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Acid-base balance and O_2 transport at high altitude

M. SAMAJA,[1] C. MARIANI,[1] A. PRESTINI[2] and P. CERRETELLI[3]

1 Department of Biomedical Science and Technology, University of Milan, Milan, Italy,
2 USSL 60, Servizio 2, Ospedale di Vimercate, Milan, Italy and
3 Department of Physiology, University of Geneva, Geneva, Switzerland

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Ear lobe blood pH_a, P_aCO_2, P_aO_2, and O_2 saturation (S_aO_2) were measured in healthy Caucasians and Sherpas at 3400 m (Namche Bazaar, Nepal, $n = 4/5$), 5050 m (Pyramid Laboratory, Lobuche, Nepal, $n = 20/5$) and 6450 m (Camp II of Mt Everest, $n = 11/7$). In the investigated altitude range, pH_a increased progressively with altitude from 7.463 ± 0.005 (mean $\pm$ SE) to 7.496 ± 0.006 in Caucasians whereas it remained essentially constant (7.45–7.46) in Sherpas. At all altitudes, P_aCO_2 was higher in Sherpas than in Caucasians ($P < 0.02$). By contrast, P_aO_2 and S_aO_2 were the same in Caucasians and Sherpas at all investigated altitudes. Moreover, in Caucasians sojourning for 3 weeks at 5050 m, P_aCO_2 kept decreasing whereas pH_a, P_aO_2 and S_aO_2 remained constant. These data suggest that: (1) respiratory alkalosis was a common finding both in Caucasians and Sherpas; (2) at 6450 m, Sherpas were less alkalotic due to higher P_aCO_2 than Caucasians, possibly a consequence of a blunted ventilatory response; (3) at 6450 m, S_aO_2 and P_aO_2 were the same in Caucasians and Sherpas despite different P_aCO_2 values. The latter finding could be the consequence of one or more of the following adjustments in Sherpas: (1), an increased efficiency of alveolar O_2 transfer, i.e. smaller alveolar-arterial O_2 gradient; (2) a decreased (arterial – mixed venous) O_2 difference, possibly due to increased cardiac output; (3) a reduced increase of the [2,3-DPG]/[Hb] ratio; but not (4) an elevated gas exchange ratio (R). It is concluded that both physiological and biochemical variables contribute to optimize the O_2 transport at altitude. Apparently a more efficient adaptation to hypoxia allows Sherpas to limit alkalosis through a lower ventilatory drive and to maintain S_aO_2 at the same P_aO_2 by decreasing the [2,3-DPG]/[Hb] ratio.

Keywords acute mountain sickness, adaptation to hypoxia, 2,3-diphosphoglycerate (2,3-DPG), high altitude, hypoxia, O_2 equilibrium curve.

High altitude exposure is a recognized model to assess responses to acute and chronic hypoxia. Although the adaptation of humans to hypoxia is less extensive than that of other mammals (Monge & Leon-Velarde 1991), several degrees of compensation are normally established at the ventilatory, circulatory, erythropoietic and metabolic level. Ventilatory and acid-base balance adjustments are primarily involved in maintaining the homeostasis of the O_2 transport system. It was shown that, under conditions of extreme hypoxia, O_2 supply to tissues can be enhanced at the expense of uncompensated respiratory alkalosis (Winslow *et al.* 1984). In fact, the increased blood O_2 affinity due to alkalosis maintains the artero-venous O_2 difference despite low-P_aO_2. However, prolonged alkalosis is not compatible with normal body functions. Indeed, when alkalosis attains extreme levels over longer periods of time, it may impair the functions of the central nervous system possibly inducing coma. Thus, the defence of tissue oxygenation during severe hypoxia with alkalosis may ultimately conflict with the renal compensation that tends to re-establish normal pH value.

