Maximal exercise performance in chronic hypoxia and acute normoxia in high-altitude natives

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Favier, Roland, Hilde Spielvogel, Dominique Desplanches, Guido Ferretti, Bengt Kayser, and Hans Hoppeler. Maximal exercise performance in chronic hypoxia and acute normoxia in high-altitude natives. *J. Appl. Physiol.* 78(5): 1868–1874, 1995.—Maximal O_2 uptake ($\dot{V}O_{2\,max}$) was determined on a bicycle ergometer in chronic hypoxia (CH) and during acute exposure to normoxia (AN) in 50 healthy young men who were born and had lived at 3,600 m altitude (La Paz, Bolivia). $\dot{V}O_{2\,max}$ was significantly improved (~8%) by AN. However, the difference in $\dot{V}O_{2\,max}$ measured in CH and AN ($\Delta\dot{V}O_{2\,max}$) was lower than that reported in sea-level natives (SN) who exercised in chronic normoxia and acute hypoxia. It is shown that high-altitude natives (HN) and SN have a similar $\dot{V}O_{2\,max}$ in normoxia, but highlanders can attain a greater $\dot{V}O_{2\,max}$ when O_2 availability is reduced by altitude exposure. In addition, in HN, the higher the subject's $\dot{V}O_{2\,max}$ in hypoxia, the smaller his $\Delta\dot{V}O_{2\,max}$. These results contrast with the data obtained in 14 lowlanders acclimatized to high altitude who showed that their $\Delta\dot{V}O_{2\,max}$ was positively related to their $\dot{V}O_{2\,max}$ in hypoxia, as previously reported in SN who exercised in acute hypoxia (A. J. Young, A. Cymerman, and R. L. Burse. *Eur. J. Appl. Physiol. Occup. Physiol.* 54: 12–15, 1985). Furthermore, arterial O_2 saturation of HN behaved differently from acclimatized lowland natives, inasmuch as it fell less during exercise both in CH and AN. HN with high aerobic capacity display a lower exercise ventilation and a reduced arterial saturation, which could explain their inability to improve $\dot{V}O_{2\,max}$ with normoxia. Plasma lactate levels during maximal exercise were in the same range (8–10 mM) as values reported for SN. ΔWork efficiency reached 26–28% in CH as well as in AN, i.e., a value similar to that obtained in SN who exercised in normoxia or hypoxia.

maximal oxygen uptake; lactate; fitness; hemoglobin; chemosensitivity; work efficiency

PHYSIOLOGICAL RESPONSES to maximal exercise, particularly maximal O_2 uptake ($\dot{V}O_{2\,max}$), have often been used to measure adaptation of the cardiorespiratory system to hypoxia. The fall of $\dot{V}O_{2\,max}$ in hypoxia has been analyzed by numerous investigators (5, 9, 13, 15, 17, 20, 21, 23–25, 27, 28, 30). There exists marked interindividual variability between subjects (30) that is partly linked to the training status of the individual (15, 25), but, on average, for each 1,000-m increase in altitude >700 m, $\dot{V}O_{2\,max}$ decreases by 8% (12). Most of these data were obtained in lowland natives acclimatized to high altitude (LNA). By contrast, there are only a few studies (13, 20, 27) on $\dot{V}O_{2\,max}$ increment with acute normoxia (AN) in high-altitude natives (HN). In addition, no plausible interpretation of the observed variability of $\dot{V}O_{2\,max}$ increments in AN is available yet. Hochachka and co-workers (13, 17, 19) have proposed that HN may have undergone a number of functional and structural adaptations, namely by maximizing *1*) the amount of ATP obtained per mole of fuel substrate metabolized (decreased contribution of anaerobic pathways), *2*) the amount of ATP obtained per mole of O_2 consumed (preferential use of carbohydrate), and *3*) the work achieved per mole ATP used (increased work efficiency). Furthermore, these alleged metabolic adaptations resemble (genetically or developmentally) fixed characteristics, since they seem to persist even after 6 wk of deacclimation at sea level (13).

We therefore conducted the present study to verify whether $\dot{V}O_{2\,max}$ in HN changes in a different way from LNA when inspired P_{O_2} ($P_{I_{O_2}}$) is varied. Maximal exercise performance was assessed in a young representative population of HN (n = 50) in their natural hypoxic environment [chronic hypoxia (CH), La Paz, Bolivia, 3,600 m; barometric pressure (P_B) ~500 mmHg; inspired O_2 fraction ($F_{I_{O_2}}$) 0.209; $P_{I_{O_2}}$ ~100 Torr] and during exposure to acute normoxia (AN) (P_B ~500 mmHg; $F_{I_{O_2}}$ 0.314; $P_{I_{O_2}}$ ~150 Torr). The results were compared with a group of LNA (n = 14) who had lived at high altitude from 3 mo to 3 yr. Care was taken to include only subjects with normal hematocrits for the altitude of La Paz and normal lung function tests and resting electrocardiogram (ECG).

MATERIALS AND METHODS

Subjects. Fifty males, aged 20–30 yr, who were born and had lived at high altitude (HN), volunteered for the present study. Genetically, the subjects ranged from Amerindian to European, with most being Mestizo of predominantly Amerindian ancestry. In addition, a group of 14 sea-level dwellers (mean age 30.2 ± 1.8 yr) who had lived 17 ± 5 mo (range 3 mo to 3 yr) at 3,500–4,000 m altitude (LNA) was submitted to the same exercise protocol. Each volunteer was carefully informed of the experimental protocol and procedures as well as potential risks from participation, and each signed a statement of informed consent. Before participation, each volunteer was screened by a physician; this procedure included medical history, physical examination, resting ECG, pulmonary function tests, and hematocrit measurement. Bases for exclusion from participation included evidence of anemia, excessive polycythemia, cardiopulmonary disease, or any condition or illness that contraindicated performance of heavy work. In addition, potential HN subjects were excluded from participation if they had resided for >1 mo at low altitude within 3 yr before the study.

