Plasticity in Respiratory Motor Control: Selected Contribution: Acute and sustained ventilatory responses to hypoxia in high-altitude natives living at sea level

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highlighted topics

Plasticity in Respiratory Motor Control
Selected Contribution: Acute and sustained ventilatory responses to hypoxia in high-altitude natives living at sea level

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Gamboa, Alfredo, Fabiola León-Velarde, Maria Rivera-Ch, Jose-Antonio Palacios, Timothy R. Pragnell, David F. O'Connor, and Peter A. Robbins. Selected Contribution: Acute and sustained ventilatory responses to hypoxia in high-altitude natives living at sea level. *J Appl Physiol* 94: 1255–1262, 2003. First published November 27, 2002; 10.1152/japplphysiol.00856.2002. High-altitude (HA) natives have blunted ventilatory responses to hypoxia (HVR), but studies differ as to whether this blunting is lost when HA natives migrate to live at sea level (SL), possibly because HVR has been assessed with different durations of hypoxic exposure (acute vs. sustained). To investigate this, 50 HA natives (>3,500 m, for >20 yr) now resident at SL were compared with 50 SL natives as controls. Isocapnic HVR was assessed by using two protocols: *protocol 1*, progressive stepwise induction of hypoxia over 5–6 min; and *protocol 2*, sustained (20-min) hypoxia (end-tidal P_{O_2} = 50 Torr). Acute HVR was assessed from both protocols, and sustained HVR from *protocol 2*. For HA natives, acute HVR was 79% [95% confidence interval (CI): 52–106%, P = not significant] of SL controls for *protocol 1* and 74% (95% CI: 52–96%, $P < 0.05$) for *protocol 2*. By contrast, sustained HVR after 20-min hypoxia was only 30% (95% CI: −7–67%, $P < 0.001$) of SL control values. The persistent blunting of HVR of HA natives resident at SL is substantially less to acute than to sustained hypoxia, when hypoxic ventilatory depression can develop.

regulation of ventilation; human; Andean natives; hypoxic ventilatory depression; chemoreflex; blunting

IT HAS LONG BEEN RECOGNIZED that natives of high altitude (HA) have a blunted respiratory response to hypoxia (4, 6, 8, 10, 15, 19, 21). Furthermore, a number of reports have suggested that, once this blunting has developed, it is permanent and cannot be reversed by subsequent residence at sea level (SL) (7, 16, 19). More recently, however, a study by Vargas et al. (18) found that natives of HA who were resident at SL had a relatively normal acute ventilatory response to hypoxia (AHVR). They speculated that the difference between their findings and those of previous studies lay in the duration of the hypoxic exposure. In the study by Vargas et al., they had attempted to minimize the total exposure to hypoxia to minimize the degree of hypoxic ventilatory depression (HVD) that occurred during the measurement of the ventilatory response to hypoxia.

The first part of this study sought to repeat the measurements of Vargas et al. (18), while, at the same time, address a number of the technical concerns associated with that study. The second part of this study explicitly sought to test the speculation of Vargas et al. that there was a much greater difference in the ventilatory response to sustained hypoxia between SL natives and HA natives resident at SL than in the ventilatory responses to acute hypoxia.

METHODS

Subjects. One hundred subjects who were living in Lima, Peru, were recruited for this study. All were men and between the ages of 20 and 65 yr. Fifty were natives of SL (SL group), and 50 were natives of HA (HAT group). All HA natives had lived at >3,500m for the first ≥20 yr of their

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lives. Twenty-five had the additional criteria that they had resided at SL for <5 yr (HA1 group), and 25 that they had resided at SL for >5 yr (HA2 group). The SL natives were recruited from the same neighborhoods as the HA natives.

Protocols. In a preliminary procedure, the subjects' residence history was documented, their general physical characteristics noted, and a brief medical history and examination conducted to exclude major disease. The end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) and end-tidal P_{O_2} ($P_{ET_{O_2}}$) of each subject were determined by using a fine nasal catheter so as to disturb the subject as little as possible. An instantaneous value for the respiratory quotient was calculated as a further check to ensure that the subject was not hyperventilating.

After the preliminary procedures had been completed, the subjects undertook three protocols, each of which involved imposing certain profiles for $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ using an end-tidal forcing system. *Protocol 1* was designed to assess AHVR by a short, progressive, stepwise induction of hypoxia. *Protocol 2* was designed to assess the ventilatory response to sustained (20-min) hypoxia. However, it also provided a second, alternative index of AHVR from the response to the first 2 min of hypoxia. *Protocol 3* was a control protocol for *protocol 2*.

Protocol 1 had been devised by Mou et al. (11) and validated further by Zhang and Robbins (22). Its purpose was to determine a value for AHVR by progressive induction of hypoxia over a sufficiently brief time interval so as to minimize the confounding effects of HVD on the assessment of AHVR. $P_{ET_{CO_2}}$ was held at ~2 Torr above the subjects' natural value throughout. A settling period of 5 min was employed, during which $P_{ET_{O_2}}$ was held at 100 Torr. After this settling period, $P_{ET_{O_2}}$ was lowered stepwise in a set of seven steps from 100 to 45 Torr, with each step lasting for 50 s. Values for $P_{ET_{O_2}}$ for the five intervening steps had been calculated so as to provide approximately even reductions in saturation between steps and, consequently, approximately even increases in ventilation between steps.

The second and third protocols were directed at determining the subjects' response to sustained hypoxia, although, by analyzing the first 2 min of the response to hypoxia, an alternative measure of AHVR was also obtained. In both protocols, $P_{ET_{CO_2}}$ was again held at ~2 Torr above the subjects' natural resting value throughout. In *protocol 2*, $P_{ET_{O_2}}$ was held at 100 Torr for the first 10 min, then at 50 Torr for the next 20 min, and finally at 100 Torr again for a final 10 min. *Protocol 3* served as a control protocol in relation to *protocol 2*. In this protocol, $P_{ET_{O_2}}$ was held at 100 Torr throughout.