The above issue may have important biological and clinical implications. In fact, it is important to establish if and to what extent alkalosis may be able to partially reduce the effects of hypoxia. Therefore, validating earlier preliminary acid-base data at altitude (Winslow *et al.* 1984) might result in a better understanding of the mechanisms underlying adaptation of humans to hypoxia. Since then, only a few investigations have been carried out to this purpose. Among these, two

Correspondence: Dr Michele Samaja, Dipartimento di Scienze e Tecnologie Biomediche, via Fratelli Cervi 93, I-20090 Segrate (Milano) Italy.

studies were performed at altitudes ⩽ 5050 m (Bender *et al.* 1989, Kayser *et al.* 1993) whilst another one was carried out in a hypobaric chamber (Sutton *et al.* 1988). In 1994, we participated in the 'Extreme Altitude Survival Test (EAST)' Project, sponsored by the Italian Research Council and carried out by a group of high altitude climbers in the upper Khumbu glacier above the Icefall on the way to the South Col of Mt Everest, Nepal. Within this Project, arterial blood pH and gas values were measured in subjects exposed to altitudes in the 3400–6450 m range.

It is questionable whether full adaptation to hypoxia may ever be reached by humans at altitudes exceeding 5500 m. Therefore, comparing Caucasians with Sherpas may be of interest as Sherpa altitude natives are individuals whose adaptation to hypoxia (2500–4500 m) should be considered as acquired. This issue is supported by the following observations: (1) Sherpa blood has lower haematocrit (Cerretelli 1976, Beall *et al.* 1990) and erythropoietin level (Winslow *et al.* 1989), both features indicating a reduced hypoxic stress; (2) Sherpas are virtually immune from acute mountain sickness (Wabnig 1994); (3) Sherpas appear to be particularly fit even at very high altitudes as many of them, including those participating in this study, are able to climb up and down the Icefall treacherous path (from 5350 to 6450 m) within the same morning every day for 2–3 weeks carrying loads of up to 25 kg; (4) Sherpas may be better adapted to hypoxia than Caucasians simply because most of them participate to between three and four high-altitude expeditions every year.

So far, to our knowledge, blood gas and pH of Sherpas adapted to carry out heavy work at the indicated altitudes have never been investigated. In the present study, it was possible to obtain what, to the authors' knowledge, is a unique set of respiratory and haematological variables comparing Caucasians and Sherpas exposed to extreme altitude.

SUBJECTS AND METHODS

Organization

The present data were obtained during September-October 1994 within the EAST Project. A total of 24 Caucasians (C, age range 23–43 years, see Figure 1) and 17 Sherpas (S, age range 20–32 years) participated in this study. Ancestry and living habits of S were verified by interview. All subjects signed an informed consent and were examined daily by a staff physician for assessment of Acute Mountain Sickness (AMS) score. Some subjects were included in two or more groups.

A permanent high altitude research station (the 'Pyramid', barometric pressure = 425 mmHg or 56.53 kPa, P_IO_2 = 79.1 mmHg or 10.52 kPa) provided laboratory facilities for studies at 5050 m, and logistic and technical support for two field laboratories temporarily set at 6450 and 3400 m. At the Pyramid, three groups of subjects were investigated: a group of C (n = 20), 1–2 days after arrival from lower altitudes (2700–5050 m trekking for 5–6 days); part of the same group (n = 8), after a 3 weeks sojourn at 5050 m; and a group of altitude S (n = 5) dwelling at that altitude for > 4 weeks. Data were obtained also from two C subjects affected by AMS. A field laboratory was set up at 6450 m (Camp II of Mt Everest, average barometric pressure = 308 mmHg or 40.96 kPa, P_IO_2 = 54.6 mmHg or 7.26 kPa). Here, two groups of subjects were examined: a group of C (n = 11), 1–3 days after arrival and a previous total exposure to altitudes of 2700–5350 m exceeding 15–20 days; and a group of altitude S (n = 7), 1–2 days after reaching the laboratory. The other field laboratory was set up at 3400 m (Namche Bazaar, Nepal, average barometric pressure = 514 mmHg or 68.36 kPa, P_IO_2 = 97.7 mmHg or 12.99 kPa). Here, two groups were examined: a group of C (n = 4), 1 day after arrival on the way back after 1 month exposure to altitudes ⩾ 5050 m; and a group of local S dwellers (n = 5).