Body mass and height were measured with an electronic

scale (Selus, Italy; precision ±100 g) and an anthropometer (Harpenden, UK), respectively. Midarm muscle plus bone cross-sectional area was calculated from measurements of maximum circumference with a spring-loaded metal tape, and skinfolds were measured with a caliper (Holtain, UK) after conversion of biceps and triceps skinfolds into mean adipose tissue thickness. Body composition was estimated from percent body fat, and lean body mass was calculated from skinfolds and body weight (8).

All measurements were performed at the Instituto Boliviano de Biologia de Altura (La Paz, mean altitude = 3,600 m).

$\dot{V}O_{2\,max}$. $\dot{V}O_{2\,max}$ tests were conducted on a bicycle ergometer. The seat height on the ergometer was adjusted before each exercise bout so that each leg was in a position of slight flexion at the nadir of the downstroke. The exercise test began with a 4-min warm-up at a power output of 60 W (70 rpm). Thereafter, the power output was increased by 30 W every 4 min until the subject could not maintain the desired power output. Subjects were verbally encouraged to continue exercise as long as possible, and only tests that satisfied three of four of the following criteria were retained for statistical analysis: *1*) identification of a plateau in O_2 uptake ($\dot{V}O_2$) with an increase in workload, *2*) respiratory exchange ratio of ≥1.1, *3*) peak heart rate (HR) (±5% of the age-predicted maximum), and *4*) lactate in arterialized blood of ≥7 mM.

Timed collections of expired air were obtained as subjects breathed through a low-resistance nonrebreathing valve (no. 2700, Hans Rudolph) into Douglas bags for the determination of ventilatory and metabolic parameters. Expired gas was analyzed with a paramagnetic O_2 analyzer (Servomex 570A) and an infrared CO_2 analyzer (Gould, Capnograph, Mark III). Expired air volume was measured by emptying the content of the Douglas bag into a Tissot spirometer. Thus, discrete measurements of $\dot{V}O_2$, CO_2 production ($\dot{V}CO_2$), respiratory exchange ratio, and ventilation ($\dot{V}E$) (BTPS) were obtained.

HR was monitored continuously by bipolar ECG telemetry (Sport tester). Arterial O_2 saturation (Sa_{O_2}) measurements were made with an ear oximeter (Ohmeda, Biox 3000). The ear lobe was cleansed and massaged vigorously to increase perfusion before ear clip attachment.

Blood samples from the fingertip were drawn at rest and during the last minute of each exercise level for measurements of lactate (lactate analyzer, Yellow Springs Instruments). Blood arterialization was achieved by inducing hyperemia with an ointment (Trafuril, Ciba Geigy, Switzerland). In addition, blood samples were taken in HN at rest and during the last minute of the maximal exercise level for measurements of P_{O_2}, P_{CO_2}, and pH (model 280, Ciba Corning). The instrument was calibrated with known standards.

Each subject completed an incremental cycle ergometry test while breathing one of two treatment gases: hypoxic (CH, P_B ~500 mmHg, $F_{I_{O_2}}$ 0.209) or normoxic (AN, P_B ~500 mmHg, $F_{I_{O_2}}$ 0.314). The normoxic gas was designed to give a $P_{I_{O_2}}$ of ~150 Torr, which corresponds to sea level. The normoxic gas mixture was obtained by a vacuum cleaner that provided air in which the O_2 concentration was adjusted by adding O_2 from a tank through a flowmeter. The gas was then introduced into a 200-liter plastic container that acted as a mixing chamber and reservoir. The concentration of O_2 in the mixture was monitored at the outlet of the plastic tank, i.e., close to the mouth of the subject.

Analysis of variance followed by a post hoc Fisher's protected least significant difference test was used to analyze the data. The level of significance was established at $P < 0.05$.

RESULTS

The means ± SE of anthropometric variables for the two populations are shown in Table 1.

Maximal exercise. Respiratory gas exchanges and hematologic parameters measured at rest and during maximal exercise in CH and AN in HN are shown in Table 2. In CH, $\dot{V}O_{2\,max}$, which ranged from 29 to 56 $ml \cdot min^{-1} \cdot kg^{-1}$, was similar to the usual values observed in healthy adult males of comparable age. Maximal exercise in CH was accompanied by metabolic acidosis, a significant arterial hypocapnia, and a decreased Sa_{O_2}. The inhalation of the normoxic gas mixture (AN) was accompanied by a significant increase in arterial P_{O_2} (Pa_{O_2}) and Sa_{O_2}, with no changes in arterial P_{CO_2} (Pa_{CO_2}) and pH. $\dot{V}O_{2\,max}$ was significantly improved in AN by ~0.214 ± 0.029 l/min, or 3.5 ± 0.42 $ml \cdot min^{-1} \cdot kg^{-1}$ (~8%). A marked interindividual variation in $\dot{V}O_{2\,max}$ improvement with AN was observed. Indeed, we found a significant relationship between the $\dot{V}O_{2\,max}$ increment ($\Delta\dot{V}O_{2\,max}$) with AN and $\dot{V}O_{2\,max}$ measured in hypoxia (Fig. 1*A*). The correlation coefficient between these two variables is 0.37, which indicates that the slope is significantly different from zero ($P < 0.05$). However, only 14% of the variance in the $\dot{V}O_2$ increment was accounted for by $\dot{V}O_{2\,max}$ in hypoxia.