Apparatus and techniques. The technique of end-tidal forcing was used to generate the desired profiles in $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$. In this technique, a computational model of the cardiorespiratory system and gas stores is first used to calculate the profiles for inspiratory P_{CO_2} and P_{O_2} that are likely to generate the desired $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$, respectively. Once these values have been calculated, a computer connected to a fast gas-mixing system can be used to generate the inspiratory gas mixtures. The experiment starts with the computer mixing the predicted inspiratory gas mixtures. In general, these predicted inspiratory gas mixtures will not of themselves generate the desired end-tidal values with sufficient precision because the physiology of the individual deviates from the assumptions of the cardiorespiratory model. To overcome this, these predicted inspiratory values are modified during the course of the experiment by using breath-by-breath feedback from the measured $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$. These measured values for $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ are compared with the desired values, and an integral-proportional feedback control algorithm is used to calculate the actual adjustments required for the inspiratory P_{CO_2} and P_{O_2}.

The apparatus and software for undertaking these studies in Peru were revised and updated from those that had been in use in our laboratory in Oxford (5, 13). In this implementation, the gas was still mixed in a small mixing chamber close to the subject, and inspiratory and expiratory volumes were still recorded via a turbine volume-measuring device (VMM 400, Interface Associates, Laguna Niguel, CA). However, the fast gas-mixing system was constructed by using commercially available mass flow controllers (type 1559A, MKS Instruments, Altringham, UK), and a commercially available medical gas analyzer (Normocap Oxy, Datex Ohmeda, Hatfield, UK) was used to measure inspiratory P_{CO_2}, inspiratory P_{O_2}, $P_{ET_{CO_2}}$, and $P_{ET_{O_2}}$ (in the instrument used, the software was modified to disable the hourly automatic zeroing to ensure that it did not interfere with the experiment). The real-time software was written in LabView (National Instruments, Austin, TX) and run on a portable computer under the Microsoft Windows operating system. The equipment was interfaced to the computer by using National Instruments interface cards (DAQCard-1200 and DAQCard-AO-2DC).

In all experiments, the subject sat upright and breathed to and from the gas-mixing chamber via a mouthpiece while wearing a nose clip.

Data analysis. Numerical values for AHVR were calculated from the data from the first protocol in two different ways. In the first, average values for ventilation ($\dot{V}_E$) and $P_{ET_{O_2}}$ were calculated over the last 20 s for each of the seven steps. The average values for $P_{ET_{O_2}}$ were converted into calculated values for arterial saturation (14), and a slope and intercept were calculated via linear regression for the relationship between $\dot{V}_E$ and desaturation. In the second method, a dynamic respiratory model [*model 3* of Clement and Robbins (2)] was fitted to the whole data set for the seven steps. This yielded a gain term (Gp) as the measure of AHVR and a bias term ($\dot{V}c$) that reflects $\dot{V}_E$ in the absence of hypoxia. (The values for Gp and $\dot{V}c$ are directly comparable with the values of the slope and intercept of AHVR from the first method of calculation.) In addition, the model yielded values for the time constant and pure delay for the chemoreflex response to hypoxia.

For *protocol 2*, minute averages were calculated for $\dot{V}_E$, $P_{ET_{CO_2}}$, and $P_{ET_{O_2}}$ for the last minute of euoxia before the induction of hypoxia at *minute 10* of the protocol [denoted as $\dot{V}_E$(P2–10), where P2 indicates that the value comes from *protocol 2*, which involves hypoxia, and 10 indicates that the value is the mean for the 10th min of the protocol]; for the 2nd min of the period of hypoxia at *minute 12* of the protocol [$\dot{V}_E$(P2–12)]; for the last minute of the period of hypoxia at *minute 30* of the protocol [$\dot{V}_E$(P2–30)]; and for the 2nd min of the period of euoxia following hypoxia at *minute 32* of the protocol [$\dot{V}_E$(P2–32)]. Control values for these variables were calculated at the same time periods from the data from *protocol 3* [denoted as $\dot{V}_E$(P3-*x*), where P3 indicates that the value comes from *protocol 3*, which involved just euoxia, and *x* indicates that the value is the mean for the *x*th minute of the protocol]. In addition to us obtaining a measure of the sustained ventilatory response to hypoxia, we calculated measurements of AHVR at the onset and offset of hypoxia, together with measures of HVD during hypoxia, from these values, as described in RESULTS.

Results between the different groups of subjects were compared by using ANOVA. Where any comparisons were drawn within a group of subjects, the intersubject variability was removed from the comparison by including "subjects" as a random factor. Statistical significance was accepted at $P <$

0.05. For post hoc tests following ANOVA, the least squared difference technique was used, which makes an allowance for the total number of comparisons being drawn.

RESULTS

Subjects. General characteristics of the subjects are shown in Table 1. As well as showing average data for the entire HAT group, the HA natives were also split into the HA1 and HA2 groups. The HA2 group was significantly older than the SL or HA1 groups. This age difference is presumably an effect arising from the selection criteria in which the subjects in the HA2 group had to have lived at HA for >20 yr and then at SL for >5 yr. It is also worth noting that the HAT group was both significantly shorter and had significantly greater lung volumes than the SL group, which is in keeping with their HA origins.

