Similar hypoxic ventilatory responses in sea-level natives and high-altitude Andean natives living at sea level

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Natives of high altitude (HA) are generally accepted as having a reduced (blunted) ventilatory sensitivity to hypoxia. This reduction in ventilatory sensitivity has been determined in a number of ways, including 1) a reduction in the difference between the hyperoxic and hypoxic ventilatory response to CO₂ (15, 18), 2) a reduction in the isocapnic hypoxic response slopes (7, 22), and 3) a reduction in response to brief stimulation by a few breaths of nitrogen (11, 13, 21). Originally it was proposed that subjects had to be born at HA to show such blunting, but it has subsequently been shown that natives of near sea level (SL) may develop blunted hypoxic responses through residence at HA (7, 22). Both the elevation and duration of HA exposure required for blunting to develop are uncertain. For Sherpas, an interaction between these two factors has been reported (8). For Tibetans, blunting has been reported for subjects resident at 4,400 m but not for those at 3,658 m (3, 23). In terms of duration, blunting has been reported by some (19) but to develop early in childhood but by others (2, 10) to develop only between late childhood and adulthood. For SL natives migrating to altitude, the development of blunting has been reported to be complete within a few years for adolescents (7) but to take much longer for an adult (22).

A number of reports suggest that, once blunting has developed, it is permanent and is not reversible by residence at SL (12, 20, 21). However, Lahiri (unpublished observations) has suggested that adult migrants from HA to Tacna, Peru (elevation 800 m) may have recovered some of their sensitivity to hypoxia after 5–15 yr at the lower altitude (9). Furthermore, two reports suggest that the blunting of the ventilatory response associated with cyanotic congenital heart disease is reversed after surgery and the abolition of hypoxemia (1, 6). The aim of the present study was to reexamine the possibility that blunting may be reversed in HA natives when they migrate to SL.

An important methodological consideration relates to the technique employed to assess the ventilatory sensitivity to hypoxia. The response to a step change into steady isocapnic hypoxia is characterized by a reasonably rapid increase in ventilation (Ve) initially, followed by a gradual “roll-off” that is known as hypoxic ventilatory depression or decline (5). Thus measures of hypoxic sensitivity are dependent on the overall duration of hypoxic exposure. In the present study, a protocol for determining the ventilatory sensitivity to hypoxia was chosen that was similar to one in which the rate of change of PO₂ had been shown to be sufficiently slow to allow the development of a full ventilatory response but sufficiently fast to prevent a significant degree of ventilatory decline from occurring (16).

METHODS

Subjects. Two separate sets of experiments were performed. In the first set of experiments (study A), a subset of subjects employed in a previous study (14) was used. This group of subjects (group A) consisted of 24 HA subjects who were born at an altitude >3,000 m and of 23 SL controls recruited from the same neighborhood. All subjects were residing in Lima, Peru.

In the second set of experiments (study B), a stricter set of criteria was used to select the HA natives. The HA natives in this group of subjects (group B) had been born and raised at an altitude >3,500 m for >20 yr and had been residing at SL for <5 yr. The SL controls of group B were recruited from the same neighborhoods as the HA subjects of group B. Overall, there were 25 HA natives in group B and 25 SL controls. Again, all subjects were residing in Lima, Peru.

Additional inclusion criteria for both groups were that the subjects should be men, should be between the ages of 18 and
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65 yr (group A) or 20 and 65 yr (group B), should not have visited HA on more than four occasions in the previous year, and should not have been at HA within 3 mo of the study. The study was approved by the Ethics Committee of the Scientific Research Office of Cayetano Heredia University.

Experimental assessment of sensitivity to hypoxia. The protocol for assessing sensitivity to hypoxia involved administering seven different gas mixtures. The first mixture [inspired O2 fraction (FiO2) = 0.182; inspired CO2 fraction (FiCO2) = 0.014] was administered for the first 5 min. The subsequent six mixtures contained a progressively decreasing FiO2, and a progressively increasing FiCO2, and were administered contiguously, each mixture for 1 min. The FiO2 values of the six mixtures were 0.137, 0.112, 0.096, 0.085, 0.082, and 0.077; the FiCO2 values of the mixtures were 0.024, 0.027, 0.033, 0.039, 0.041, and 0.044. These mixtures were designed to try to maintain isocapnia and to provide data evenly spaced in terms of the arterial saturation. Of course, the actual end-tidal and arterial PO2 and PCO2 values will vary somewhat from experiment to experiment, depending on the subjects’ responses. The gases were mixed during each experiment by using a bank of rotameters. A change in inspired gas composition normally took <10 s to complete.