These results obtained in HN contrast with the data measured in LNA (Fig. 1*B*). First, $\Delta\dot{V}O_{2\,max}$ was greater in LNA than in HN (0.315 ± 0.051 l/min, i.e., ~13%) and $\Delta\dot{V}O_{2\,max}$ was positively related to $\dot{V}O_{2\,max}$ in hypoxia. Despite a similar Sa_{O_2} at rest (93.4 ± 0.4 vs. 93.7 ± 0.4% for LNA and HN, respectively), the LNA group displayed a significantly greater drop in Sa_{O_2} during maximal exercise not only in CH but also in AN. However, because exercise-induced arterial hypoxemia has been shown to be related to aerobic capacity (5, 14, 24), we paired each LNA subject with a corresponding HN subject according to their respective normoxic $\dot{V}O_{2\,max}$ (Fig. 2). The subset of HN used for matching to LNA was similar to the HN group as a whole with respect to normoxic $\dot{V}O_{2\,max}$ (44.1 ± 1.8 ml $O_2 \cdot min^{-1} \cdot kg^{-1}$), maximal HR (188 ± 2 beats/min), and $\Delta\dot{V}O_{2\,max}$ (3.5 ± 0.9 $ml \cdot min^{-1} \cdot kg^{-1}$) (see Table 2 and above). From Fig.

TABLE 1. *Anthropometric characteristics of HN and LNA*

Group	Age, yr	BW, kg	Height, cm	BMI, kg/m²	BSA, m²	%Fat	Body Density
HN	24.4±0.5	61.4±1.1	167.9±0.9	21.46±0.32	1.687±0.018	15.13±0.70	1.064±0.002
LNA	30.2±1.8	65.8±1.8	172.7±1.3	21.64±0.54	1.781±0.031	19.17±1.17	1.055±0.003

Values are means ± SE. HN, high-altitude natives; LNA, lowland natives acclimatized to high altitude; BW, body weight; BMI, body mass index; BSA, body surface area.

TABLE 2. *Respiratory gas exchanges and hematologic parameters at rest and during maximal exercise in CH and AN in HN*

	$\dot{V}O_2$, l/min	$\dot{V}CO_2$, l/min	RER	HR, beats/min	Lactate, mM	Pa_{O_2}, Torr	Pa_{CO_2}, Torr	pH	Sa_{O_2}, %	[Hb], g/dl
Rest										
CH	0.338±0.011	0.336±0.014	0.987±0.019	78.1±2.1	1.19±0.08	57.2±0.6	29.1±0.4	7.40±0.006	93.7±0.4	17.01±0.14
AN	0.432±0.021	0.348±0.018	0.81±0.034	71.1±1.8	1.12±0.08	79.7±1.5	29.5±0.5	7.40±0.004	98.2±0.2	17.28±0.15
Maximal exercise										
CH	2.761±0.058	3.184±0.095	1.138±0.01	186.4±1.4	8.42±0.24	59.5±0.7	23.9±0.4	7.26±0.008	88.8±0.4	18.1±0.2
AN	2.992±0.059	3.358±0.090	1.107±0.009	184.5±1.3	8.31±0.23	92.8±0.9	25.7±0.4	7.24±0.007	96.2±0.3	18.5±0.2

Values are means ± SE. CH, chronic hypoxia; AN, acute normoxia; $\dot{V}O_2$, O_2 uptake; $\dot{V}CO_2$, CO_2 production; RER, respiratory exchange ratio; HR, heart rate; Pa_{O_2}, arterial P_{O_2}; Pa_{CO_2}, arterial P_{CO_2}; Sa_{O_2}, arterial O_2 saturation; [Hb], hemoglobin concentration in blood.

2, it appears that LNA displayed a significantly greater desaturation and $\Delta\dot{V}O_{2\,max}$ increment than their corresponding HN counterparts despite a similar ventilatory equivalent ($\dot{V}E/\dot{V}O_2$).

Submaximal exercise. Figure 3 shows a plot of $\dot{V}O_2$, HR, Sa_{O_2}, and lactate as a function of the workload in both hypoxia and normoxia in HN and LNA. There is no difference in $\dot{V}O_2$ between CH and AN at any submaximal workload in both HN and LNA. By contrast, both HR and blood lactate were significantly reduced during submaximal exercise in AN compared with CH.

ΔWork efficiency[1] (η) of HN averaged 26.8 ± 0.15% (SE) in hypoxia and 27.7 ± 0.30% in normoxia. In LNA, the relationship between $\dot{V}O_{2\,max}$ and power output was identical to that obtained in HN. In addition, η in LNA averaged 28.5 ± 0.7 and 28.1 ± 0.4% in CH and AN, respectively, i.e., values similar to those obtained in HN.

DISCUSSION

The effects of CH on physical performance and the physiological variables of performance have been examined in considerable detail during the past three decades (5, 9, 13, 15, 17, 20, 21, 23–25, 27, 28, 30). However, most of the studies were conducted in sea-level natives (SN) acclimatized to high altitude and are not representative of subjects living in hypoxia. On the other hand, population groups that resided at high altitude for many generations have been investigated (13, 17, 19, 20, 23, 27, 31), but variables that affect $\dot{V}O_{2\,max}$, i.e., age, body size and composition, nutritional status, and physical and health conditions, have not been taken into account when comparing physical performance and associated physiological differences.

Even though we did not check the energy intake in our altitude natives, it has been shown that body mass index [weight (kg)/height (m^2)] can be considered as a relatively good index of nutritional status (10). The anthropometric data of our population show that height, weight, body mass index, and percent fat are within the standard range. Also, the hematologic variables [hemoglobin concentration ([Hb]), Pa_{O_2}, Pa_{CO_2}, and pH] are similar (Table 2) to the data previously reported for HN who reside at 3,600–3,700 m (1, 2, 26), suggesting that the subjects of the present study are representative of a population adapted to high altitude.