Resting $P_{ET_{CO_2}}$. Perhaps the most important physiological observation to note is that the HA2 group had an air-breathing $P_{ET_{CO_2}}$ that was ~1.5 Torr below that for both the SL and HA1 groups (Table 1). The reasons for this are unclear. The instantaneous respiratory exchange ratios associated with these observations were not different between groups, which suggests that the subjects of the HA2 group were not hyperventilating relative to the subjects of the SL and HA1 groups during these measurements. Incorporating age as a covariate in the ANOVA conducted on the resting $P_{ET_{CO_2}}$ of the three groups rendered the differences between the three groups just not significant (P = 0.051), although the regression coefficient for the fall in $P_{ET_{CO_2}}$ with age of −0.05 Torr/yr [95% confidence interval (CI): −0.10–0.02] failed to reach significance. Selection of a subset (n = 25) of the SL group to form an age-matched control group for the HA2 group also resulted in a comparison that was just nonsignificant (SL subset $P_{ET_{CO_2}}$ = 38.4 Torr, HA2 $P_{ET_{CO_2}}$ = 37.3 Torr, P = 0.072). Thus age probably underlies part, but not all, of the difference.

Measurements of AHVR from protocol 1. Example breath-by-breath records of the measurement of AHVR using incremental steps of hypoxia are shown in Fig. 1. Figure 2 illustrates the variability in individual responses to hypoxia in the form of 20-s average values for each subject for each level of $P_{ET_{O_2}}$. Figure 3 shows the 20-s average values averaged over all subjects in each group, together with the regression lines resulting from averaging the regression coefficients.

In general, control over both $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ was good. The uneven spacing of $P_{ET_{O_2}}$ resulted in a reasonably linear fall in calculated saturation over time (shown by the even spacing of the points along the x-axis in Fig. 3). The data from the individual subjects in Fig. 2 show that there is considerable overlap in AHVR among subjects from all three groups, although there does appear to be a dearth of high responders in the HA2 group compared with the SL and HA1 groups. The averaged ventilatory responses (Fig. 3) appear to be relatively linear for all three groups, although a little curvilinearity (concave upwards) is present in all three groups. The averaged regression coefficients produce regression lines that are good fits to the averaged data, but, because of the slight curvilinearity of the data, the (extrapolated) intercepts of the lines with the y-axis (arterial O_2 saturation = 100%) most likely underestimate the values for $\dot{V}_E$ in the absence of hypoxia.

Parameter estimates from the measurements made in *protocol 1* are given in Table 2. The two techniques (linear regression and modeling) for estimating AHVR from these data gave very similar results, so only the values from the modeling procedure have been reported. The average $P_{ET_{CO_2}}$ over the test was significantly lower in the HA2 group compared with the SL and HA1 groups, reflecting their lower initial values for $P_{ET_{CO_2}}$. However, $\dot{V}_E$ at $P_{ET_{O_2}}$ = 100 Torr was not different between the groups, suggesting that, on average, the subjects were subjected to the same degree of ventilatory stimulation before the induction of hypoxia.

Values for Gp, which provides the numerical estimate for AHVR, appeared somewhat lower in the HA subjects overall compared with the SL group (HAT sensitivities: ~79% of SL sensitivities; 95% CI: 52–106% of SL sensitivity), but this did not reach statistical significance unless a one-sided test was used.

Table 1. *General characteristics of the subjects*

	SL	HA1	HA2	HAT
Age, yr	30.8 ± 6.9	29.5 ± 7.3	35.8 ± 8.0†‡	32.6 ± 8.2
Weight, kg	67.6 ± 11.9	63.8 ± 9.2	65.8 ± 11.5	64.8 ± 10.4
Height, m	1.65 ± 0.06	1.62 ± 0.04*	1.64 ± 0.05	1.63 ± 0.05§
Surface area, m^2	1.33 ± 0.19	1.27 ± 0.13	1.30 ± 0.16	1.28 ± 0.15
Vital capacity, l/m^2	4.26 ± 0.60	4.61 ± 0.67*	4.75 ± 0.76†	4.68 ± 0.71§
FEV_1, l/m^2	3.81 ± 0.53	4.07 ± 0.48*	4.03 ± 0.53	4.05 ± 0.50§
Altitude of birth, m	150	3,891 ± 332	3,876 ± 308	3,883 ± 317
Age of migration to SL, yr		26.8 ± 7.2	23.6 ± 3.4	25.2 ± 5.8
Time at SL, yr		2.92 ± 1.4	12.1 ± 7.1‡	7.5 ± 6.8
$P_{ET_{CO_2}}$, Torr	38.7 ± 2.2	38.9 ± 1.6	37.3 ± 2.3†‡	38.1 ± 2.1
$P_{ET_{O_2}}$, Torr	105.8 ± 2.2	104.9 ± 1.9	107.2 ± 2.8†‡	106.1 ± 2.6

Values are means ± SD. SL, sea-level natives; HA1, high-altitude natives resident at SL for <5 yr; HA2, high-altitude natives resident at SL for >5 yr; HAT, combined HA native group; FEV_1, forced expiratory volume in 1 s; $P_{ET_{CO2}}$, air-breathing end-tidal P_{CO_2}; $P_{ET_{O2}}$, air-breathing end-tidal P_{O_2}. Values are significant when $P < 0.05$: *HA1 significantly different from SL; †HA2 significantly different from SL; ‡HA2 significantly different from HA1; §HAT significantly different from SL.

