

Pulmonary gas exchange and acid-base state at 5,260 m in high-altitude Bolivians and acclimatized lowlanders

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Wagner, Peter D., Mauricio Araoz, Robert Boushel, José A. L. Calbet, Birgitte Jessen, Göran Rådegran, Hilde Spielvogel, Hans Søndegaard, Harrieth Wagner, and Bengt Saltin. Pulmonary gas exchange and acid-base state at 5,260 m in high-altitude Bolivians and acclimatized lowlanders. *J Appl Physiol* 92: 1393–1400, 2002. First published November 16, 2001; 10.1152/jappphysiol.00093.2001.—Pulmonary gas exchange and acid-base state were compared in nine Danish lowlanders (L) acclimatized to 5,260 m for 9 wk and seven native Bolivian residents (N) of La Paz (altitude 3,600–4,100 m) brought acutely to this altitude. We evaluated normalcy of arterial pH and assessed pulmonary gas exchange and acid-base balance at rest and during peak exercise when breathing room air and 55% O₂. Despite 9 wk at 5,260 m and considerable renal bicarbonate excretion (arterial plasma HCO₃⁻ concentration = 15.1 meq/l), resting arterial pH in L was 7.48 ± 0.007 (significantly greater than 7.40). On the other hand, arterial pH in N was only 7.43 ± 0.004 (despite arterial O₂ saturation of 77%) after ascent from 3,600–4,100 to 5,260 m in 2 h. Maximal power output was similar in the two groups breathing air, whereas on 55% O₂ only L showed a significant increase. During exercise in air, arterial PCO₂ was 8 Torr lower in L than in N (*P* < 0.001), yet PO₂ was the same such that, at maximal O₂ uptake, alveolar-arterial PO₂ difference was lower in N (5.3 ± 1.3 Torr) than in L (10.5 ± 0.8 Torr), *P* = 0.004. Calculated O₂ diffusing capacity was 40% higher in N than in L and, if referenced to maximal hyperoxic work, capacity was 73% greater in N. Buffering of lactic acid was greater in N, with 20% less increase in base deficit per millimole per liter rise in lactate. These data show in L persistent alkalosis even after 9 wk at 5,260 m. In N, the data show 1) insignificant reduction in exercise capacity when breathing air at 5,260 m compared with breathing 55% O₂; 2) very little ventilatory response to acute hypoxemia (judged by arterial pH and arterial PCO₂ responses to hyperoxia); 3) during exercise, greater pulmonary diffusing capacity than in L, allowing maintenance of arterial PO₂ despite lower ventilation; and 4) better buffering of lactic acid. These results support and extend similar observations concerning adaptation in lung function in these and other high-altitude native groups previously performed at much lower altitudes.

hypoxia; ventilation; acid-base balance; diffusing capacity

THE REMARKABLE ABILITIES of high-altitude natives to perform work at altitude are well known (15), and much research has been carried out to understand the physiological basis of this phenomenon. Considerable attention has been focused on the lungs, and several studies point to differences in lung structure and function between high-altitude natives and lowlanders of Tibet (23), South America (15), and even the United States (6). Some of the differences appear to be inherited adaptations consequent to generations of living at altitude. Others may result from individual lifelong or at least long-term high-altitude residence, whereas others may occur over the short term of days to weeks. Principal observations are that lung volumes are greater than predicted by sea-level tables (15, 23) and that diffusing capacity is also elevated (4–6, 9, 15). Reduced ventilatory response to hypoxia is often (6, 15) but not always (22) seen, resulting in arterial PCO₂ values that are higher in high-altitude natives than in lowlanders. Despite this, arterial oxygenation is defended during exercise by a smaller alveolar-arterial PO₂ difference [(A-a)PO₂] in natives compared with lowlanders, such that arterial O₂ saturation is similar between groups (6) or even higher in natives (23). These findings have mostly been obtained at or below 4,000 m.

During a recent expedition to Mt. Chacaltaya (altitude 5,260 m) near La Paz, Bolivia, we took the opportunity to further explore differences in pulmonary function between South American high-altitude natives and lowlanders. This expedition was focused primarily on circulatory and skeletal muscle changes with acclimatization, and this required arterial blood sampling at rest and during exercise. Thus, whereas pulmonary function was not a primary target of the expedition, the gas-exchange and acid-base differences seen in the lowlanders compared with natives were substantial, prompting their description in the present report. What this study offered beyond those described above

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was a side-by-side comparison of lowlanders and Andean natives using identical methods and with direct arterial blood sampling not available in Schoene et al.'s work (15) in subjects of similar population ancestry. An unusual additional aspect of the present study was that the lowlanders had acclimatized for 9 wk at the chosen altitude before measurements. Most acclimatization studies have not allowed such a long period at a single altitude but have followed subjects as they inexorably continued to ascend, preventing attainment of steady-state conditions at any point. Moreover, the studies of Dempsey et al. (6), Zhuang et al. (23), and Schoene et al. (15) were all carried out at substantially lower altitudes (3,100, 3,658, and 3,900 m, respectively) than the present effort, which took place at 5,260 m. In the present study, measurements were made both at rest and during exercise and addressed the following questions: 1) Does 9 wk at this constant high altitude permit complete pH normalization (i.e., restoration of arterial pH to near 7.40) in lowlanders? 2) Does acute hypoxia in natives (who were necessarily transported on the day of the study from La Paz, altitude 3,600–4,100 m, to 5,260 m) produce a substantial additional stimulus to breathing at rest or during exercise, and a measurable reduction in exercise capacity as would occur for lowlanders moving between these altitudes? 3) Is arterial oxygenation during exercise still defended in natives at 5,260 m as appears to be the case at lower altitudes, and, if so, are the physiological mechanisms similar to those described above in prior studies [higher diffusing capacity and lower (A-a)PO₂]? 4) Is arterial acid-base regulation similar in natives and acclimatized lowlanders?