Measurements

The barometric pressure was monitored daily by a factory-calibrated digital barometer (Alti-plus K2, Pretel, France). Resting blood pH_a, P_aO_2 and P_aCO_2 were measured by a Ciba Corning M238 blood gas analyser on loan from the factory branch in Milano, Italy. Arterial blood samples were obtained from a pre-heated ear lobe after 3–5 min of gentle scratching. Blood was collected into heparinized 100 μL-capillaries and was analysed immediately. Haemoglobin O_2 saturation (S_aO_2) was determined by ear oximetry (Biox 3740 pulse oximeter, Ohmeda, Denver, CO, USA) carried out simultaneously with blood gas analyses on the contralateral lobe.

The concentration of 2,3-diphosphoglycerate (2,3-DPG) was measured in venous blood samples collected from the antecubital vein in heparinized vacuum tubes using kits supplied by Boehringer Biochemia (Mannheim, Germany). At the Pyramid, the assay was performed < 4 h after collection. Blood samples from 6450 m were shipped to the Pyramid laboratory and assayed 20 h after collection.

Total haemoglobin concentration ([Hb]) was measured in the Pyramid by a Coulter Counter (Instru-

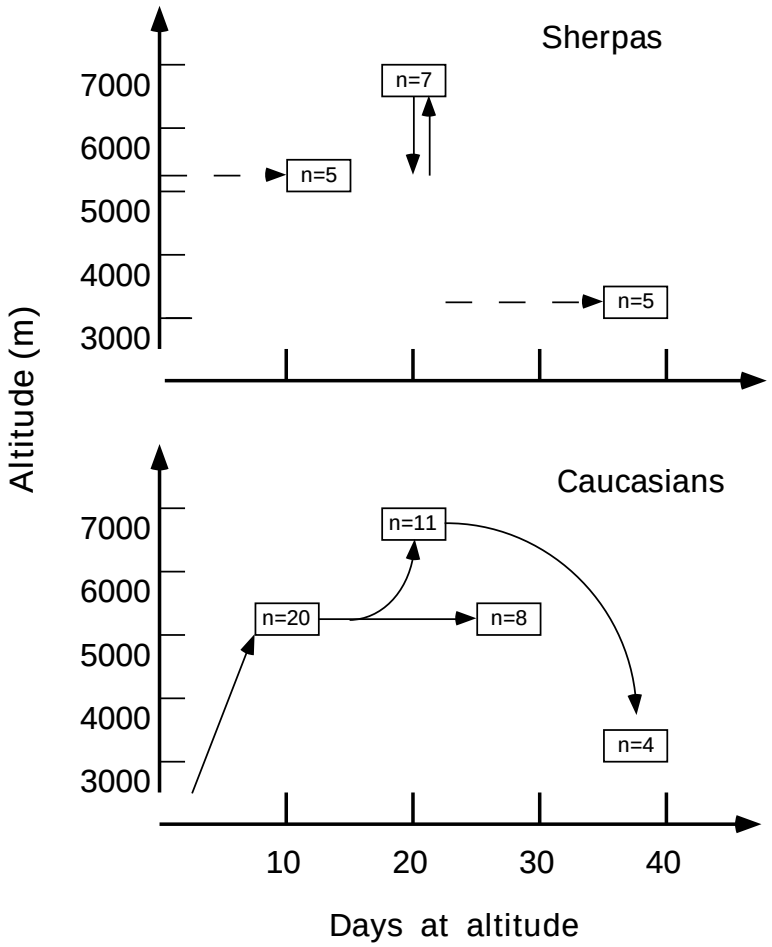

Figure 1 Diagram representing the number of investigated subjects studied and their altitude exposure. (Upper panel) Sherpas: the horizontal dashed lines mean that those subjects were residential at that altitude for times spanning from months (at 5050 m) to years (at 3400 m). The seven subjects tested at 6450 m were studied 1–2 days after reaching that altitude. None of the subjects tested at 6450 m was also studied at lower altitudes. (Lower panel) Caucasians: twenty subjects were studied 1–2 days after trekking for 5–6 days at 2700–5050 m; part of the same group ($n = 8$) after a 3 weeks sojourn at 5050 m; 11 subjects were studied 1–3 days after arrival to 6450 m. Four of these subjects were also studied at 3400 m on their way back from the mountains.