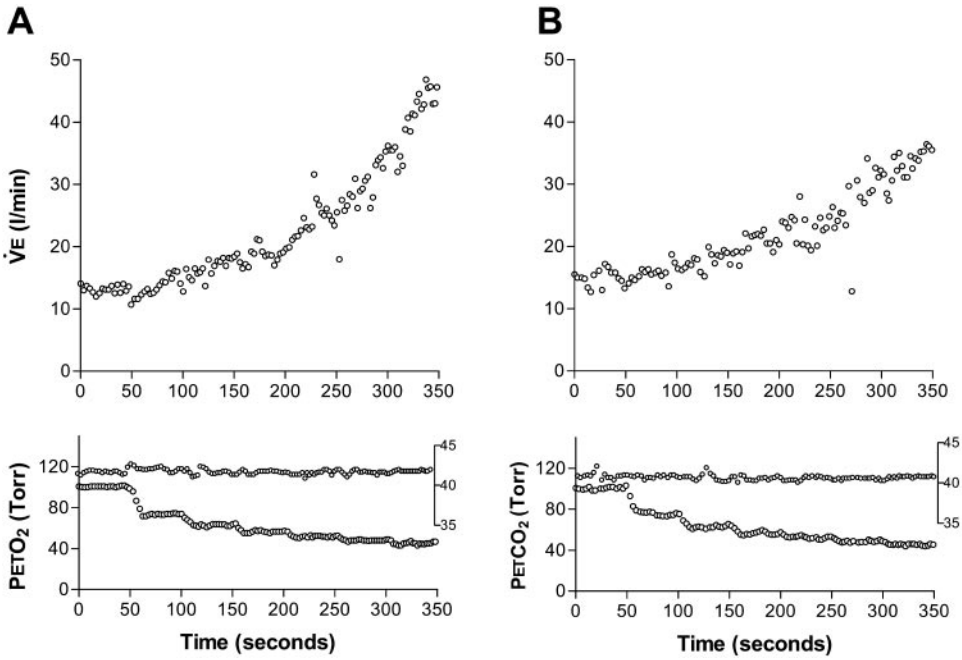

Fig. 1. Examples of breath-by-breath records for the measurement of the acute hypoxic ventilatory response in 2 subjects (*A*: high responder; *B*: low responder) using incremental steps of hypoxia (*protocol 1*). *Top*: ventilation ($\dot{V}_E$); *bottom*: end-tidal P_{CO_2} ($P_{ET_{CO_2}}$; *top* traces) and P_{O_2} ($P_{ET_{O_2}}$; *bottom* traces).

Separating the HAT group into HA1 and HA2 revealed that Gp for the HA2 group was significantly lower than for the SL group (HA2 sensitivities: ~61% of SL sensitivities; 95% CI: 28–93%). The sensitivities for the HA1 and SL groups were quite similar (HA1 sensitivities: ~98% of SL sensitivities; 95% CI: 65–130%).

Values for $\dot{V}_C$, which provides an estimate for $\dot{V}_E$ in the absence of hypoxic stimulation, were significantly larger for the HA1 group compared with the SL group, but other comparisons were not significant. There were no significant differences in the dynamic parameters from the model for any of the protocols. Normalization of the ventilatory parameters by body surface area did not alter these statistical comparisons.

Measurements of ventilatory responses to sustained hypoxia from protocol 2. Example responses (1-min averages) for two subjects (one SL, one HA) to the 20-min period of hypoxia are shown in Fig. 4. The individual responses for the two subjects show abrupt changes in $P_{ET_{O_2}}$ at the onset and offset of hypoxia, with

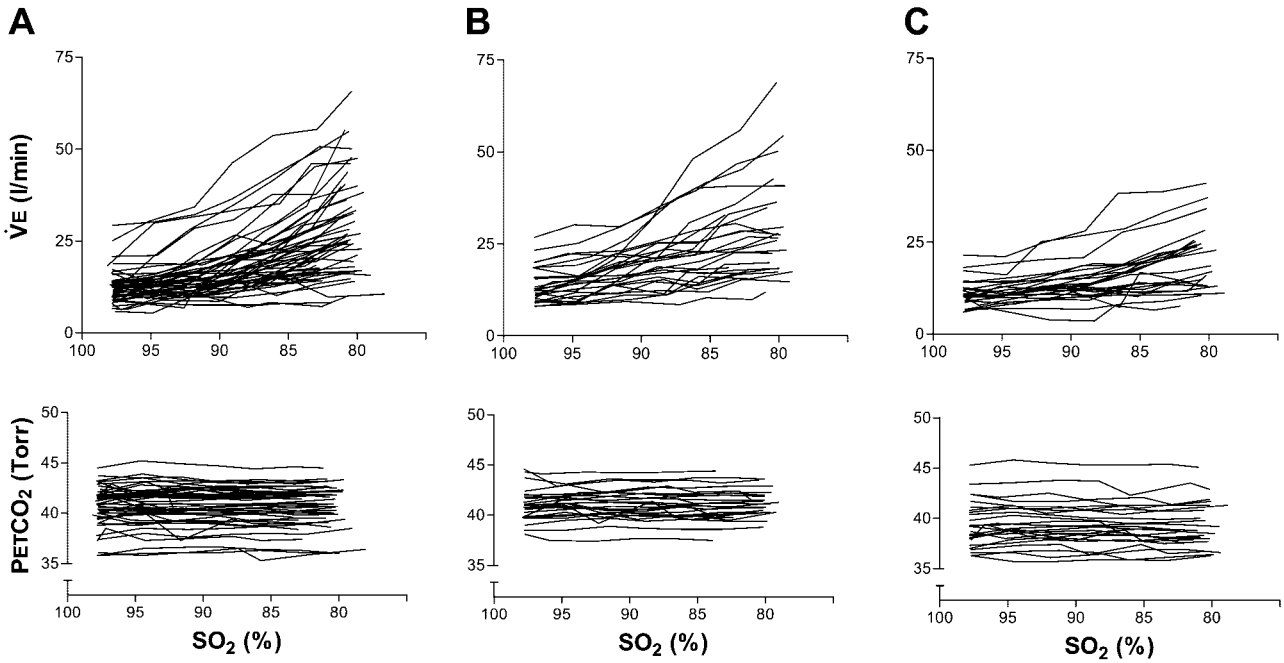

Fig. 2. Individual ventilatory responses to incremental hypoxia (20-s average value for each level of hypoxia) of *protocol 1* for the sea-level natives (SL; *A*) and for the high-altitude natives who had resided at SL for <5 yr (HA1; *B*) and >5 yr (HA2; *C*). Also shown are the corresponding values for $P_{ET_{CO_2}}$. S_{O_2}, calculated arterial O_2 saturation.