Significant decrements in $\dot{V}O_{2\,max}$ have been consistently reported for individuals exposed to hypoxia compared with $\dot{V}O_{2\,max}$ obtained at sea level (5, 9, 13, 15, 20, 23–25, 27, 30). However, to our knowledge, there exist no comprehensive data on the improvement of $\dot{V}O_{2\,max}$ with acute exposure to normoxia in HN. The results of the present study show that the increment of $\dot{V}O_{2\,max}$ with AN in HN averaged 8.2 ± 1.1%. Thus, it appears that the difference between normoxic and hypoxic $\dot{V}O_{2\,max}$ in HN (Table 2; Refs. 13, 27) is considerably lower (8–16%) than the difference measured in lowlanders (25–30%) when tested in chronic normoxia and during acute hypoxia corresponding to our altitude

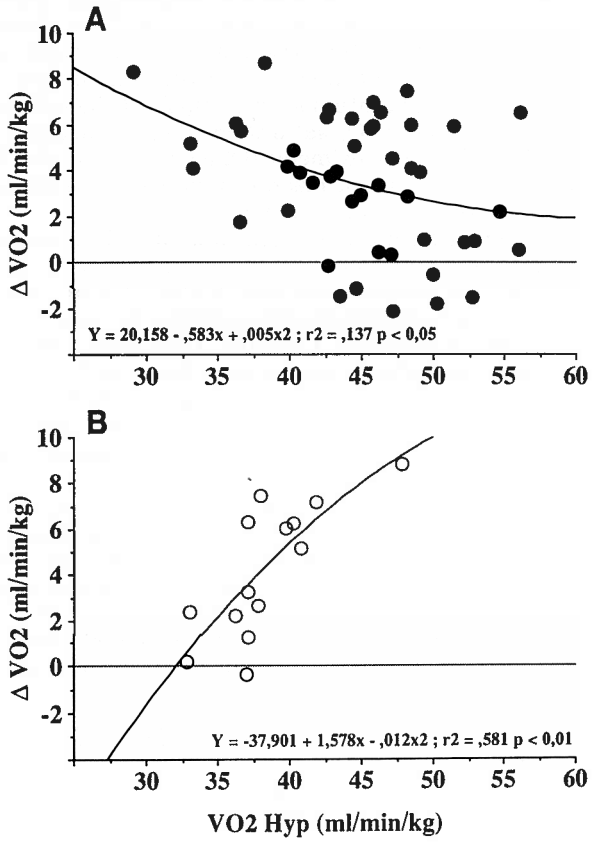

FIG. 1. Relationship between maximal O_2 uptake ($\dot{V}O_2$) difference ($\Delta\dot{V}O_{2\,max}$) under normoxic (Nor) and hypoxic (Hyp) conditions and Hyp $\dot{V}O_{2\,max}$ in high-altitude natives (HN; *A*) and lowland natives acclimatized to altitude (LNA; *B*).

[1] Change in work efficiency = change in work accomplished/change in energy expanded = $(\Delta W/\Delta E) \times 100$, where ΔW is caloric equivalent of increment in work performed above previous work rate and ΔE is increment in caloric output above that at a previous work rate (11).

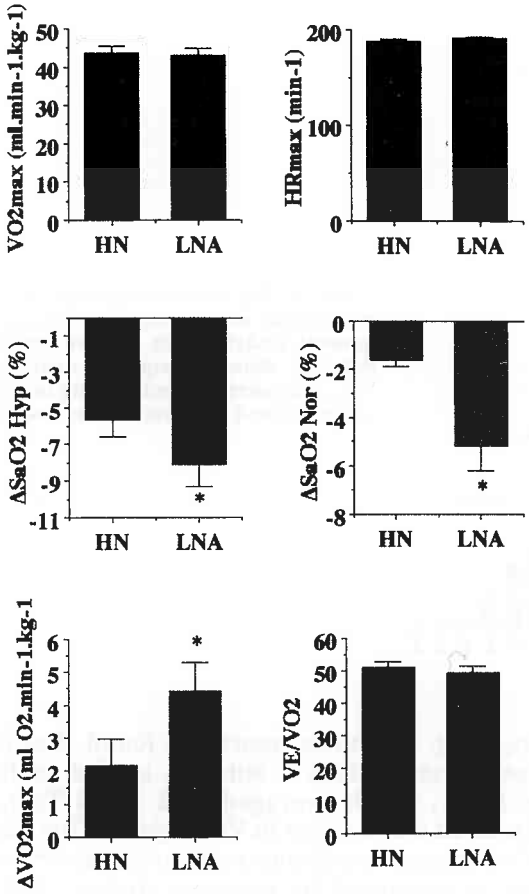

FIG. 2. Comparison of metabolic and hematologic parameters of HN (n = 14) and LNA (n = 14) with similar $\dot{V}O_{2\,max}$ in acute Nor (AN). Values are means ± SE. ΔSa_{O_2}, arterial O_2 desaturation during exercise in Hyp and Nor; HR_{max}, maximal heart rate (HR); $\Delta\dot{V}O_{2\,max}$, difference between $\dot{V}O_{2\,max}$ in Nor and Hyp; maximal $\dot{V}E/\dot{V}O_2$, ventilatory equivalent (LBTPS/LSTPD) at maximal exercise.

level (12, 28, 30). In one of these latter studies (30), the influence of acute hypoxia on $\dot{V}O_{2\,max}$ was examined in a large (n = 51) group of SN, and these data were compared with those from our group (n = 50) of HN (Fig. 4, *top*). From Fig. 4, *top*, it appears that the relationship between $\Delta\dot{V}O_{2\,max}$ and hypoxic $\dot{V}O_{2\,max}$ differs between the two populations. From the frequency distribution of $\dot{V}O_{2\,max}$ in normoxia and hypoxia (Fig. 4, *bottom*), it can be seen that normoxic $\dot{V}O_{2\,max}$ was normally distributed in both SN and HN and that the two populations were superimposable. By contrast, in hypoxia, the frequency distribution of $\dot{V}O_{2\,max}$ of HN is shifted to the right, i.e., HN can better maintain $\dot{V}O_{2\,max}$ in hypoxia than SN. This greater $\dot{V}O_{2\,max}$ in hypoxia could have been due to improved performance of one (or several) of the steps of the O_2 transport system: *1*) increased alveolar ventilation, *2*) greater lung diffusing capacity, *3*) higher circulatory O_2 transport, and *4*) increased tissue O_2 extraction.

