger oximeter. During the first 6 min of hypoxia, heart rates were obtained over 15-sec time intervals; only enough of these data points are included to illustrate the overall response pattern. Approximate times during which MRS data were acquired are indicated by shading.

stages (Fig. 2) indicate good resolution of at least three identifiable phosphate metabolites: ATP (three phosphates), PCr (one phosphate), and 2,3-diphosphoglycerate (2,3DPG; two phosphates). Previous studies have closely examined the tissue origins of these components and demonstrated that the first two metabolite signals derive primarily from heart (with no MRS visible contribution from the blood), while the 2,3DPG signal derives from erythrocytes in blood and the cardiac microcirculation (19). Because the 2,3DPG chemical shift overlaps with that of inorganic phosphate (P_i), the presence of 2,3DPG in the tissue sites under interrogation precludes quantifying heart P_i concentration ([P_i]). In contrast, in similar spectra of the chest wall, 2,3DPG becomes MRS-invisible (Fig. 2 *Upper*), while a small P_i peak usually is evident (but not MRS visible in Fig. 2 *Upper* spectrum). Because these chemical shifts are overlapping, workers in this field rely upon the ratio of [PCr]/[ATP] to yield information on the energetic status of heart tissue (18–21, 31–35).

The concentration ratios of PCr to ATP in the hearts of Sherpas under acclimated and deacclimating normoxic and hypoxic conditions varied between 0.5 and 1.6 and on average were close to unity (Tables 1 and 2). These values are substantially lower than any found in the healthy lowlander subjects (1.76, range 1.68–1.83) studied in the same laboratory under identical experimental circumstances in the 2 weeks prior to the Sherpa data acquisition (Table 1). *t*-test comparisons of the lowlander data vs. acclimated normoxic Sherpas

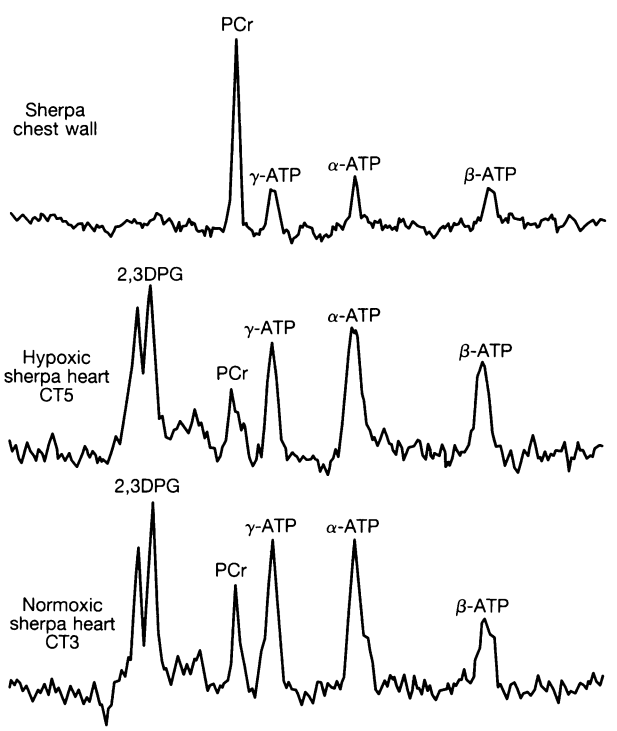

FIG. 2. ^{31}P magnetic resonance spectra from the heart of an individual Sherpa at 4 T during normoxia (CT3) (*Bottom*) and hypoxia (CT5) (*Middle*). (*Top*) Representative spectrum of the chest wall. The 2,3DPG signals arise from erythrocytes. The high-energy phosphate peaks arise from the left ventricle wall and the septal wall. The voxel size was 60 cm^3, and the acquisition time was 12 min for a 3-D acquisition. A 90-degree adiabatic radiofrequency pulse used for excitation triggered every second heart beat, leading to partial saturation of the metabolites. This saturation was corrected as described in refs. 19 and 21. The saturation-corrected heart PCr/ATP ratio in this subject was 0.8 under normoxia and 1.0 under hypoxia, substantially different from the 1.8 average value found in normal lowlanders and from the average value of 6.0 found for the chest wall muscles measured during the same protocol (*Top*). The chest wall PCr/ATP ratio in Sherpas is typical of that found in lowlanders.