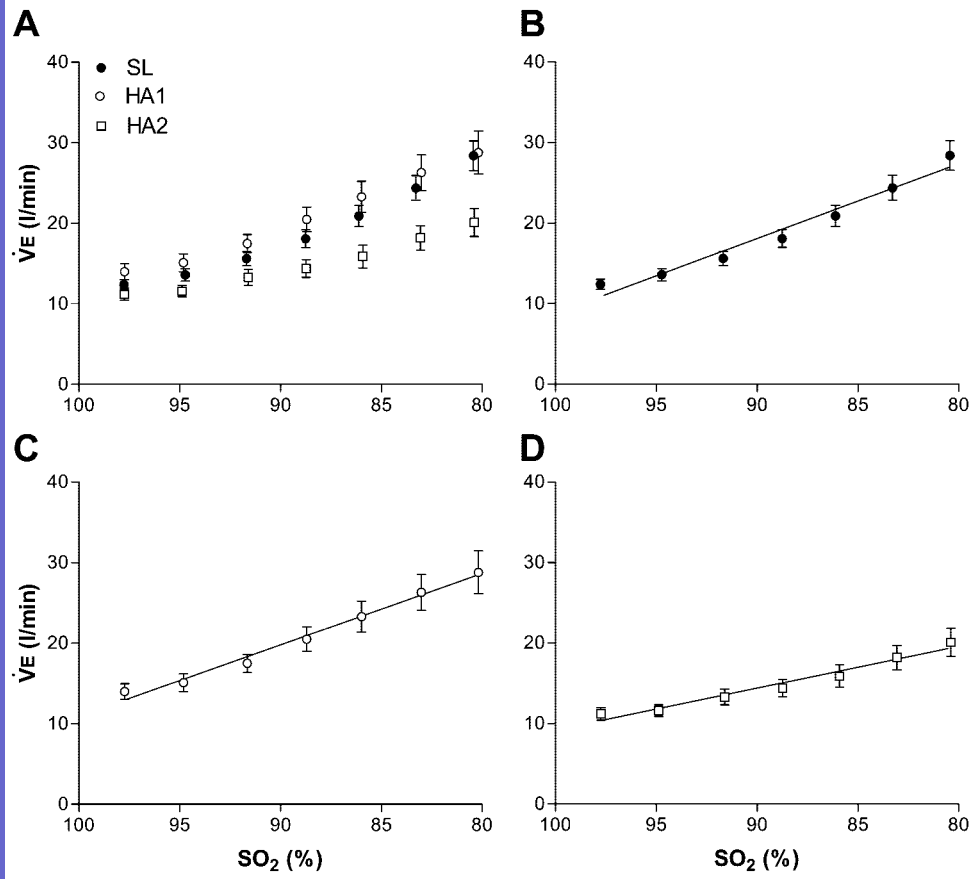

Fig. 3. Overall averages (*A*) for $\dot{V}_E$ for each group [SL (*B*), HA1 (*C*), HA2 (*D*)] for each level of hypoxia in *protocol 1*. Overall averages were obtained from the individual 20-s averages for each subject. Regression lines were calculated from the average of the regression coefficients for the fits to the individual subject data. Error bars are ±1 SE.

good control over $P_{ET_{CO_2}}$. This was the case for almost all subjects and is reflected in the averaged responses in Fig. 5.

In Fig. 5, the average ventilatory responses of the HA natives appear to differ from those of the SL natives. Repeated-measures ANOVA on the differences at each minute between the hypoxia protocol and the control protocol confirms that the overall response of the SL natives was different from that of the HA$_T$ group ($P < 0.001$), but that the responses of the HA1 and HA2 groups did not differ significantly overall.

Quantitative comparisons relating to specific components of the response to sustained hypoxia are given in Table 3. Apart from $P_{ET_{CO_2}}$, this table shows $\dot{V}_E$ for *protocol 2* at 10, 12, 30, and 32 min of the protocol, and $\dot{V}_E$ for *protocol 3* at 12 and 30 min of the protocol, together with parameters that have been derived from these values. The background $P_{ET_{CO_2}}$ against which the experiment was conducted was lower in the HA2 group compared with the other groups, which is a result of their lower average value for resting $P_{ET_{CO_2}}$. However, in contrast to the data from *protocol 1*, $\dot{V}_E$ at a $P_{ET_{O_2}}$ of

Table 2. *Average parameter values from the acute stepwise induction of hypoxia (protocol 1) in SL and HA natives resident at SL*

	SL	HA1	HA2	HA$_T$
n	50	25	25	50
$P_{ET_{CO_2}}$, Torr	40.8 ± 1.9	41.0 ± 1.9	39.5 ± 2.0†‡	40.3 ± 2.1
$\dot{V}_E$ (100 Torr), l/min	12.5 ± 4.4	13.4 ± 5.0	12.2 ± 4.0	12.8 ± 4.5
Gp, l·min^{-1}·%$^{-1}$	0.97 ± 0.64	0.95 ± 0.86	0.59 ± 0.38†	0.77 ± 0.68
$\dot{V}_c$, l/min	9.6 ± 3.8	11.5 ± 5.6*	9.3 ± 2.6‡	10.4 ± 4.5
T, s	15.2 ± 12.9	15.4 ± 14.0	11.2 ± 12.4	13.3 ± 13.3
d, s	7.5 ± 4.7	8.0 ± 5.3	9.9 ± 6.0	8.9 ± 5.6
	Normalized by surface area, m^2			
Gp, l·min^{-1}·%$^{-1}$·m^{-2}	0.74 ± 0.48	0.75 ± 0.67	0.46 ± 0.30†‡	0.61 ± 0.53
$\dot{V}_c$, l·min^{-1}·m^{-2}	7.3 ± 2.9	9.2 ± 4.5*	7.2 ± 2.2‡	8.2 ± 3.6

Values are means ± SD; *n*, no. of subjects. $P_{ET_{CO_2}}$ is average value over the duration of the stepwise induction of hypoxia; $\dot{V}_E$ (100 Torr), average ventilation over 50-s step for which $P_{ET_{O_2}}$ = 100 Torr; Gp, model parameter for acute hypoxic ventilatory response; $\dot{V}_c$, $\dot{V}_E$ in the absence of a hypoxic stimulus to breathe; *T*, time constant; d, time delay. Values are significant when $P < 0.05$: *HA1 significantly different from SL; †HA2 significantly different from SL; ‡HA2 significantly different from HA1.