mentation Laboratory, Milano, Italy) on loan from the company. Some control samples were also analysed in Milano with the standard Drabkin's method.

The AMS score was assessed by a staff physician according to an empirical scale (Ferrazzini *et al*. 1987). The symptoms were scored as follows: 1 point each for mild pulmonary rales, headache, ataxia, peripheral oedema (one location), nausea, insomnia, dypsnoea. Two points each were assigned for more severe symptoms, peripheral oedema (two or more locations), and vomiting. Diagnosis of AMS was established when AMS score was $\geqslant 3$.

Calculations

The base excess (BE) was evaluated from pH_a, blood gas measurements, [Hb] and S_aO_2 determinations using a known algorithm (Thomas 1972). Whole blood O_2 equilibrium curves (OEC) were simulated from pH, Pco_2 and the [2,3-DPG]/[Hb] ratio using a reported algorithm (Winslow *et al*. 1983). Blood P_{50} (Po_2 at which Hb is half-saturated with O_2) was obtained by interpolating the calculated OEC at the actually measured or assumed pH value. For all calculations, we assumed a constant body temperature of 37 °C.

Statistics

Data are expressed as means $\pm$ SE. When two groups of subjects were compared, the Student's *t*-test for unpaired observations was used. When three or more groups were compared, one-way analysis of variance was performed, followed by the Fisher's multiple test comparison (StatView 4 software, Abacus Concept, Berkeley, CA, USA). The limit of significance was set to $P = 0.05$ (two-tailed).

RESULTS

With the exception of two individuals, who shall be considered separately, the AMS score of the investigated subjects did never exceed 2. The reliability of arterial blood gas analyses was routinely checked by

Table 1 Arterial blood acid-base and hematological data obtained in this and other studies

	Altitudes	*n*	pH_a	P_aco_2 mmHg	P_ao_2 mmHg	% o_2 saturation	Base excess mEq L^{-1}	[Hb] g L^{-1}	[DPG]/[Hb]
Caucasians	3400	4	7.463 ± 0.005	22.0 ± 0.4	51.5 ± 2.7	–	−5.6 ± 0.4	170 ± 12§	1.03 ± 0.15§
	5050	20	7.474 ± 0.005	23.9 ± 0.5	43.7 ± 0.9*	88.1 ± 0.9	−4.0 ± 0.3*	191 ± 9	0.95 ± 0.03
	5050‡	8	7.478 ± 0.011	21.0 ± 1.0	43.5 ± 1.1	– (83 ± 1)**	−5.6 ± 0.4	217 ± 5	1.04 ± 0.08 (1.28 ± 0.05)**
	6450	11	7.496 ± 0.006*	18.7 ± 0.5*	33.6 ± 1.1*	73.4 ± 3.0*	−6.1 ± 0.2*	201 ± 6	1.36 ± 0.24*
Sherpas	3400	5	7.462 ± 0.011	28.8 ± 1.2†	52.6 ± 1.4	–	−2.0 ± 0.4†	169 ± 12§	1.01 ± 0.21§
	5050	5	7.448 ± 0.017†	26.8 ± 1.1†	42.0 ± 0.8*	–	−3.9 ± 1.0*	186 ± 5¶	1.04 ± 0.04¶
	6450	7	7.454 ± 0.015†	22.4 ± 0.7†*	33.4 ± 1.7*	74.3 ± 2.2	−6.2 ± 0.8*	–	1.2††

Means ± SE; *, $P < 0.05$ from lower altitude within the same group (ANOVA and Fisher's tests); †, $P < 0.05$ from Caucasians at the same altitude (unpaired Student *t*-test); ‡, after 3 weeks at that altitude; § Winslow *et al.*, 1989, data obtained at 3800 m; ¶ Samaja *et al.*, 1993; **, same study, but after 5 weeks at that altitude; ††, estimated value (see Discussion). 1 mmHg = 0.133 KPa.

running repeated appropriate standards. Table 1 reports all data obtained in the present study and, for the sake of comparison, some entries from other studies by our group.