Table 1. Ratios of PCr/γ-ATP in the left ventricle wall of six individual Sherpas under two (21% and 11% F_iO_2) conditions in acclimated and deacclimating states* compared with four lowlanders

Subject		PCr/γ-ATP ratio	
Type	ID	21% O_2	11% O_2
Sherpas			
Acclimated†	CT	0.804	0.996
	AM	0.586	0.691
	MN	1.174	0.952
	NN	1.146	0.983
	NK	1.449	0.568
	PN	1.622	1.014
	Mean	0.96	0.87
	SEM	0.22	0.09
Deacclimating†	CT	0.701	0.769
	AM	0.503	0.898
	MN	1.281	1.216
	NN	1.390	0.888
	NK	1.031	0.839
	PN	1.339	1.153
	Mean	1.04	1.13
	SEM	0.15	0.20
Lowlanders	SK	1.833	
	KH‡	1.675	
	JW	1.742	
	KS	1.774	
	Mean	1.76	
	SEM	0.03	

*See Table 2 for statistical analysis of Sherpa data.
†Acclimated state, as soon as possible after arrival from altitude; deacclimating state, after 27 days at low altitude.
‡Female subject. *t*-test comparisons of the data for normoxic conditions (21% O_2) indicate that the differences between Sherpas and lowlanders are significant at $P < 0.02$ level of confidence (see text for further details).

indicated that the differences were significant at the $P < 0.02$ level of confidence [$t = 3.51$; degrees of freedom (df) = 5.22]. *t*-test comparisons of the lowlander data vs. the deacclimating normoxic Sherpas indicated that the differences were significant at the $P < 0.01$ level of confidence ($t = 4.66$; df = 5.47). The lowlander subjects could not be examined under hypoxic conditions; hence, comparisons of the two groups under hypoxic conditions was not possible. The PCr/ATP ratio of 1.76 for the heart of the lowlanders is very similar to the average for hearts of humans analyzed in five independent recent studies (35). Thus, we assumed that the unusual Sherpa heart PCr/ATP ratios were of biological origin and not technical artifacts.

The question of whether the heart PCr/ATP values for Sherpas altered with deacclimation or with acute hypoxia exposure also was addressed by using a two-way repeated measure analysis of variance (i.e., two within factors, acclimated vs. deacclimating and normoxic vs. hypoxic conditions). To confirm that the experimental hypoxia was effective, heart rate and percentage HbO_2 were analyzed in a similar manner.

The means, standard deviations (in parentheses), and *F* values for the respective conditions are presented in Table 2 for PCr/ATP ratios, heart rates, and hemoglobin measures. As expected, breathing a hypoxic gas mixture led to significant changes in heart rate (increased by about 20 beats per min) and decreased into the 70–80% range of $\%HbO_2$ ($F_{1,5} = 63.1$ and 114.5, respectively, with a *P* value < 0.001). In contrast, these analyses showed that the Sherpa heart PCr/ATP ratios were not significantly altered by either acute change in inspired O_2 fraction (F_iO_2) or by weeks-long exposure to low altitudes. Thus, our results indicate (*i*) that average heart PCr/ATP ratios are substantially lower in Sherpas than in lowlanders and

Table 2. Heart rate (HR), % HbO_2, and heart PCr/ATP ratios in Sherpas under acclimated conditions (MRS day 1) and deacclimating conditions (MRS day 2) under normoxic (N) and hypoxic (H) conditions

	MRS day 1		MRS day 2		*F* values*		
	Normoxia	Hypoxia	Normoxia	Hypoxia	*F*-day*	*F*-H	*F*-day × H
HR	70.0	91.8	67.0	89.2	0.9	63.1	0.01
	(9.1)	(13.6)	(9.5)	(2.0)			
%HbO_2	97.3	76.0	97.7	81.2	10.1	114.6	4.77
	(0.8)	(5.3)	(0.5)	(4.2)			
PCr/ATP	0.96	0.87	1.04	1.13	0.0	1.84	1.44
	(0.4)	(0.2)	(0.4)	(0.2)			

Numbers in parentheses refer to the standard deviation.
*F-day, F-H, F-day × H are the respective F values for MRS day 1 vs. day 2, normoxia vs. hypoxia, and the interaction of these two effects.

(*ii*) that these ratios are relatively stable in terms of deacclimation and variations in F_iO_2.

DISCUSSION

In evaluating these data it is useful at the outset to recall that creatine phosphokinase (CPK) is a high-activity enzyme capable of maintaining the following reaction at near-equilibrium essentially at all times:

$$\text{ADP} + \text{PCr} \overset{\text{CPK}}{\leftrightarrow} \text{Cr} + \text{ATP}. \quad [1]$$