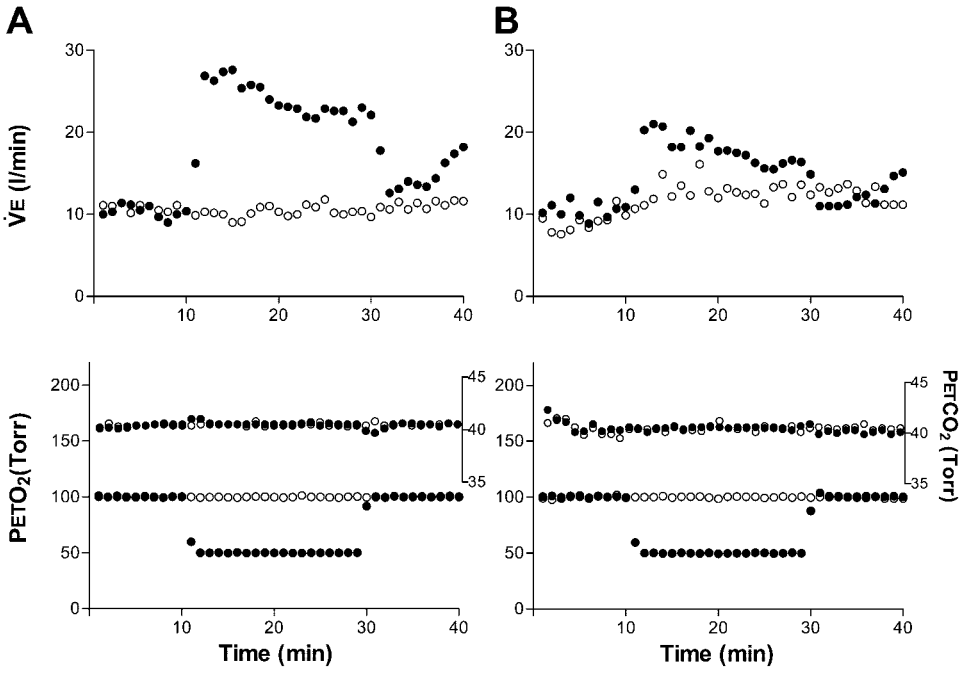

Fig. 4. Example records (1-min averages) for the ventilatory response to sustained hypoxia (*protocols 2* and *3*) in 2 subjects (*A*: SL native; *B*: HA native). *Top*: $\dot{V}_E$; *bottom*: $P_{ET_{CO_2}}$ (*top* traces) and $P_{ET_{O_2}}$ (*bottom* traces). ●, *Protocol 2*; ○, *protocol 3*.

100 Torr was lower for HA2 than for the other subject groups [see $\dot{V}_E$(P2–10) and $\dot{V}_E$(P3–12) of Table 3]. This implies that the hypoxic stimulus was introduced against a lower prevailing background level of ventilatory stimulation than for the other two groups.

An index for the ventilatory response to sustained hypoxia was calculated as the difference between $\dot{V}_E$(P2–30) and $\dot{V}_E$(P3–30), which is a measure of the ventilatory stimulation by hypoxia that remained after 20-min exposure to hypoxia. This index was denoted as ON_s (sustained on response), from which a corresponding ventilatory sensitivity to sustained hypoxia was also calculated. ON_s was markedly reduced in both HA groups to 30% (95% CI: −7–67%) of the value for the SL group. This reduction in ON_s would appear to have its origins in two distinct components of the ventilatory response to hypoxia. The first of these is a more modest reduction in AHVR, and the second of these is an increase in HVD (see following paragraphs).

An index of AHVR was calculated as the difference between $\dot{V}_E$(P2–12) and $\dot{V}_E$(P2–10). This index was denoted as ON_f (fast on response), from which a