METHODS

Subjects. This study used nine lowlanders from Denmark and seven Bolivian natives of mixed European and Amerindian population ancestry, lifetime residents of La Paz at between 3,600 and 4,100 m. All provided informed consent to protocols approved by both Danish and Bolivian ethical committees (Copenhagen-Fredericksberg Ethical Review Committee and Comité de Ética del Colegio Médico de La Paz). Anthropometric and key additional physiological attributes are given in Table 1. All 16 subjects were healthy, habitually active, and nonsmokers. The Danes were physically active

college students with an interest in outdoor recreation, whereas the Bolivians indulged in a variety of regular social activities including soccer. Only one Bolivian was a trained athlete (marathon runner). There were small differences in age (Bolivians 3 yr older, $P = 0.05$) and height (Bolivians 12 cm shorter, $P = 0.01$), but weight and body mass index were not significantly different. Both hemoglobin concentration and hemoglobin PO₂ at 50% saturation of hemoglobin (P₅₀) were similar in the two groups (Table 1) as well. Note from Table 1 that maximal cycling power output (that is, highest power sustainable for the 5 min required for stabilization and data collection) and associated O₂ uptake ($\dot{V}O_2$) when breathing ambient air at 5,260 m were also similar between groups.

The lowlanders spent 9 wk at 5,260 m, and the studies were done in the last week. The lowlanders all undertook two brief (2–3 day) climbs of neighboring 6,000 m peaks (one in week 2 and one in week 7) and a 1-day recreational bicycle descent to 2,000 m in week 6. Otherwise, they all remained at Mt. Chacaltaya at 5,260 m for the entire period. None displayed evidence of high-altitude pulmonary or cerebral edema at any time.

Subject preparation. The protocols were designed to simultaneously address several questions, many of which were well beyond those pertaining to pulmonary function, and thus required several catheters whose purposes are unrelated to the present report. Under local anesthesia and with sterile technique, catheters were placed in a femoral vein (94-030-2.5F TD probe, Edwards Edslab, Baxter, Irvine, CA) and artery (18-gauge Hydrocath, Ohmeda, Swindon, UK) to enable both blood sampling and measurements of femoral venous blood flow by thermodilution (1). A peripheral venous catheter was placed in an antecubital vein in the lowlanders, to be used for indocyanine green dye injection for cardiac output measurements. Cardiac output was also measured in the high-altitude natives, but with the use of an acetylene uptake method (2) to avoid additional catheters and blood sampling unacceptable to the subjects.

Subjects were then seated on a cycle ergometer (Monark 824E, Varberg, Sweden) and fitted with a mouthpiece and nose clip in standard fashion to enable measurements of ventilation, $\dot{V}O_2$, and CO₂ production ($\dot{V}CO_2$) from expired gas (using ParvoMedics True Max 2400, Consentius Technologies, UT). An electrocardiogram monitor was attached with standard leads to record heart rate and oversee rhythm.

Protocol. Both lowlanders and high-altitude natives undertook identical protocols as follows. After resting measurements, a submaximal work rate averaging 120 W was selected, and subjects pedaled at this power output for 10 min, with duplicate measurements made in the final 5 min. After

Table 1. Anthropometric and exercise capacity characteristics of high-altitude natives and of lowlanders after acclimatization

	High-Altitude Natives	Lowlanders	P
<i>n</i>	7	9	
Age, yr	27.6 ± 1.6	24.3 ± 0.5	0.05
Weight, kg	62.6 ± 2.2	67.0 ± 3.4	NS
Height, cm	164 ± 2	176 ± 3	0.01
Maximal cycling, W (ambient air at 5,260 m)	217 ± 5	229 ± 13	NS
$\dot{V}O_2$, l/min (ambient air at 5,260 m)	2.47 ± 0.09	2.43 ± 0.16	NS
Maximal cycling, W (55% O ₂ at 5,260 m)	229 ± 8	282 ± 15	0.01
	NS compared with air	$P < 0.001$ compared with air	
[Hb], g/dl (maximal exercise)	20.0 ± 0.4	19.2 ± 0.7	NS
Hb-P ₅₀ , Torr at 37°C, pH = 7.40 and PCO ₂ = 40 Torr	29.4 ± 0.2	30.5 ± 0.7	NS

Values are means ± SE; *n*, no. of subjects. $\dot{V}O_2$, O₂ uptake; [Hb], hemoglobin concentration; P₅₀, PO₂ at 50% saturation of hemoglobin.

a 10-min rest, subjects again cycled at 120 W for 2 min, after which work rate was rapidly raised to the previously determined individual peak rate known to be sustainable for 5 min. During the final 2 min of this 5-min period, duplicate measurements were again obtained. With subjects still pedaling, a higher work rate was imposed if subjects indicated ability to continue, and measurements were repeated within 2 min. When each subject could increment work rate no further, the inspired gas was switched from ambient air [barometric pressure = 408 Torr; inspiratory P_{O_2} ($P_{I_{O_2}}$) = 75 Torr] to ~55% O_2 ($P_{I_{O_2}}$ = 195–200 Torr) while the subject continued to pedal. After 2 min, another set of measurements was taken, and work rate was further incremented individually if tolerated to attain a new peak power output. A final set of measurements was then obtained under these conditions.