In the hearts of normoxic lowlanders, the concentration ratios of PCr/ATP are about 2, whereas in resting skeletal muscles, these ratios are in the 3–6 range (18–23, 35). Recent thermodynamic studies of CPK at pH 7 (37°C) and saturating Mg^{2+} concentrations (9) indicate that the equilibrium constant *K* or the ratio [Cr][ATP]/[ADP][PCr] equals 146, fractionally lower than the value (166) usually assumed by earlier workers in this field. If, for example, we assume that under normal pH 7 conditions [ATP] is 7.5 $\mu mol \cdot g^{-1}$ and that the total creatine pool in heart is equal to about 30 $\mu mol \cdot g^{-1}$ and is 50% phosphorylated, then a [PCr]/[ATP] ratio of 2 in a healthy normoxic heart reflects free [ADP] at about 51 $\mu mol \cdot g^{-1}$. The value herein, as in other studies (18–22), is above the apparent K_m(ADP) for mitochondrial oxidative phosphorylation (22, 23) and is an important reason why many current theories of metabolic regulation assume that changes in [ADP] are not critically involved in regulation of heart mitochondrial metabolism (22). When one assumes the same conditions as above, it easily can be shown that Sherpa hearts displaying [PCr]/[ATP] ratios of 1 would sustain a free ADP concentration of about 154 $\mu mol \cdot g^{-1}$—i.e., some 3-fold higher than in the case of the heart of lowlanders. In this range, free ADP would be an even less effective modulator of mitochondrial metabolism (concentrations too close to saturating) because, with such a mechanism, little room is left for expanding metabolic rate beyond that found at rest. In contrast, in other muscles, especially skeletal muscles, the *in vivo* [ADP] values may be much lower than the apparent K_m, and thus ADP here may play a regulatory role in fine-tuning mitochondrial respiratory rate (10). This is consistent with our studies of [[PCr]/[ATP] ratios in chest wall muscles of Sherpas (Fig. 2 *Top*), showing values (about 6) that were much higher than for the heart and that did not change with deacclimation or with acute hypoxia (data not shown). It is because of these kinds of considerations (10, 19, 22, 23, 27–29, 31–34) that metabolic biochemists consider the [PCr]/[ATP] ratio to be an important indicator of the energetic or regulatory status of the heart (or, for that matter, of any other tissue containing PCr and displaying an aerobic metabolic capacity).

The close to 2-fold difference between Sherpas and lowlanders in a heart "energy status" parameter as fundamental as the [PCr]/[ATP] ratio is quite without precedent in other heart studies (18–22, 31–35). The result is so striking that the rest of the paper mainly addresses this finding and attempts to explain its metabolic meaning. This is important because the myocardial phosphagen/ATP ratio is used as an index of altered energy metabolism in several common disease states (37–39). From current understanding of metabolic organization and control, the three most likely causes for low steady concentration ratios of PCr/ATP are (*i*) O_2 limitation to cell metabolism severe enough to invoke significant anaerobic contribution to ATP turnover rates, (*ii*) accelerated work of the heart under resting whole-body conditions, and (*iii*) altered carbon and energy sources fueling the cardiac "engine."

We can rule out the first alternative almost from basic principles. First and foremost, altitude-adapted natives are known to down-regulate anaerobic contributions to metabolism under hypobaric hypoxia, not to up-regulate them (14, 15, 24); their metabolism and performance are clearly designed to remain aerobic and to use O_2 efficiently (4). At low altitude the possibility of O_2 limitation under resting conditions for these subjects becomes even more remote. For these reasons, it is not at all surprising to find that switching from 21% to 11% O_2 has essentially no effect on the [PCr]/[ATP] ratios in the hearts of Sherpas (Table 1), even if the percentage saturation of arterial blood falls into the 70–80% range.

We can rule out alternative *ii* above in a similar manner. First of all, it is now well established that energy-demand–energy-supply pathways are so closely regulated in the heart that even large changes in the work rate of the heart do not cause large concentration changes in metabolites such as PCr and ATP (22). Although in our study we could not directly measure heart work, the switch to hypoxia caused a substantial increase in heart rates (which we tenatively assume means a proportionate increase in cardiac output and hence heart work rates). However, analysis of changes in [PCr]/[ATP] vs. changes in heart rates indicated no significant trends (data not shown). Thus, we tentatively conclude that the low [PCr]/[ATP] ratios cannot be readily explained by assuming that, at rest, the Sherpa heart operates at a relatively higher work rate than that typical of lowlanders.

The third possible explanation of low [PCr]/[ATP] ratios in Sherpa hearts is a biochemical one and involves an up-regulation of carbohydrate contribution to aerobic ATP turnover rates of the Sherpa heart. The point of departure for this concept (25) is the observation that the K_m values for ADP-requiring kinases in aerobic glycolysis are >100 μM, or substantially higher than for mitochondrial metabolism (about 28 μM). As pointed out above, ADP is also a cosubstrate for the near-equilibrium reaction catalyzed by CPK. Maintaining [ADP] in the K_m range for phosphoglycerate kinase (PGK) or pyruvate kinase (PK) would necessarily be reflected in automatic, CPK-catalyzed adjustments in the [PCr]/[ATP] ratio (Fig. 3).