As expected, P_ao_2 and P_aco_2 decreased with increasing altitude. No differences were found in P_aO_2 between C and S, whereas, at each investigated altitude, P_aco_2 was found to be significantly higher in S than in C ($P = 0.0004$, 0.02 and 0.002 at 3400, 5050 and 6450 m, respectively). After a 3 weeks sojourn at 5050 m, C were characterized by significantly lower ($P = 0.008$) P_aco_2 values than upon arrival.

Mean pH_a at 3400 m was the same in C and S even though S data were more scattered than those for C. At higher altitudes, C showed a trend toward more pronounced alkalosis, whereas pH_a in S did not change significantly. The differences in pH_a between C and S were statistically significant at 5050 and 6450 m ($P = 0.05$ and 0.008, respectively). During the 3-weeks sojourn at the Pyramid, pH_a of C did not change (7.474 ± 0.005 vs. 7.478 ± 0.011) despite lower P_aco_2 (23.9 ± 0.5 vs. 21.0 ± 1.0). In the two subjects with high AMS scores (5–6), pH_a was 7.56.

DISCUSSION

Acid-base balance and 2,3-*DPG*

The preservation of an adequate tissue O_2 supply is obviously crucial during adaptation to hypoxia. Hyperventilation is an early and powerful adaptive response aimed at preserving high P_ao_2, but is necessarily accompanied by hypocapnia (Rahn & Otis 1949). The decrease of P_aco_2 induces a condition of respiratory alkalosis which, in the investigated subjects, was only partially counterbalanced by metabolic acidosis. Actually, at 6450 m, BE was near −6 mEq L^{-1} in both C and S, whereas a BE of −10 to −9 mEq L^{-1} would have been necessary for complete metabolic compensation. At 3400 m, C apparently did compensate less than S, but this finding may be due to the fact that C were studied on their way back from the mountains, 1 day after leaving the Pyramid. It is therefore plausible that, in the latter group, the mechanism of compensation was not yet back to normal, the measured BE still reflecting the value for subjects adapted at 5050 m. Therefore, it may be reasonably assumed that metabolic compensations are not primarily involved during adaptation to hypoxia because BE was not significantly different in C and S at all altitudes.

As is well known, the blood 2,3-DPG level is influenced by several, often uncontrollable factors. At altitude, the increase of 2,3-DPG is mainly caused by: (1) alkalosis, that stimulates the enzymes synthetizing 2,3-DPG (Lenfant *et al.* 1971, Espinos *et al.* 1982); (2) the increased fraction of deoxygenated Hb, that enhances binding of 2,3-DPG to Hb thereby decreasing the amount of free 2,3-DPG (Duhm & Gerlach 1971); and (3) the erythropoietic stimulation, that increases the fraction of young, 2,3-DPG-rich red cells (Mairbaurl *et al.* 1990, Samaja *et al.* 1993). Whereas mechanisms (1) and (2) take place relatively rapidly (days), (3) may require weeks to become functionally relevant.