It should be noted that the above was actually a subset of the entire day's protocol. Those elements that pertained to questions other than lung-related issues are not described here. These include submaximal and maximal exercise runs using single-leg knee extensor effort and also cycle exercise after parasympathetic nervous system blockade (reported elsewhere, Ref. 3). The knee extensor runs were done before those described for the present study and were separated from the present cycle exercise by an hour of rest, but the parasympathetic blockade experiments were always done after the present study had been completed.

Measurements. Other than \dot{V}_{O_2} , \dot{V}_{CO_2} , and ventilation, the principal data were obtained from arterial blood samples and consisted of P_{O_2} , P_{CO_2} , and pH (Radiometer ABL5); saturation and hemoglobin concentration (Radiometer OSM3); and plasma lactate levels (ABL5). All values of P_{O_2} , P_{CO_2} , and pH were corrected to blood temperature measured by the femoral venous catheter thermistor. Cardiac output was measured in lowlanders by indocyanine green dye dilution with injection in a peripheral (antecubital) vein and femoral arterial sampling (3). In natives, a noninvasive method for measuring cardiac output was chosen to minimize catheter placements and blood loss. We used the acetylene uptake method (2) and employed the SensorMedics $\dot{V}_{O_2 \max}$ system (SensorMedics, Yorba Linda, CA) to measure acetylene (and an insoluble reference gas, methane) concentrations at the mouth. This system also measures ventilation and O_2 and CO_2 concentrations and so provided all of the input data required for calculation of cardiac output as explained in Barker et al.'s paper (2). Without any equipment to measure acetylene solubility, we assumed for all subjects an average blood:gas partition coefficient of 0.8 on the basis of Barkers' results and an estimate from Jibelian et al. (10) of the contribution of the higher than sea-level hemoglobin concentration.

Calculations. Oxygen-diffusing capacity of the lungs (DL_{O_2}) was not directly measured at rest or during exercise. However, a value for DL_{O_2} could be calculated from the measured blood-gas data by use of a numerical forward-integration algorithm (19) as follows. First, by using the measured pulmonary \dot{V}_{O_2} , cardiac output, and arterial O_2 concentrations, mixed venous O_2 levels were computed for each subject. Similar calculations were performed for CO_2 . Alveolar P_{O_2} was also determined for each subject by using the alveolar gas equation and taking alveolar P_{CO_2} to be equal to arterial P_{CO_2} . Between these venous and alveolar values for P_{O_2} and P_{CO_2} , a value of DL_{O_2} was found (by using the numerical integration procedure in an iterative manner) that predicted the measured arterial P_{O_2} and P_{CO_2} for each subject. The key assumption, made for both subject groups, was that all of the (A-a) P_{O_2} found during exercise at 5,260 m was due to diffu-

sion limitation and none was caused by ventilation-perfusion inequality. The diffusing capacity was therefore calculated by assuming a homogeneous lung and, as a result, is a conservative lowest estimate. This assumption is seen in DISCUSSION.

Analysis of data. The principal objective of this study was to compare several elements of exercise performance between high-altitude natives and acclimatized lowlanders. This was done by two-way ANOVA (subjects \times exercise levels, the latter by repeated measures) followed by unpaired *t*-tests comparing subject groups at any exercise level when ANOVA indicated significant group effects. Data in figures and tables are given as means \pm SE because the major interest is in mean differences between the two subject groups.

RESULTS

Resting gas exchange. Lowlanders hyperventilated compared with natives. Figure 1 shows resting arterial P_{O_2} , arterial P_{CO_2} , and (A-a) P_{O_2} in both groups. P_{O_2} was 8 Torr higher (50.0 ± 1.1 vs. 42.1 ± 0.7 , $P < 0.001$) and P_{CO_2} 9 Torr lower (21.1 ± 0.9 vs. 30.0 ± 0.3 , $P < 0.001$) in lowlanders. However, in both groups, (A-a) P_{O_2} was similar and not different from zero.

Arterial pH was significantly higher in the lowlanders at 7.48 ± 0.007 vs. 7.43 ± 0.004 in the natives, $P < 0.001$, whereas bicarbonate levels were lower (15.1 ± 0.5 meq/l in lowlanders; 19.4 ± 0.3 meq/l in natives, $P < 0.001$). As a result, calculated base excess was more negative in the lowlanders (-5.6 vs. -3.5 meq/l respectively, $P < 0.001$). Resting arterial blood lactate levels were similar (1.5 and 1.4 mmol/l, P not significant). The lowlanders showed greater perturbation of acid-base balance than the natives. It is remarkable that in the natives, despite rapid ascent from 3,600–4,100 to 5,260 m over 2 h and an arterial O_2 saturation of 77%, arterial pH was 7.43, hardly different from a normal pH of 7.40 or from values of resting arterial pH of 7.41 reported previously in such natives at 3,600 m (17).