With respect to the first step, we found that maximal $\dot{V}E$ and ventilatory equivalent ($\dot{V}E/\dot{V}O_2$) were similar in HN and LNA. However, it has been reported that highland natives display greater lung volumes and chest diameter (20, 22, 23, 31) in conjunction with a lower respiratory frequency (23). Such an adaptation in breathing pattern could possibly be a contributing factor in the better ability of HN to increase O_2 ventilatory transport at altitude.

Concerning the second possibility (increased lung diffusing capacity), Wagner (29) showed that at altitude lung diffusion characteristics become more important and Lawler et al. (15) and Terrados et al. (25) suggested that the $\dot{V}O_{2\,max}$ decrement during exercise in hypoxia is related to arterial desaturation. Although alveolar-arterial O_2 gradient was not measured in the present study, some investigators (7) reported a greater lung diffusing capacity of HN in relation to an increased alveolar area and capillary blood volume. This would allow HN to reduce arterial desaturation during exercise. Indeed, we found that HN display a higher Sa_{O_2} during hypoxic and normoxic maximal exercise compared with LNA and are able to better maintain $\dot{V}O_{2\,max}$ in hypoxia (Fig. 2).

Concerning the third possibility (higher circulatory O_2 transport), Vogel et al. (26) showed that the cardiovascular system contributes importantly in the adaptation of HN to the hypoxic environment. Thus HN are able to maintain cardiac output during maximal exercise in hypoxia (27), whereas sea-level residents display a significant reduction in stroke volume and HR (28) that could be accounted for by the sustained reduction of $\dot{V}O_{2\,max}$ in acute hypoxia. With prolonged hypoxia, Reeves et al. (21) showed a preservation of cardiac function that could possibly explain the lower reduction in $\dot{V}O_{2\,max}$ with hypoxia observed in our LNA subjects (~13%) compared with SN exposed to acute hypoxia (25–30%) (15, 28, 30).

Concerning the fourth possibility (increased tissue O_2 extraction), Vogel et al. (27) reported that arteriovenous O_2 difference at maximal work is higher in HN than in SN (28). Interestingly, we found from ultrastructural analysis of muscle biopsies taken from 30 HN subjects that the mitochondrial volume density is

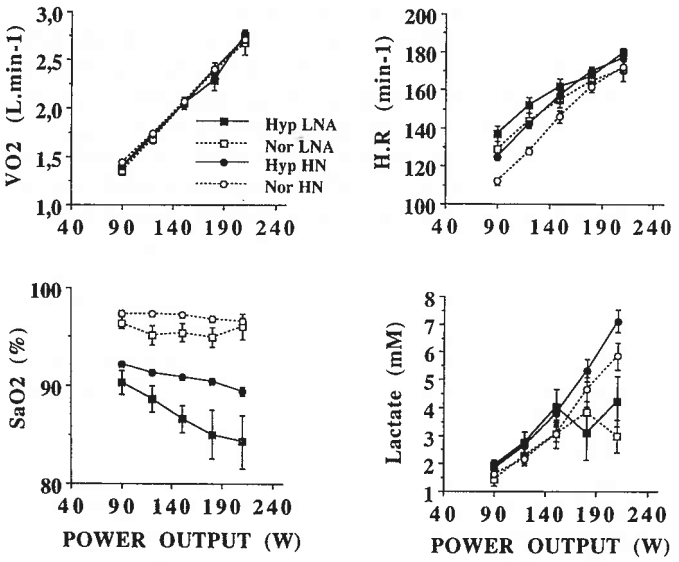

FIG. 3. $\dot{V}O_2$, HR, blood lactate, and arterial O_2 saturation (Sa_{O_2}) against mechanical power measured in chronic Hyp and AN (Nor) in HN and LNA. Values are means ± SE. In some cases, size of SE falls within size of symbol.

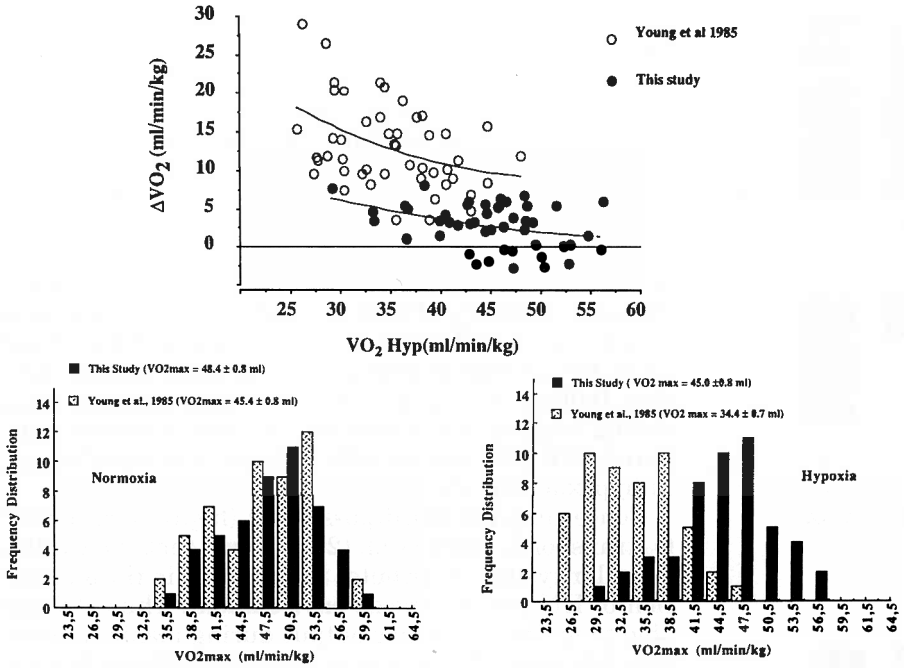

FIG. 4. *Top*: relationship between $\Delta\dot{V}O_{2\,max}$ and hypoxic aerobic capacity ($\dot{V}O_{2\,max}$) in HN (present study) and in sea-level natives (see Ref. 30). *Bottom*: frequency distribution of $\dot{V}O_{2\,max}$ in normoxia and hypoxia in HN (present study) and sea-level natives (see Ref. 30).