Blood O_2 *affinity*

Whereas alkalosis increases the blood O_2 affinity by the Bohr effect, 2,3-DPG decreases it both by direct interaction with haemoglobin and the 2,3-DPG-induced decrease of intra-erythrocytic pH (Samaja & Winslow 1979). To quantitatively assess the effects of alkalosis and 2,3-DPG on the O_2 transport, an algorithm can be adopted that allows to predict the OEC from pH, Pco_2 and the [2,3-DPG]/[Hb]ratio (Winslow *et al.* 1983). It is assumed that the applied equations are valid for both S and C blood even under extreme conditions of pH, Pco_2 and [2,3-DPG]/[Hb] ratio. Indeed, even under such conditions, the

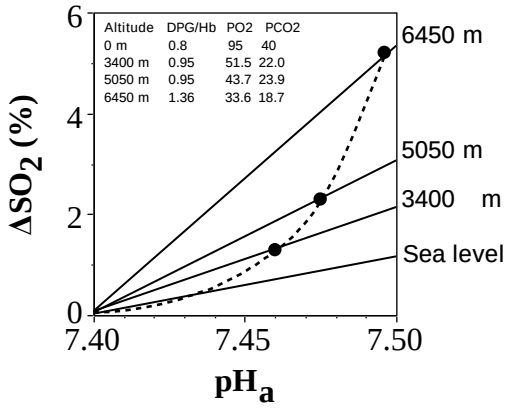

Figure 2 Increasing arterial pH (ΔpH_a) always leads to a rise of arterial O_2 saturation (ΔS_aO_2), but $\Delta S_aO_2/\Delta pH_a$ increases with altitude. The O_2 equilibrium curves were simulated as explained in the text from the actual values found in Caucasians (shown in the inset). The dashed curve represents the gain in S_aO_2 as from the actual pH_a values at the various altitudes.

discrepancy between the measured P_{50} and the P_{50} derived from the algorithm accounts for 0.2–0.4 mmHg or 27–53 Pa (Winslow *et al.* 1984). In any case, the algorithm is used here not to obtain absolute values, but rather to provide differential information on the effects of pH_a, P_aCO_2 and 2,3-DPG on the OEC.

At 6450 m, the calculated P_{50} of C is 30.1 mmHg or 4.00 kPa, in good agreement with the value of 29.8 ± 2.2 mmHg or 3.96 ± 0.29 kPa previously found in 14 subjects at 6300 m (Winslow *et al.* 1984). Thus, taking as reference the sea level P_{50} of 27.5 mmHg or 4.19 kPa (Samaja *et al.* 1981), it appears that the rightward shift caused by increased 2,3-DPG is greater than the leftward displacement caused by alkalosis. As a matter of fact, an increase of the [2,3-DPG]/[Hb] molar ratio from 0.80 (sea level) to 1.36 (6450 m) would have required an increase of pH_a from 7.40 to 7.66 for complete compensation. On the other hand, should alkalosis be fully compensated by metabolic acidosis, then P_{50} would have been 33 mmHg or 4.4 kPa, instead of 30 mmHg or 4.0 kPa.

To assess the contribution of alkalosis on the blood O_2-carrying properties, the theoretical S_aO_2 gain due to blood alkalinization was calculated (Figure 2). It appears that, despite the apparently small differences in P_{50}, the increase of S_aO_2 (ΔS_aO_2) for a given ΔpH_a becomes progressively greater as altitude increases. This is due to the peculiar shape of the OEC, that becomes progressively steeper as Po_2 decreases below 70–80 mmHg or 9.3–10.6 kPa. Even a slight alkalosis can therefore be considered beneficial as far as O_2-loading in the pulmonary capillary is concerned. At 6450 m, O_2-loading in the lungs may indeed be more important than O_2-unloading in the peripheral capillary. Theoretical considerations indicate that, whereas a rightward shift of the OEC is useful to unload extra-O_2 up to an altitude of 5500 m, it becomes a maladaptive response at higher altitudes (Samaja *et al.* 1986). It follows that, at 6450 m, the O_2 content difference between arterial and mixed venous blood is best protected by increasing alkalosis. However, this conclusion should be taken with caution as a given alteration of the blood O_2 carrying properties may have different effects in organs with different O_2 uptake and end-capillary Po_2. There are wide differences in terms of O_2 requirements and blood supply among organs and tissues (Samaja 1988), but no data appears to be available to describe the consequences of alkalosis on the O_2 transport in individual organs.