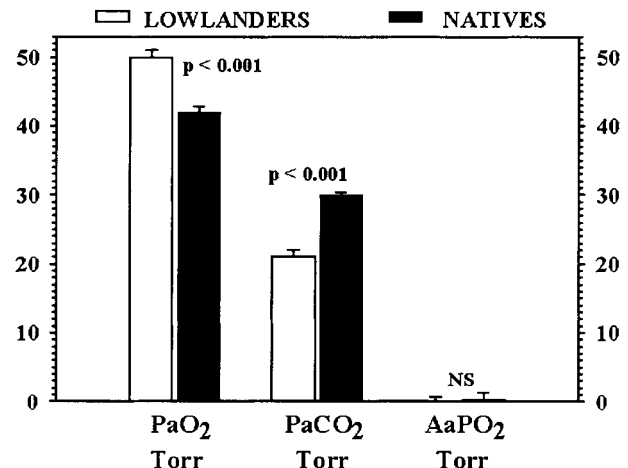


Fig. 1. Resting arterial P_{O_2} ($P_{a_{O_2}}$) and P_{CO_2} ($P_{a_{CO_2}}$) and alveolar-arterial P_{O_2} difference [(A-a) P_{O_2}] at 5,260 m in subjects breathing ambient air. Lowlanders hyperventilate compared with high-altitude natives, but (A-a) P_{O_2} is essentially zero in both groups. Values are means \pm SE.

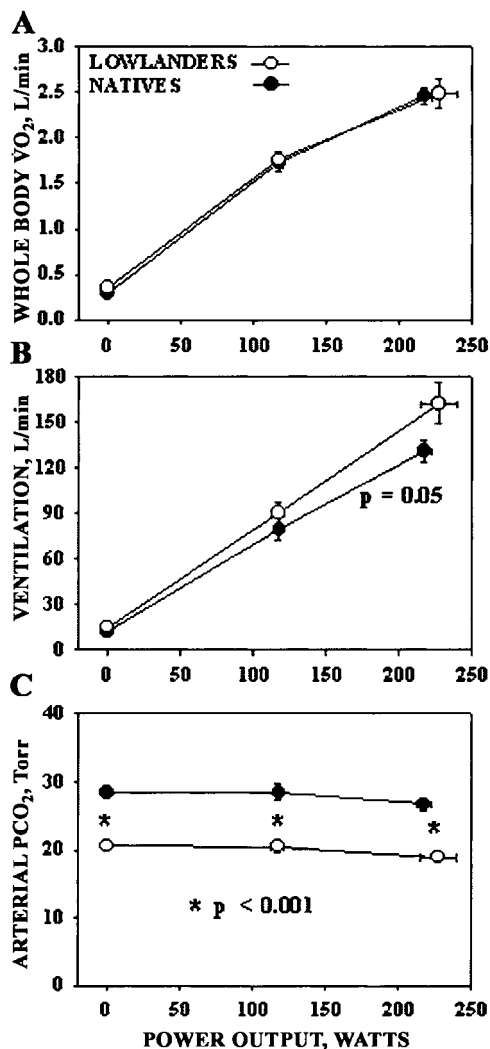


Fig. 2. O_2 uptake ($\dot{V}O_2$), ventilation, and arterial PCO_2 during exercise at 5,260 m. A: $\dot{V}O_2$ increases similarly in both groups to indistinguishable maximal values. B: compared with natives, lowlanders continue to hyperventilate throughout exercise. C: arterial PCO_2 is ~ 8 Torr lower in lowlanders at rest and throughout the range of exercise. Values are means \pm SE.

Ventilatory response to exercise. Figure 2A shows that O_2 consumption at rest, submaximal exercise, and maximal exercise while breathing ambient air at 5,260 m was essentially identical in the two groups, allowing a comparison that is not encumbered by questions of relative vs. absolute work rates nor by differences in efficiency of O_2 utilization. Figure 2B shows that lowlanders continued to mount a greater ventilatory response than natives throughout exercise. At maximal $\dot{V}O_2$ ($\dot{V}O_{2\max}$), minute ventilation was 163 l/min in the lowlanders vs. 131 l/min in the natives, a difference of 24%, $P = 0.05$. Not surprisingly, arterial PCO_2 remained lower in the lowlanders throughout exercise as shown in Fig. 2C. At $\dot{V}O_{2\max}$, arterial PCO_2 was 7.4 Torr lower in the lowlanders (19.3 vs. 26.7, $P < 0.001$). Arterial PCO_2 fell slightly from rest to exercise in both groups (by 2 Torr in lowlanders and 3 Torr in natives, P not significant).

These differences in ventilation at $\dot{V}O_{2\max}$ occurred in the face of identical arterial PO_2 [45.6 (lowlanders) and 46.0 Torr (natives)] and O_2 saturation [72.1 (lowlanders) and 72.3% (natives)], an arterial pH that was higher in the lowlanders (7.37 vs. 7.33, $P = 0.04$), and an arterial blood lactate concentration that was lower in the lowlanders (8.7 vs. 11.5 mmol/l, $P = 0.04$).

Comparing arterial PCO_2 values during peak exercise in air and (at the same power output) in 55% O_2 provides additional insight into the ventilatory responsiveness to hypoxia. Recall that, during air breathing, both maximal cycling power output and arterial PO_2 were similar in the two groups. In the natives, arterial PCO_2 rose 6.4% from 26.7 ± 1.0 to 28.4 ± 0.8 Torr, $P = 0.02$. In the lowlanders, PCO_2 rose 22.8% from 19.3 ± 0.8 to 23.7 ± 0.8 Torr, $P < 0.001$. The relative increase in PCO_2 (and therefore fall in alveolar ventilation) was thus 3.6-fold greater in lowlanders than in natives when hypoxia was eliminated.