According to this concept, in a heart metabolism organized to preferentially utilize carbohydrate for complete aerobic metabolism, the higher steady state concentrations of ADP

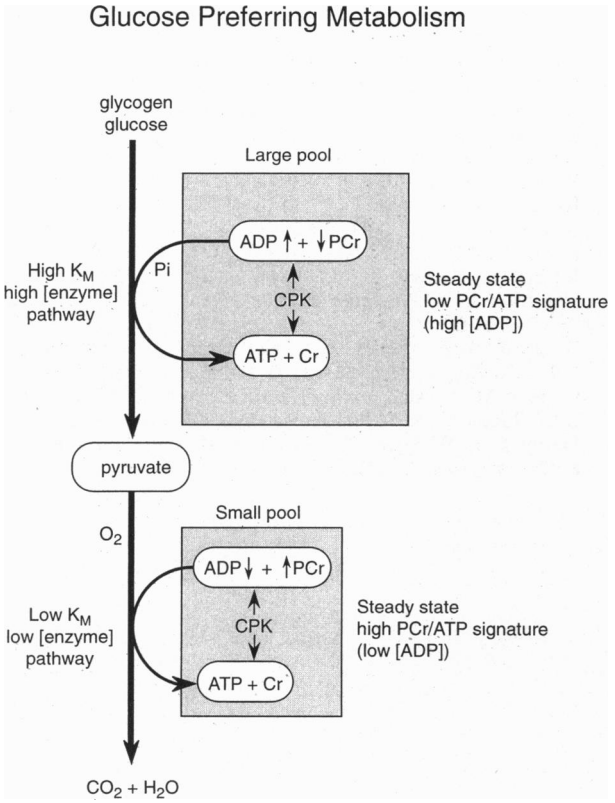

FIG. 3. A diagrammatic summary of how and why an elevated glucose (or glycogen) contribution to ATP turnover rates of heart or skeletal muscle would be expected to lead to lower steady-state [PCr]/[ATP] ratios.

required to prime PGK and PK in glycolysis would be sustained at the expense of reduced [PCr]/[ATP] ratios. In a heart metabolism organized to preferentially utilize FFA [the normal situation in the postfasting state (26–29)], the low [ADP] required for mitochondrial metabolism would be satisfied by higher [PCr]/[ATP] ratios. Exactly the same considerations would apply to skeletal muscle burning carbohydrates vs. lipids, with the complication that the adenylate and total creatine pool sizes are different.

Although these kinds of regulatory interactions were explored in the 1950s by Racker and his coworkers (30), their significance has been largely overlooked. A notable exception was a review published a decade ago (25) which pointed out that switching from fuels such as FFA to carbohydrates would necessarily require higher steady-state ADP concentrations to satisfy the higher K_m values for PGK and PK. More recently, Veech and his coworkers (36), found that over a 2- to 3-fold range of aerobic glucose metabolism, the highest glycolytic flux correlated with the lowest [PCr], also over about a 2- to 3-fold range. Similar earlier MRS studies in perfused hearts also demonstrated a strong dependence of [PCr]/[ATP] ratios, and consequently of free [ADP] levels, on available carbon and energy source (31). Our own positron emission tomographic studies of ^{18}F-labeled deoxyglucose uptake by the heart suggested elevated glucose preference of heart metabolism in altitude-adapted natives (8) and thus also agree with this hypothesis (Fig. 3).

These results are most consistent with alternative *iii* above; in fact, one can make a case for suggesting that a high-carbohydrate contribution to heart aerobic energy metabolism necessarily means reduced [PCr]/[ATP] ratios because of the ADP requirements of the glycolytic path. The question still remains, however, of the metabolic meaning of this biochemical characteristic of the Sherpa heart. Although we have no direct data bearing on this issue in this study, it is well known from much previous work (11–13) that the O_2 efficiency of glucose oxidation is substantially higher than the O_2 efficiency of FFA oxidation. Although the mechanism underlying the FFA "O_2 wasting effect" is unknown, the Sherpa heart would be expected to get 25–60% more ATP per mol of O_2 when burning carbohydrate than when burning FFA (11–13). Whereas the traditional view (27–29) that glucose is "good for the heart" when O_2 is limiting assumes that glucose primes ATP production by anaerobic glycolytic or by anapleurotic functions, our studies indicate that glucose is also advantageous for aerobic metabolism *when O_2 is present but at a premium*. Under the hypobaric hypoxia of the Himalayan environment, this property of heart metabolism in Sherpas clearly would be advantageous. It probably represents a true biochemical adaptation for human life under hypobaric hypoxia.

Whether or not similar metabolic, hypoxia-defense adaptations are used during development of heart disease in humans in our own society remains unknown at this time. If they are not used, perhaps they should be.

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