Sherpas vs Caucasians

It is well known that, at rest as well as at exercise, S ventilate less than C at all altitudes (Lahiri *et al.* 1969). The reasons are still unclear and are beyond the purposes of this study. Solving this problem would require an understanding of the mechanisms of human adaptation to hypoxia, both at a metabolic (Kayser *et al.* 1991) and a genetic (Winslow *et al.* 1989, Kayser *et al.* 1994) level, as well as an explanation for the failure of the kidney to fully compensate alkalosis at very high altitude. Nevertheless, a blunted ventilatory response may be considered the result of a better adaptation to hypoxia. In addition, a blunted ventilatory response may also be beneficial because it is associated with a decreased O_2 cost of ventilation. Indeed, at sea level, an increase of ventilation from 8 to 40 L min^{-1} raises the total O_2 uptake by only 20–40 mL min^{-1} (Otis 1964). However, at higher ventilation rates as those expected during exercise at very high altitude, the difference in the O_2 cost of the ventilatory pump could greatly exceed the gain in total O_2 uptake (Cerretelli 1980). Thus, it should be expected that in S, despite reduced air density, a lower ventilation ultimately enhances the availability of O_2 to locomotory muscles.

As a consequence of the reduced respiratory drive and assuming the same pulmonary gas exchange ratio (R), an equal efficiency of the alveolar gas transfer, the same cardiac output and the same mixed venous blood shunt in the lung, one would expect lower P_aO_2 and higher P_aCO_2 in S than C. Whereas the latter prediction is confirmed by the present results, the former is not: at 6450 m, P_aO_2 and S_aO_2 of S were the same as in C, despite different P_aCO_2 and pH_a levels. The apparent paradox of identical P_aO_2 and S_aO_2 at different P_aCO_2 and pH_a levels may have several explanations.

(1) A greater efficiency in S of the alveolar O_2 transfer. The subsequent decrease of the ventilation/perfusion inequality and/or decrease of diffusion limitation would lead to a smaller alveolar-arterial O_2 gradient.
(2) A higher P_vo_2 in the mixed venous blood (if it is assumed that the ventilation/perfusion distribution and lung O_2 diffusion are the same in S and C). This would lead either to a decreased artero-venous O_2 difference, or to an increased cardiac output. The latter factor would reduce the effect of venous-arterial shunt on the alveolar-arterial O_2 gradient.
(3) An elevated R in S compared with C. Recent measurements (Marzorati *et al.*, personal communication), however, indicate that this is not the case. In fact, in a group of altitude S at 5050 m, R at rest was found to be 0.97 ± 0.07 ($n = 8$), a figure to be compared with an average value of 0.99 ± 0.09 ($n = 7$) in C sojourning 3–5 weeks at the same altitude.
(4) A different 2,3-DPG level in S and C. As indicated above, 2,3-DPG could not be measured in S at 6450 m. However, two lines of evidence support the view that the [2,3-DPG]/[Hb] ratio in S was less than that in C. First, although at 3800 m the [2,3-DPG]/[Hb] ratio was the same in the two groups (Samaja *et al.* 1979, Winslow *et al.* 1989), at 5050 m it was definitely lower in S than in C (1.04 ± 0.04 vs. 1.28 ± 0.05, respectively). It is likely that such trend does continue even at higher altitudes. Second, when the [2,3-DPG]/[Hb] ratio was calculated in S by the algorithm from actual P_ao_2, P_aco_2, pH_a and S_aO_2 data, it was estimated at near 1.2, a value to be compared with 1.36 ± 0.24 found for C (see Table 1). Another factor that may contribute to lower 2,3-DPG in S is the shorter exposure of S compared to C to 6450 m (24 vs. 48–72 h) and the corresponding lower alkalosis inducing a weaker drive for 2,3-DPG synthesis. A lower [2,3-DPG]/[Hb] ratio coupled with different P_aco_2 values would justify the similar S_aO_2 values in C and S.