Arterial oxygenation and diffusing capacity during exercise. With note taken of a similar cardiac output response to exercise (Fig. 3A), important to diffusion equilibration, arterial PO_2 during exercise was not different between groups (Fig. 3B). This contrasts with the higher PO_2 in lowlanders at rest and occurred despite the substantial differences in ventilation shown in Fig. 2. Arterial O_2 saturation followed arterial PO_2 (Fig. 3C), resulting in similar values for arterial O_2 concentration (not shown).

With the lower arterial PCO_2 yet similar PO_2 during exercise, (A-a) PO_2 was higher in the lowlanders (Fig. 3D). Although the absolute differences are not large, they occurred on the steep region of the O_2 -hemoglobin dissociation curve and thus are important for O_2 transport.

O_2 diffusing capacity calculated during maximal exercise was 40% lower in the lowlanders [119 ± 6 ml/(min·Torr)] than in the natives [167 ± 15 ml/(min·Torr)], $P = 0.01$.

Acid-base balance at rest and during exercise. During maximal exercise, arterial pH fell from resting levels by similar amounts in the two groups (7.48 to 7.37 in the lowlanders, a difference of 0.11; 7.43 to 7.33 in the natives, a difference of 0.10). Although arterial PCO_2 values also fell by similar amounts (2 and 3 Torr, respectively), there was a significant difference in the arterial blood lactate concentrations: 8.7 ± 0.8 mmol/l in lowlanders and 11.5 ± 1.0 mmol/l in natives, $P = 0.04$. Despite the lower blood lactate levels, calculated base deficit was not smaller in the lowlanders. In fact, base deficit was 12.0 ± 0.5 meq/l compared with 10.7 ± 0.7 in the natives. Figure 4 brings out these differences in the relationship between base deficit and lactate levels for the two groups. The scatter about the regression lines comes mostly from differences between subjects in each group, given that individual regressions all had correlation coefficients of ≥ 0.8 . A comparison of the slopes and intercepts of the base deficit-lactate relationship revealed that both the slope and intercept were higher in the lowlanders ($P < 0.001$ each). In particular, the slope was 20% higher in the lowlanders

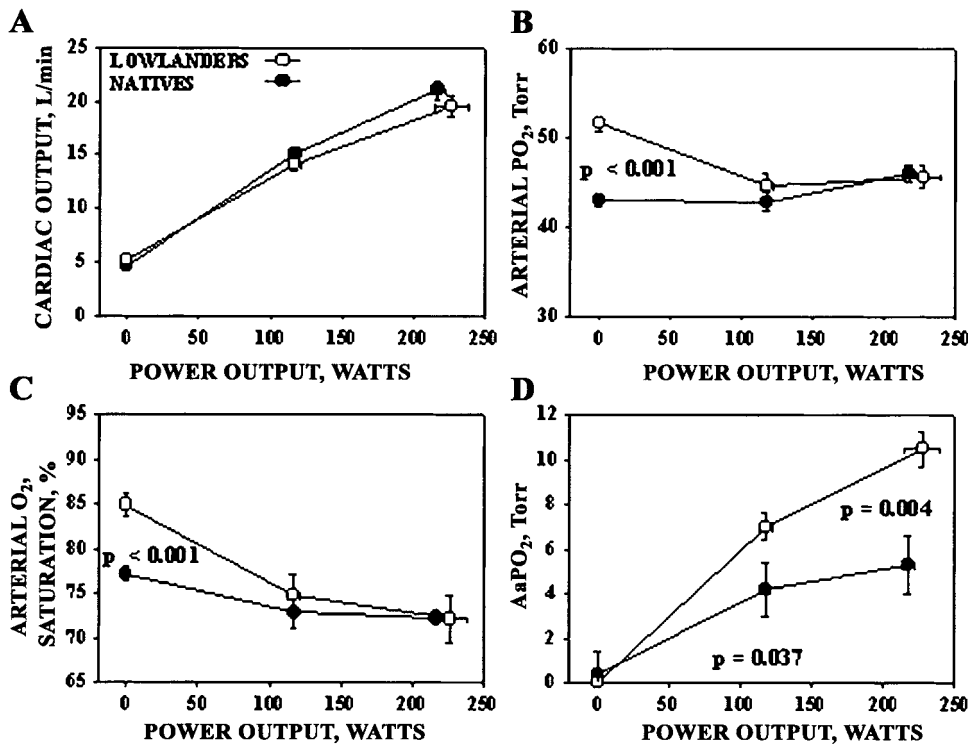


Fig. 3. Cardiac output and gas exchange during exercise at 5,260 m. *A*: cardiac output responses to exercise are similar in the 2 groups. *B*: arterial PO_2 , higher in lowlanders at rest, falls with exercise to levels seen in natives in whom PO_2 is maintained. *C*: arterial O_2 saturation in both groups generally follows PO_2 but with a slight decrease during exercise because of rightward shifts in the O_2 dissociation curve. *D*: (A-a) PO_2 increases with exercise in both groups, but more so in lowlanders. Values are means \pm SE.

(0.97 ± 0.02 meq/mmol compared with 0.81 ± 0.03 in the natives), implying less ability to buffer lactic acid during exercise, despite the similarity in hemoglobin concentrations (Table 1).

DISCUSSION

The discussion corresponds to the four questions laid out in the introduction.