significantly lower (~20%) than in SN (D. Desplanches and H. Hoppeler, unpublished observations). The mechanism by which $\dot{V}O_2$ is closely geared to work rate relates to the coupling of phosphorylation of ADP to electron transport. As HN are able to maintain (normoxia) or even increase (hypoxia) (Fig. 4) $\dot{V}O_2$ with less mitochondria, this would indicate a tighter coupling of oxidative phosphorylations in HN compared with SN. Such a mechanism has been proposed recently by Hochachka and co-workers (13, 17) and needs to be explored in greater detail in future studies.

The origin of the physiological adaptations of the O_2 transport system displayed by HN cannot be delineated in the present study but could be related either to phenotypic or to genotypic adaptations (18).

In our HN population, there exists a significant relationship between $\Delta\dot{V}O_{2\,max}$ and hypoxic $\dot{V}O_{2\,max}$ (Fig. 1). As in SN (30), the present study indicates that the degree of aerobic fitness, as evaluated by $\dot{V}O_{2\,max}$, accounts for relatively little (~14%) of the variability in $\Delta\dot{V}O_{2\,max}$. This finding on HN and previous data on SN are based on results from large sample sizes having a wide range of individual aerobic fitness and increment in $\dot{V}O_{2\,max}$ with normoxia, and therefore most of the variability in $\Delta\dot{V}O_{2\,max}$ must be accounted for by factors other than physical fitness. Among these factors, arterial desaturation during maximal exercise in aerobically trained subjects can be evoked (6, 15, 25). Indeed, the subjects with a very high $\dot{V}O_{2\,max}$ (VH) ($\geq$50 $ml \cdot min^{-1} \cdot kg^{-1}$; $n = 9$) display a greater desaturation compared with subjects with a very low $\dot{V}O_{2\,max}$ (VL) ($\leq$40 $ml \cdot min^{-1} \cdot kg^{-1}$, $n = 9$) whether they exercised in hypoxia ($\Delta Sa_{O_2} = -6.6 \pm 0.7$ vs. $-3.3 \pm 1.3\%$ for VH and VL, respectively) or in normoxia ($\Delta Sa_{O_2} = -2 \pm 0.4\%$ vs. $-0.9 \pm 0.3\%$ for VH and VL, respectively). This greater desaturation during exercise of fit subjects could be related to their lower ventilatory equivalent ($\dot{V}E/\dot{V}O_2$) (Fig. 5). Furthermore, we found that during exercise in normoxia VH subjects tended to have a higher Pa_{CO_2}, which averaged 26.2 $\pm$ 1.2 Torr, compared with 24.0 $\pm$ 1.1 Torr in VL subjects. This assumption of a reduced ventilatory response in aerobically fit subjects is supported by previous studies that show that HN have a blunted chemosensitivity (14) and a lower ventilatory responsiveness, and reduced exercise $\dot{V}E$ has been found in athletes at sea level (3, 16, 25).

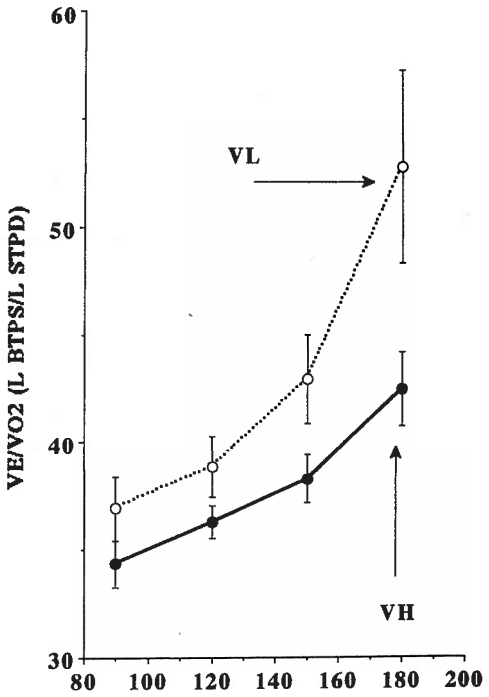

FIG. 5. Ventilatory equivalent ($\dot{V}E/\dot{V}O_2$) vs. mechanical power (in W) in HN with very low (VL) or very high (VH) $\dot{V}O_{2\,max}$ in AN. Data are means $\pm$ SE.

Recent studies (13, 17, 19) reported that HN display a number of metabolic adaptations (i.e., decreased contribution of anaerobic pathways, increased contribution of carbohydrate to energy production, and increased work efficiency) that were refractory to the transition from hypoxia to normoxia.