The data obtained in this study do not allow to definitely rule out any of the above hypotheses. However, we find it unlikely that changes in ventilation/perfusion distribution may account for the observed paradox of identical P_ao_2 and S_aO_2 at different P_aco_2 and pH_a levels in favour of blood chemistry-related factors. Indeed, the hypothesis that changes in ventilation/perfusion distribution determine different performances at altitude was already considered doubtful by other authors (West *et al.* 1983a). In addition, it is expected that, during exposure to very high altitude, the topographical matching of ventilation to blood flow becomes more favourable (Dawson 1972). Under such conditions, any change of the ventilation/perfusion distribution can only be explained with inequalities at the alveolar level

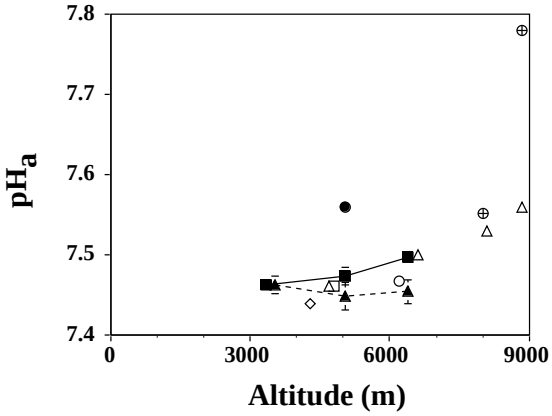

Figure 3 Arterial pH (pH_a) in the investigated subjects at altitudes ranging from 3400 to 6450 m (mean ± SE), and as reported from other studies at altitudes in the 3400–8848 m range (SE bars omitted for clarity). AMS = Acute Mountain Sickness subjects (●). Key: Caucasians (–■–), Sherpas (–▲––), Winslow *et al.* 1984. (○), Winslow *et al.* 1984 (estimated; ⊕), Sutton et al. 1988 (chamber; △), Bender *et al.* 1989 (◇), and Kayser *et al.* 1993 (□).

(Cerretelli 1980). Thus, should the present findings be justified only by a different ventilation/perfusion distribution, then the respiratory exchange rate also should be substantially different, which appears not to be the case (see 3 above).

Alkalosis and adaptation to altitude

The pH_a values found in C are in agreement with literature data showing a steady increase of pH_a with altitude (Figure 3). By contrast, in S, pH_a remains almost constant in the 3400–6450 m altitude range. Thus, the need to increase S_aO_2 through hyperventilation and consequent alkalosis appears to be much less in S than in C. It is not possible at present to state whether lower alkalosis is a consequence of a better adaptation to hypoxia or if the latter depends on alkalosis. However, an analysis of some altitude-related pathological conditions characterized by extremely high pH_a values may contribute to gain some insight into this possible link. Indeed, lack of adaptation to hypoxia of two among the investigated subjects (those developing AMS) was accompanied by extreme hyperventilation and nearly uncompensated respiratory alkalosis. It may be hypothesized that the latter was aimed at protecting S_aO_2. On the other hand, the high pH_a value estimated for a mountaineer who reached the summit of Mt Everest (Winslow *et al.* 1984) was probably also the consequence of extreme hyperventilation that could have been beneficial for blood oxygen loading. Indeed, this subject had an extremely powerful ventilatory drive due to exercise and the need to take off his oxygen mask 10 min before sampling (West *et al.* 1983b).

CONCLUSION

Comparing acid/base balance and blood O_2 transport in Sherpas with those in Caucasians at extreme altitude may provide a better insight into the mechanisms underlying human adaptation to hypoxia. At 6450 m both Caucasians and Sherpas developed respiratory alkalosis, which was only partially compensated by metabolic acidosis. Sherpas, however, were less alkalotic than Caucasians and were characterized by a lower blood [2,3-DPG]/[Hb] ratio. Their reduced ventilatory drive is possibly a sign of better adaptation to hypoxia. There may also be other factors that make Sherpas better adapted to hypoxia than Caucasians.

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