Rate of acclimatization in lowlanders at altitude. This study shows that, even after 9 wk at an altitude of 5,260 m, resting arterial pH is still alkaline (7.48), despite considerable renal bicarbonate excretion.

These results contrast with those of Dempsey et al. (6), in which resting arterial pH was 7.42 for both sojourners and natives despite the latter having acclimatized for less time (4–45 days). However, this was at 3,100 m, substantially lower than in Bolivia. That arterial pH eventually normalizes at 5,260 m is suggested by the present native data. Their pH was 7.43 despite having ascended from La Paz (3,600–4,000 m, P_{IO_2} of 95 Torr) to Chacaltaya (5,260 m, P_{IO_2} of 75 Torr) in just 2 h and thus having been acutely exposed to significantly greater hypoxia than at their altitude of residence. The data of Vincent et al. (17) further support this conclusion: Arterial pH at La Paz was 7.41 and PCO_2 was 31.3 Torr in natives breathing air at rest, barely different from our data at 5,260 m.

Zhuang et al. (23) showed that, at 3,658 m, high-altitude natives in Tibet also have a resting arterial pH of 7.40 and PCO_2 of 30 Torr. They additionally assessed lowlanders who had been at 3,658 m for 1–2 yr and found pH to be 7.45, with arterial PCO_2 at 28 Torr. Why were the lowlanders in both the present study and that of Zhuang hyperventilating to maintain pH at 7.45–7.48 after 9 wk to 2 yr at altitude? Acute hyperventilation associated with catheterization or the mouthpiece is a possibility but seems unlikely. Our lowlanders were young Danish students used to mouthpieces, catheters, and research studies, whereas for the natives this was a completely new experience, especially catheter placement, blood sampling, breathing on a mouthpiece, and being subjected to additional acute hypoxia. If anything, acute hyperventilation would have been expected in the natives, the opposite of what was observed. Moreover, Zhuang et al. (22)

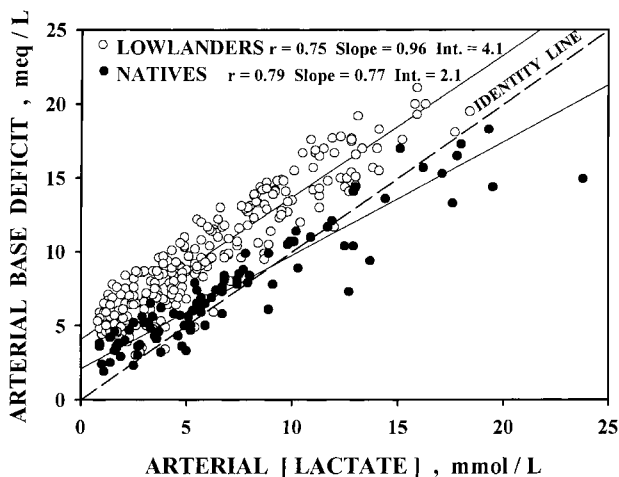


Fig. 4. Relationship between arterial lactate concentration ([lactate]) levels and base deficit in all subjects. Both the slope and intercept are higher in lowlanders, indicating less capacity to buffer lactic acid during exercise.

found that arterial saturation was unaffected by presence of a mouthpiece. A second possibility is that the classical Rahn and Otis (13) line depicting alveolar PO_2 and PCO_2 in acclimatized subjects does not represent complete acclimatization, which produces even greater ventilation with more time at altitude. Plotting the lowlander data on the Rahn and Otis diagram (Fig. 5) indicates that our subjects had an alveolar $\text{PO}_2 \sim 5$ Torr higher and PCO_2 4 Torr lower than expected.

This suggests a response in which the time to reach a pH of 7.40 increases with increasing altitude. In Operation Everest II, mean resting arterial pH was 7.44, 7.46, 7.50, 7.53, and 7.56 at altitudes equivalent to 0, 4,750, 6,100, 7,620, and 8,848 m, respectively (16). Data from Grassi et al. (8) and Samaja et al. (14) show the same trend. What prevents normalization of pH at higher altitudes despite apparently normal renal function is obscure. It seems unlikely that, in our subjects, any progression of ventilation over the 9 wk was happening at a rate sufficient to prevent renal function from keeping pace.

Possible influence on natives of rapid ascent from La Paz to Chacaltaya. Because our equipment could not be duplicated in La Paz nor readily moved between Chacaltaya and La Paz, the natives were studied at Chacaltaya (5,260 m) on arrival after a 2-h drive from La Paz (3,600–4,100 m). We therefore anticipated acute hyperventilation because P_{IO_2} was 20 Torr lower than in La Paz. However, despite a resting arterial PO_2 of 42 Torr (saturation 77%), PCO_2 was 30 Torr and pH 7.43. Vincent et al.'s (17) La Paz data in similar resting subjects showed that arterial PO_2 was 56 Torr (saturation estimated at about 90%), PCO_2 was 31.3 Torr, and pH was 7.41. Thus, despite the large drop in saturation, there was evidence of very little increase in ventilation.