The data reported in the present study suggest that some of these metabolic adaptations cannot be entirely attributed to prolonged exposure to hypoxia. First, it was claimed that at all exercise intensities up to fatigue, plasma lactate concentrations were notably lower in HN than in lowlanders (13) and reached the 5-mM range at maximal exercise, i.e., one-half that commonly reported in lowlanders. However, in our HN subjects, plasma lactate levels during maximal exercise (Table 2) were in the same range (8–10 mM) as those reported for SN (24) and blood lactate accumulation during graded exercise was greater in hypoxia than in normoxia in a similar fashion to SN when exposed to hypoxia. These results are in contrast to the data of Hochachka et al. (13), who claimed that Quechuas (Indian Andean natives) produce less lactate for a given amount of work (the so-called lactate paradox) and that this metabolic trait appeared to be refractory to changes in O_2 availability, leading the investigators to conclude that Andean natives have acquired (developmentally or genetically) this metabolic organization. Nevertheless, it must be underlined that the subjects examined by Hochachka et al. were anemic and that anemia is known to cause a relative decrease in blood lactate concentration during exercise (4). It is thus likely that the "fixed characteristic of metabolic organization" displayed by the Andean natives from the study of Hochachka et al. (13) was due to an acquired anemia rather than altitude acclimatization. Second, the last but not least important metabolic adaptation reported in HN was a significant increase in net work efficiency (15–20% higher than the efficiency of lowland athletes). If η is defined as the ratio of change in work accomplished over change in energy expended, as originally proposed by Gaesser and Brooks (11), we found that η was similar in CH and AN in both HN and LNA. Similarly, from the data reported by Hochachka et al. (13), it can be deduced that η (equivalent to the slope of the plots of power output vs. metabolic power output; Fig. 7 of Ref. 13) was similar in highlanders and lowlanders. Because lactate accumulation shows parallel changes with changes in $\dot{V}O_2$ as power output increases (Fig. 3), and, although we do not have a measure of lactate production because most lactate is removed by oxidation, $\dot{V}O_2$ remains a valid measure of energy flux and the efficiency of exercise is valid as defined above.

Because the results of the present study are considerably different from those reported previously in HN (13, 17, 19), we must look at the mechanism(s) that could explain such discrepancies. Thus, although not indicated in the studies that deal with metabolic and cardiovascular adaptations of Andean natives (13, 17), it was reported subsequently (19) that [Hb] of the Quechuas examined by Hochachka and co-workers (12, 16, 18) averaged 15.7 ± 1.1 g/day. This value is well below [Hb] found in Peruvians (20.1 g/day) and Chileans (18.4 g/day) native to the same altitude (2). Furthermore, Tufts et al. (26) determined a cut-off point of [Hb] for anemia of 15.8 g/day in a large population (n = 526) of adult males native to ~3,700 m. The cause(s) of anemia of the Quechuas examined by Hochachka and co-workers (13, 17, 19) is not known, but low [Hb] increases work efficiency (H. Spielvogel, T. Brutsaert, and J. D. Haas, unpublished observations). Therefore, it is likely that the metabolic adaptations during exercise reported for HN (13) were linked to anemia (18) and not to genetically or developmentally hypoxia-induced peripheral adaptations.

In summary, the present study shows that acute exposure to normoxia results in an increased $\dot{V}O_{2\,max}$ in HN as in lowlanders. However, the difference in $\dot{V}O_{2\,max}$ between hypoxia and normoxia is considerably lower in HN compared with acclimatized lowlanders. The ability of HN to better maintain $\dot{V}O_{2\,max}$ in hypoxia is likely due to ventilatory, circulatory, and peripheral adaptations during growth at altitude. In addition, HN with high aerobic capacity are less susceptible to improve $\dot{V}O_{2\,max}$ when exposed to AN. This inability to enhance $\dot{V}O_{2\,max}$ when $P_{I_{O_2}}$ is increased could be related to a lower ventilatory response to exercise of individuals with high $\dot{V}O_{2\,max}$. ΔWork efficiency of HN is comparable to LNA and is similar in CH and AN.

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REFERENCES

1. **Beall, C. M., K. P. Strohl, B. Gothe, G. M. Brittenham, M. Barragan, and E. Vargas.** Respiratory and hematological adaptations of young and older Aymara men native to 3600 m. *Am. J. Hum. Biol.* 4: 17–26, 1992.
2. **Bouverot, P.** Circulatory adaptations. In: *Adaptation to Altitude-Hypoxia in Vertebrates.* New York: Springer Verlag, 1985, p. 63–68.
3. **Byrne-Quinn, E., J. V. Weil, I. E. Sodal, G. F. Filley, and R. F. Grover.** Ventilatory control in athletes. *J. Appl. Physiol.* 30: 91–98, 1971.
4. **Celsing, F., and B. Ekblom.** Anemia causes a relative decrease in blood lactate concentration during exercise. *Eur. J. Appl. Physiol. Occup. Physiol.* 55: 74–78, 1986.
5. **Cerretelli, P.** Gas exchange at altitude: organism and environment. In: *Pulmonary Gas Exchange*, edited by J. B. West. New York: Academic, 1980, vol. II, p. 297–339.
6. **Dempsey, J. A., P. G. Hanson, and K. S. Henderson.** Exercise-induced arterial hypoxemia in healthy human subjects at sea level. *J. Physiol. Lond.* 355: 161–175, 1984.
7. **Dempsey, J. A., W. G. Reddan, M. L. Birnbaum, H. V. Forster, J. S. Thoden, R. F. Grover, and J. Rankin.** Effects of acute through life-long hypoxic exposure on exercise pulmonary gas exchange. *Respir. Physiol.* 13: 62–89, 1971.