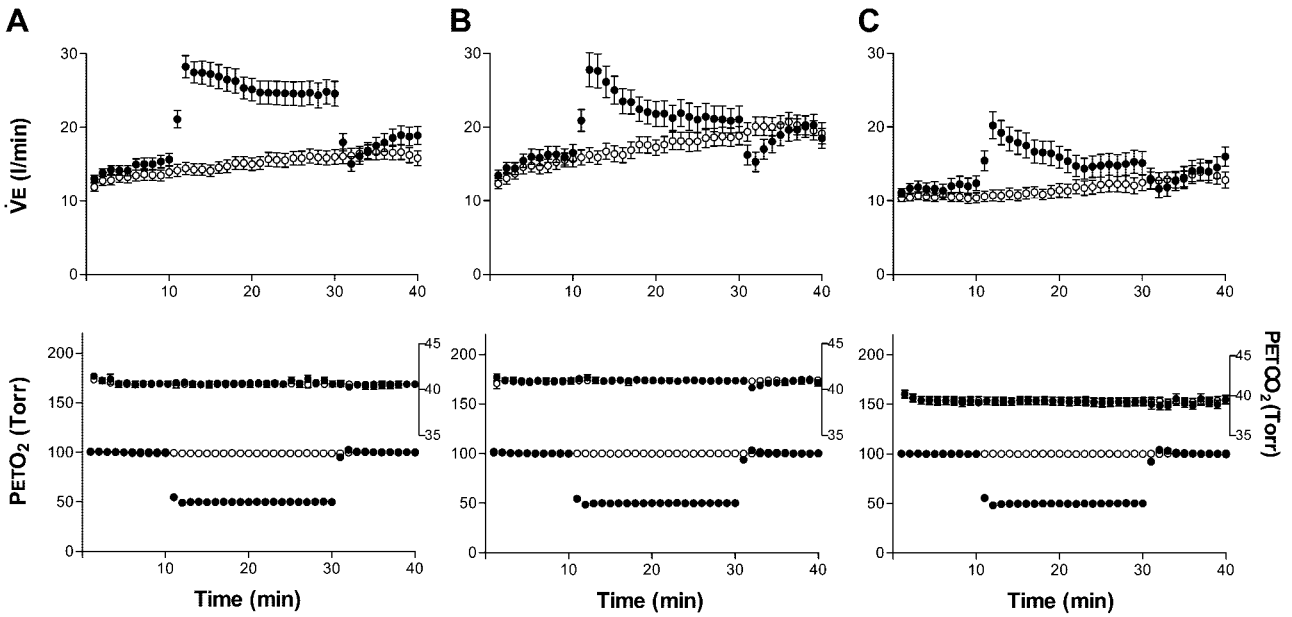

Fig. 5. Averaged ventilatory responses to sustained hypoxia (*protocols 2* and *3*) for the SL (*A*), HA1 (*B*), and HA2 (*C*) subject groups. *Top*: $\dot{V}_E$; *bottom*: $P_{ET_{CO_2}}$ (*top* traces) and $P_{ET_{O_2}}$ (*bottom* traces). ●, *Protocol 2*; ○, *protocol 3*. Error bars are ±1 SE.

Table 3. *Ventilatory responses to the induction of sustained hypoxia (protocols 2 and 3) in SL and HA natives resident at SL*

	SL	HA1	HA2	HAT
n	50	25	25	50
$P_{ET_{CO_2}}$, Torr	40.7 ± 2.0	40.9 ± 1.5	39.3 ± 2.3†‡	40.1 ± 2.1
$\dot{V}_E$(P2–10), l/min	15.3 ± 5.8	16.5 ± 5.5	12.0 ± 4.9†‡	14.3 ± 5.7
$\dot{V}_E$(P2–12), l/min	28.4 ± 10.6	27.8 ± 11.6	20.2 ± 8.7†‡	24.0 ± 10.8§
$\dot{V}_E$(P2–30), l/min	24.6 ± 12.1	21.0 ± 8.9	15.1 ± 7.6†‡	18.1 ± 8.7§
$\dot{V}_E$(P2–32), l/min	15.0 ± 6.9	15.3 ± 6.6	11.2 ± 5.7†‡	13.3 ± 6.4
$\dot{V}_E$(P3–12), l/min	14.4 ± 5.8	16.2 ± 5.0	10.6 ± 3.8†‡	13.4 ± 5.2
$\dot{V}_E$(P3–30), l/min	16.1 ± 6.9	18.8 ± 6.2	12.3 ± 5.3†‡	15.5 ± 6.6
ON_s, l/min	8.5 ± 8.7	2.2 ± 8.1*	2.9 ± 5.9†	2.6 ± 7.0§
ON_f, l/min	13.2 ± 7.0	11.3 ± 9.3	8.2 ± 5.9†	9.7 ± 7.9§
OFF_f, l/min	9.5 ± 7.6	5.8 ± 5.3*	3.9 ± 3.8†	4.8 ± 4.6§
HVD, l/min	3.9 ± 7.9	6.7 ± 6.5	5.1 ± 5.2	5.9 ± 5.9
Drift, l/min	1.7 ± 2.6	2.6 ± 2.8	1.7 ± 3.0	2.1 ± 2.9
HVDc, l/min	5.6 ± 8.2	9.3 ± 6.7*	6.8 ± 6.3	8.0 ± 6.6
G_{ON_s}, $l \cdot min^{-1} \cdot \%^{-1}$	0.66 ± 0.69	0.18 ± 0.63*	0.23 ± 0.46†	0.20 ± 0.55§
G_{ON_f}, $l \cdot min^{-1} \cdot \%^{-1}$	0.99 ± 0.54	0.81 ± 0.68	0.59 ± 0.45†	0.70 ± 0.58§
G_{OFF_f}, $l \cdot min^{-1} \cdot \%^{-1}$	0.74 ± 0.60	0.45 ± 0.41*	0.30 ± 0.30†	0.37 ± 0.36§
	Normalized by surface area, m^2			
ON_s, l/min	6.4 ± 6.7	1.9 ± 6.6*	2.1 ± 4.5†	2.0 ± 5.6§
ON_f, l/min	10.0 ± 5.0	9.0 ± 7.3	6.4 ± 4.5†	7.7 ± 6.1§
OFF_f, l/min	7.2 ± 5.8	4.6 ± 4.2*	2.9 ± 2.8†	3.7 ± 3.6§
HVD, l/min	3.0 ± 6.1	5.3 ± 5.1	4.1 ± 4.3	4.7 ± 4.7
Drift, l/min	1.3 ± 2.0	2.1 ± 2.2	1.3 ± 2.4	1.6 ± 2.3
HVDc, l/min	4.3 ± 6.2	7.3 ± 5.3*	5.3 ± 5.1	6.3 ± 5.2
G_{ON_s}, $l \cdot min^{-1} \cdot \%^{-1}$	0.50 ± 0.53	0.15 ± 0.51*	0.17 ± 0.36†	0.16 ± 0.44§
G_{ON_f}, $l \cdot min^{-1} \cdot \%^{-1}$	0.75 ± 0.39	0.65 ± 0.53	0.45 ± 0.36†	0.55 ± 0.45§
G_{OFF_f}, $l \cdot min^{-1} \cdot \%^{-1}$	0.56 ± 0.45	0.36 ± 0.33*	0.22 ± 0.22†	0.29 ± 0.28§