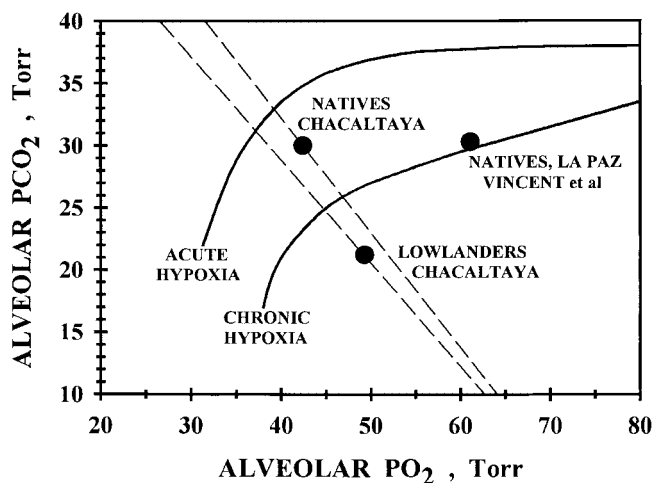


Fig. 5. Mean resting blood-gas data in lowlanders and natives plotted on a figure based on the Rahn and Otis (13) diagram. Vincent et al.'s (17) data on Bolivian natives resident at La Paz are also shown. Our native data suggest no ventilatory response to rapid ascent to 5,260 m. Our lowlander response shows substantial departure from the data of Rahn and Otis, with lower PCO_2 and higher PO_2 indicating greater ventilation.

Vincent et al.'s (17) subjects fall right on the Rahn and Otis (13) line for acclimatized subjects (at 3,600 m) shown in Fig. 5 of the present paper. Rahn and Otis further showed how acute hypoxia affects alveolar PO_2 and PCO_2 in lowland subjects already acclimatized to various altitudes. From Fig. 5 of their paper, one estimates that La Paz natives taken acutely to 5,260 m would have had an alveolar PO_2 of 45–46 Torr and PCO_2 of 27–28 Torr, whereas our subjects displayed values of 42 and 30 Torr, respectively.

Furthermore, because arterial saturation during constant-load exercise in each group was raised from 73 to 99% by breathing 55% O_2 , the natives increased arterial PCO_2 by only 6.4% (whereas lowlanders increased PCO_2 by 22.8%). These findings are compatible with the work of Schoene et al. (15), who showed that hypoxic ventilatory drive in high-altitude natives was blunted. The native responses are all the more astonishing given the low O_2 saturation during exercise (Fig. 3) and the usual carotid body sensitivity to such hypoxemia (20).

It was feared that the acute ascent not only would represent a major ventilatory stimulus, but would also compromise exercise capacity. The outcome, however, suggests otherwise. Thus maximal cycling power output was not significantly affected: 234 ± 6 W several days earlier in La Paz, compared with 217 ± 5 W at Chacaltaya. The lack of significant decrease in exercise capacity with acute ascent from 3,600–4,100 m to 5,260 m is consistent with (but more dramatic than) the findings of Favier et al. (7), who in similar subjects found only a minor (8%) decrease in $\dot{V}_{\text{O}_2 \text{ max}}$ at La Paz (3,600 m) between 31.4% O_2 , equivalent to sea-level air, and ambient air. This insensitivity of $\dot{V}_{\text{O}_2 \text{ max}}$ to P_{IO_2} suggests that muscle metabolic capacity in natives has been downregulated over time in response to reduced O_2 availability.

Pulmonary gas exchange during exercise. This study extends to 5,260 m the work of both Dempsey (6) at 3,100 m in North American high-altitude natives and Zhuang (23) at 3,658 m in Tibetan high-altitude natives. As in their work, a lower (A-a) PO_2 preserves arterial PO_2 and saturation at values seen in acclimatized lowlanders at the same work rate, despite the natives' higher arterial PCO_2 .

Because theoretical and experimental work shows that at altitude most of the (A-a) PO_2 is due to alveolar-capillary diffusion limitation (18, 21), the likely basis of the lower (A-a) PO_2 in high-altitude natives is higher diffusing capacity associated with larger lungs, as previously suggested (15, 23). Piiper and Scheid (11, 12) have shown that the degree of diffusion limitation depends on the ratio $\text{DL}_{\text{O}_2}/(\beta \cdot \dot{Q}_T)$, where DL_{O_2} is the O_2 diffusing capacity of the lungs, β is the slope of the O_2 dissociation curve, and \dot{Q}_T is cardiac output. In the present study, β and \dot{Q}_T (Fig. 3) were similar between natives and lowlanders. The β depends on hemoglobin concentration (similar, Table 1), in vivo P_{50} (similar at 31.7 and 32.0 Torr), and arterial and venous PO_2 and saturation (arterial similar, Fig. 3; venous similar by calculation from \dot{V}_{O_2} , cardiac output, and arterial val-

ues, Figs. 2 and 3). Thus it is the 40% higher calculated DL_{O_2} in natives that underlies the smaller (A-a) PO_2 and preserves arterial PO_2 .

Cardiac output was measured by dye dilution in lowlanders and by acetylene uptake in natives. The acetylene method has been validated (2), and the cardiac output- $\dot{V}O_2$ relationship was similar in the two groups (Fig. 3A), suggesting agreement. However, there may have been systematic differences between the two methods. We therefore calculated the effect of potential errors in cardiac output on estimated DL_{O_2} and found that a 10% error produces a 3.4% error in the same direction in estimated DL_{O_2} . Thus to explain the 40% higher DL_{O_2} in the natives on errors in cardiac output would require that peak cardiac output had been overestimated by 220% and was not 20 but only 9 l/min. This is impossible because even complete muscle O_2 extraction would not have provided the measured $\dot{V}O_2$. If cardiac output in the lowlanders had been lower because of blood withdrawal during its measurement, this could have reduced estimated DL_{O_2} . However, each measurement requires only 20 ml blood and moreover this was reinfused immediately. This cannot therefore explain the lower lowlander DL_{O_2} .