8. **Durnin, J. W., and J. Womersley.** Body fat assessed from total body density and its estimation from skinfold thickness measurements on 481 men and women aged from 16 to 72 years. *Br. J. Nutr.* 323: 77–97, 1974.
9. **Ferretti, G., U. Boutellier, D. R. Pendergast, C. Moia, A. E. Minetti, H. Howald, and P. E. Di Prampero IV.** Oxygen transport system before and after exposure to chronic hypoxia. *Int. J. Sports Med.* 11, *Suppl.*: S15–S20, 1990.
10. **Frisancho, A. R.** *Anthropometric Standards for the Assessment of Growth and Nutrition Status.* Ann Arbor, MI: Univ. of Michigan Press, 1990.
11. **Gaesser, G. A, and G. A. Brooks.** Muscular efficiency during steady-rate exercise: effects of speed and work rate. *J. Appl. Physiol.* 38: 1132–1139, 1975.
12. **Grover, R. F., J. V. Weil, and J. T. Reeves.** Cardiovascular adaptation to exercise at high altitude. *Exercise Sport Sci. Rev.* 14, 269–302, 1986.
13. **Hochachka, P. W., C. Stanley, G. O. Matheson, D. C. McKenzie, P. S. Allen, and W. S. Parkhouse.** Metabolic and work efficiencies during exercise in Andean natives. *J. Appl. Physiol.* 70: 1720–1730, 1991.
14. **Lahiri, S., and N. H. Edelman.** Peripheral chemoreflexes in the regulation of breathing of high altitude natives. *Respir. Physiol.* 6: 375–385, 1969.
15. **Lawler, J. S. K. Powers, and D. Thompson.** Linear relationship between $\dot{V}O_{2\,max}$ and $\dot{V}O_{2\,max}$ decrement during exposure to acute hypoxia. *J. Appl. Physiol.* 64: 1486–1492, 1988.
16. **Martin, B. J., J. V. Weil, K. E. Sparks, R. E. McCullough, and R. F. Grover.** Exercise ventilation corresponds positively with ventilatory chemoresponsiveness. *J. Appl. Physiol.* 45: 557–584, 1978.
17. **Matheson, G. O., P. S. Allen, D. C. Ellinger, C. C. Hanstock, D. Gheorghiu, D. C. McKenzie, C. Stanley, W. S. Parkhouse, and P. W. Hochachka.** Skeletal muscle metabolism and work capacity: a ^{31}P-NMR study of Andean natives and lowlanders. *J. Appl. Physiol.* 70: 1963–1976, 1991.
18. **McKenzie, D. C., L. S. Goodman, C. Nath, B. Davidson, G. O. Mathseon, W. S. Parkhouse, P. W. Hochachka, P. S. Allen, C. Stanley, and W. Ammann.** Cardiovascular adaptations in Andean natives after 6 wk of exposure to sea level. *J. Appl. Physiol.* 70: 2650–2655, 1991.
19. **Monge, C., and F. Leon-Velarde.** Physiological adaptation to high altitude: oxygen transport in mammals and birds. *Physiol. Rev.* 71: 1135–1172, 1991.
20. **Paz-Zamora, M., J. Coudert, J. Ergueta-Collao, E. Vargas, and N. Gutierrez.** Respiratory and cardiocirculatory responses of acclimatization of high altitude natives (La Paz, 3500 m) to tropical lowland (Santa Cruz, 420m). In: *Topics in Environmental Physiology and Medicine, High Altitude Physiology and Medicine*, edited by W. Brendel and R. A. Zink. New York: Springer-Verlag, 1982, chapt. 4, p. 21–27.
21. **Reeves, J. T., B. M. Groves, J. R. Sutton, P. D. Wagner, A. Cymerman, M. K. Malconian, P. B. Rock, P. M. Young, and C. S. Houston.** Operation Everest II: preservation of cardiac function at extreme altitude. *J. Appl. Physiol.* 63: 531–539, 1987.
22. **Spielvogel, H., E. Vargas, G. Antezana, L. Barragan, and L. Cudkowicz.** Effects of posture on pulmonary diffusing capacity and regional distribution of pulmonary blood flow in normal male and female high altitude dwellers at 3,650 m (12,200 ft). *Respiration* 35: 125–135, 1978.
23. **Sun, S. F., T. S. Droma, J. G. Zhang, J. X. Tao, S. Y. Huang, R. G. McCullough, C. S. Reeves, J. T. Reeves, and L. G. Moore.** Greater maximal O_2 uptakes and vital capacities in Tibetan than Han residents of Lhasa. *Respir. Physiol.* 79: 151–162, 1990.
24. **Sutton, J. R., J. T. Reeves, P. D. Wagner, B. M. Groves, A. Cymerman, M. K. Malconian, P. B. Rock, P. M. Young, S. D. Walter, and C. S. Houston.** Operation Everest II: oxygen transport during exercise at extreme simulated altitude. *J. Appl. Physiol.* 64: 1309–1321, 1988.
25. **Terrados, N., M. Mizuno, and H. Andersen.** Reduction in maximal oxygen uptake at low altitudes: role of training status and lung function. *Clin. Physiol. Oxf.* 5, *Suppl. 3*: 75–79, 1985.
26. **Tufts, D. A., J. D. Haas, J. L. Beard, and H. Spielvogel.** Distribution of hemoglobin and functional consequences of anemia in adult males at high altitude. *Am. J. Clin. Nutr.* 42: 1–11, 1985.
27. **Vogel, J. A., L. H. Hartley, and J. C. Cruz.** Cardiac output during exercise in altitude natives at sea level and high altitude. *J. Appl. Physiol.* 36: 173–176, 1974.
28. **Vogel, J. A., L. H. Hartley, J. C. Cruz, and R. P. Hogan.** Cardiac output during exercise in sea-level residents at sea level and high altitude. *J. Appl. Physiol.* 36: 169–172, 1974.
29. **Wagner, P. D.** Algebraic analysis of the determinants of $\dot{V}O_{2\,max}$. *Respir. Physiol.* 93: 221–237, 1993.
30. **Young, A. J., A. Cymerman, and R. L. Burse.** The influence of cardiorespiratory fitness on the decrement in maximal aerobic power at high altitude. *Eur. J. Appl. Physiol. Occup. Physiol.* 54: 12–15, 1985.
31. **Zhuang, J., T. Droma, S. Sun, C. Janes, R. E. McCullough, R. G. McCullough, A. Cymerman, S. Y. Huang, J. T. Reeves, and L. G. Moore.** Hypoxic ventilatory responsiveness in Tibetan compared with Han residents of 3,658 m. *J. Appl. Physiol.* 74: 303–311, 1993.