Values are means ± SD; *n,* no. of subjects. $P_{ET_{CO_2}}$ is average value over the 40-min protocol. $\dot{V}_E$ values (1/min) are for *protocol 2* (P2; 20-min hypoxic exposure from *minutes 10–30*) at 10, 12, 30, and 32 min and for *protocol 3* (P3; control euoxic exposure) at 12 and 30 min. ON_s, sustained on response: $\dot{V}_E$(P2–30) − $\dot{V}_E$(P3–30); ON_f, fast on response: $\dot{V}_E$(P2–12) − $\dot{V}_E$(P2–10); OFF_f, fast off response: $\dot{V}_E$(P2–30) − $\dot{V}_E$(P2–32); HVD, hypoxic ventilatory depression: $\dot{V}_E$(P2–12) − $\dot{V}_E$(P2–30); drift, $\dot{V}_E$(P3–30) − $\dot{V}_E$(P3–12); HVDc, corrected HVD + drift; G_{ON_s}, ON_s expressed per %desaturation; G_{ON_f}, ON_f expressed per %desaturation; G_{OFF_f}, OFF_f expressed per %desaturation. Values are significant when $P < 0.05$: *HA1 significantly different from SL; †HA2 significantly different from SL; ‡HA2 significantly different from HA1; §HAT significantly different from SL.

corresponding estimate of AHVR per %desaturation was also calculated. ON_f was well correlated with the measurements obtained from the incremental steps into hypoxia of *protocol 1* ($r = 0.79$, $P < 0.001$). In addition, the relative differences in AHVR between the different groups are similar for the two protocols (as a proportion of the SL values, the ON_f response was 85, 62, and 74% for the HA1, HA2, and HAT groups compared with 97, 60, and 78%, respectively, for the measures of AHVR from the incremental steps of hypoxia in *protocol 1*). Interestingly, the difference between the HAT and SL groups reached significance for the ON_f response, whereas this was not the case for the measures of AHVR from *protocol 1*. Although this might be related to a lower prevailing level of ventilatory stimulation before the induction of sustained hypoxia in the HA2 group (see above), there was nevertheless no reduction in the magnitude of AHVR (as a fraction of the AHVR of the SL group) in the data from *protocol 2* compared with those from *protocol 1* in this group.

The difference between $\dot{V}_E$(P2–12) and $\dot{V}_E$(P2–30) or HVD gives a measure of the decline in $\dot{V}_E$ over the sustained hypoxic period. This appears somewhat greater in the HA subjects compared with the SL group (by ~50%), but this did not reach significance. One complication is that, in the control data, there is a progressive increase in $\dot{V}_E$ over this period. This may be calculated as the difference between $\dot{V}_E$(P3–30) and $\dot{V}_E$(P3–12) and has been termed drift. The value for HVD may be corrected for this progressive rise to give the parameter HVDc. For this corrected parameterization, the magnitude of ventilatory decline with sustained hypoxia in the HA1 group was significantly larger than in the SL group.

DISCUSSION

This study has confirmed a previous result (18) that the irreversible reduction in AHVR associated with growth to adulthood at HA (>3,500 m) measured after a period of residence at SL is modest. For the HA group overall, AHVR was 79% of the response of SL natives from the incremental step protocol and 74% of the response of SL natives measured from the protocol involving sustained hypoxia. However, this study has also shown that the effects of growth to adulthood at HA on the response to sustained hypoxia are far greater. For the overall HA group, the sustained ventilatory response to hypoxia was only 30% of that of the SL group. This arises from the combined effects of the

(more modest) reduction in AHVR coupled with an increase in the magnitude of HVD.

This study, highlighting the differences between the ventilatory responses to acute and sustained hypoxia between SL and HA natives at SL, probably reconciles a number of studies in the literature. Studies of HA natives at SL that employed sustained hypoxia (7, 16) found markedly blunted responses, whereas, with a hypoxic stimulus sufficiently acute to avoid HVD, Vargas et al. (18) did not find the responses to be blunted. Patients who were chronically hypoxic from cyanotic heart disease before corrective surgery were found to remain blunted in studies in which sustained hypoxic stimuli were employed to assess AHVR (17), whereas, in studies in which shorter duration hypoxic stimuli were employed, this was not the case (1, 3).

The reasons why the HA group should show more marked HVD are not clear, not least because there is not agreement on the origins of HVD itself (12, 20). In humans, a study fitting mathematical models to data for the ventilatory response to sustained hypoxia found that only ~10% of HVD resulted from a central depression independent of the peripheral chemoreflexes in four out of six subjects, but that, in the other two subjects, this figure was ~50% (9). In the present study, the percent reduction in AHVR with sustained hypoxia [calculated as $100 * (ON_f - OFF_f)/ON_f$, where OFF_f is a measure of AHVR after it has decreased after 20 min of sustained hypoxia] was significantly greater for the HAT group than for the SL controls [52 ± 6 (SE) % for the HAT group; 30 ± 9% for the SL group; $P < 0.05$], which suggests that HA natives and SL natives differ in the degree to which sustained hypoxia alters peripheral chemoreflex sensitivity. However, there may also be a difference between the two groups in relation to a mechanism that is independent of the peripheral chemoreflex, because the undershoot in $\dot{V}_E$ after the relief of hypoxia appears larger for the HAT group than for the SL group [2.27 ± 0.75 (SE) l/min for the HAT group; 1.09 ± 0.63 l/min for the SL group], although this difference did not reach significance.

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