A specific assumption made in the calculation of DL_{O_2} is that ventilation-perfusion (\dot{V}_A/\dot{Q}) inequality plays an insignificant role in the (A-a) PO_2 of exercise at this altitude. Because neither group had an (A-a) PO_2 at rest (Fig. 1), resting \dot{V}_A/\dot{Q} inequality must have been minimal. Because effects of \dot{V}_A/\dot{Q} inequality on (A-a) PO_2 lessen with increasing hypoxia, whereas those of diffusion limitation increase (11, 12, 21), the postulate that \dot{V}_A/\dot{Q} inequality during exercise contributed little to the (A-a) PO_2 is also reasonable. Work from Operation Everest II (18), using the multiple inert gas elimination technique to distinguish diffusion limitation from \dot{V}_A/\dot{Q} mismatching, confirmed that diffusion limitation was the major contributor to the (A-a) PO_2 .

Relating exercise DL_{O_2} [119 ml/(min·Torr), lowlanders and 167 ml/(min·Torr), natives] to maximal normoxic exercise capacity (282 W, lowlanders and 229 W, natives; Table 1) provides an astonishing result: The ratio of pulmonary diffusing capacity to maximal normoxic power output is 0.73 ml/(min·Torr·W) in the natives and only 0.42 ml/(min·Torr·W) in the lowlanders. The natives therefore have 173% of the diffusing capacity of the lowlanders per watt of normoxic exercise capacity. It should be recalled that there were no differences in hemoglobin concentration to explain this (Table 1). This very large difference presumably stems from structural differences in their lungs. Whereas in the lowlanders (at sea level) spirometry revealed vital capacity (111% predicted) and resting carbon monoxide diffusing capacity (92% predicted) that were within normal limits, vital capacity (134% predicted Caucasian sea-level values, $P < 0.01$) and diffusing capacity (142% predicted, $P < 0.001$) were elevated in the natives when referenced to North American norms. The high DL_{O_2} values in natives dur-

ing exercise appear directionally compatible with these data and the literature (6, 15).

Acid-base balance during exercise. Despite similar blood Hb concentration, there appear to be acid-base control differences between the lowlanders and natives. As shown in Fig. 4, calculated base deficit rose linearly with lactate concentration in both groups, but with different slopes. The mean slope in the lowlanders (0.97 ± 0.02 meq/l per mmol/l lactate) is similar to values at sea level [for example, 1.03 in Operation Everest II (16) and 1.13 in the same Danish lowlanders studied later in Copenhagen] and is a reasonable (1:1) stoichiometric outcome. On the other hand, the slope in natives averaged only 0.81 ± 0.03 , a highly significant ($P < 0.001$) difference implying greater lactate-buffering capacity. The explanation for these unexpected differences cannot be stated with certainty but may just reflect the Henderson-Hasselbalch equation: On the Davenport diagram, flattening of PCO_2 isopleths occurs as PCO_2 falls. Thus, at a lower PCO_2 , the change in pH (x-axis) for a given change in base deficit (y-axis) at constant PCO_2 would be greater. The higher arterial PCO_2 values in the natives (Fig. 2) are consistent with this idea. It is also possible that the natives may have had a larger blood volume, because lowlanders are known to reduce plasma volume at altitude. If this were the case, it could also have contributed to the better buffering of lactate in the natives.

Whatever the mechanism, the consequences for exercise limitation may be considerable. Recall that, at $\dot{V}O_{2\max}$ in ambient air, lactate levels were higher in the natives (11.5 mmol/l) than in the lowlanders (8.7 mmol/l). Had lowlander lactate levels been as high, arterial pH (at the same PCO_2) would have been 7.25 instead of 7.37 as measured. Combined with the severe hypoxemia (73% saturation) and the evidence that ventilatory stimulation was already great (PCO_2 19 Torr, pH 7.37), it is likely that intolerable dyspnea would have occurred. We therefore suggest that the relatively lower buffering capacity of the lowlanders contributed to their exercise limitation.

In conclusion, this study, performed at 5,260 m, comparing Bolivian high-altitude natives resident at La Paz (3,600–4,100 m) to sea-level natives acclimatized for 9 wk at 5,260 m, has demonstrated a number of pulmonary and other physiological differences between them. 1) Even 9 wk of residence at 5,260 m fails to accomplish complete normalization of arterial pH in lowlanders, and ventilation is greater than expected from prior data. This raises the question of whether full acclimatization at this altitude requires much longer than previously suspected, possibly lifelong or even more than one generation of exposure. 2) Reduced ventilatory response to hypoxia in high-altitude natives, both at rest and during exercise, still occurs as in previous reports at lower altitudes, despite severe acute arterial desaturation caused by rapid ascent from La Paz. 3) (A-a) PO_2 values during exercise are smaller in natives likely because of increased diffusing capacity associated with larger lungs. This enables, at lower ventilatory cost, the same arterial saturation as

in lowlanders. When related to metabolic potential assessed by maximal exercise capacity in normoxia, pulmonary diffusing capacity is 73% greater per watt in natives than in lowlanders. 4) Lactate buffering appears enhanced in natives, defending arterial pH in the face of both higher lactate and PCO_2 levels than in acclimatized lowlanders.

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