In general, experiments on HA natives and SL controls were performed in equal numbers on each experimental day. Subjects were seated comfortably and breathed through a mouthpiece with the nose occluded. In most cases a pulse-oximeter was attached to the forefinger to monitor the oxygen saturation of arterial blood (SaO2). The mouthpiece assembly contained low-resistance inspiratory and expiratory valves, and the expiratory gas was collected in a Tissot spirometer for determinations of VE. A variable-resistance potentiometer connected to the Tissot spirometer was used to register on a pen recorder the volume changes on a breath-by-breath basis. Manual displacement of the bell of the Tissot spirometer was used to calibrate the recorder before an experiment started. Gas at the mouth was sampled continuously and analyzed for PCO2 and PO2 (Normocap Oxy, Datex). End-tidal CO2 partial pressure (PETCO2) and end-tidal O2 partial pressure (PETO2) values associated with each of the inspiratory gas mixtures were noted in the last 30 s of exposure to each gas mixture.

Data analysis. VE was averaged over the last 30 s of exposure to each gas mixture. The PETCO2 values were converted to SaO2 by using an equation described by Severinghaus (17), because these values should reach a steady state faster than the values from the pulse oximeter. The slope and intercept (at SaO2 = 100%) of the linear regression between VE and SaO2 was calculated for each subject, and the results were expressed per square meter of body surface area (4).

RESULTS

Table 1 gives the average physical characteristics and duration of residence at HA and SL for the HA natives and their respective SL controls for both groups A and B. There were no significant differences in the average age or weight between the HA natives and their SL controls in either group A or B (ANOVA). However, the average height and surface area of the HA subjects in group B were significantly less than those of its control group (ANOVA, P < 0.05). The average age, weight, height, and surface area were different between the HA subjects of groups A and B. The HA subjects in group B were younger, lighter, shorter, and had a smaller surface area than their counterparts in group A.

The individual responses for VE and PETCO2 against calculated SaO2 for all subjects from group A are shown in Fig. 1 and for all subjects from group B in Fig. 2. The impression gained is that the PETCO2 has been reasonably well controlled in both groups of experiments, and no difference is apparent between the SL and HA subjects within each group. Similarly, the ventilatory responses appear to be similar between the HA and SL natives within each group, although the subjects of group A appear to be more responsive to the hypoxia overall when compared with group B.

Table 2 gives the average values for the slopes and intercepts (at SaO2 = 100%) for the relationships between PETCO2 and SaO2 and between VE and SaO2 for groups A and B. For the PETCO2 data, there were no significant differences in the constant at SaO2 = 100% between the SL and HA subjects in either group, although the subjects of group B appear to be more responsive to the hypoxia overall when compared with group B.

Table 1. Anthropological parameters of subjects for group A (HA subjects born above 3,000 m) and for group B (HA subjects born and raised above 3,500 m for >20 yr and who have lived at SL for <5 yr)

<table>
<thead>
<tr>
<th></th>
<th>Sea Level</th>
<th>High Altitude</th>
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<tbody>
<tr>
<td><strong>Group A (n = 47 subjects)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>34±11</td>
<td>38±11†</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>65±8</td>
<td>70±11†</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165±6*</td>
<td>168±7</td>
</tr>
<tr>
<td>Surface area, m²</td>
<td>1.72±0.13</td>
<td>1.79±0.14†</td>
</tr>
<tr>
<td>Time at altitude, yr</td>
<td>14±9</td>
<td></td>
</tr>
<tr>
<td>Range, yr</td>
<td>1–40</td>
<td></td>
</tr>
<tr>
<td>Time at sea level, yr</td>
<td>34±11</td>
<td>23±9</td>
</tr>
<tr>
<td>Range, yr</td>
<td>21–58</td>
<td>10–47</td>
</tr>
<tr>
<td><strong>Group B (n = 50 subjects)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>31±8</td>
<td>30±5†</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>65±11</td>
<td>59±5</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167±6*</td>
<td>163±5†</td>
</tr>
<tr>
<td>Surface area, m²</td>
<td>1.73±0.15†</td>
<td>1.63±0.09†</td>
</tr>
<tr>
<td>Time at altitude, yr</td>
<td>27±5</td>
<td></td>
</tr>
<tr>
<td>Range, yr</td>
<td>20–40</td>
<td></td>
</tr>
<tr>
<td>Time at sea level, yr</td>
<td>31±8</td>
<td>3±1</td>
</tr>
<tr>
<td>Range, yr</td>
<td>22–49</td>
<td>1.25–5</td>
</tr>
</tbody>
</table>

Values are means ± SD. HA, high-altitude; SL, sea level. *P < 0.05 for comparisons between SL and HA; †P < 0.05 for comparisons between HA subjects of groups A and B.
that PETCO₂ increased slightly as saturation decreased. The slopes for the results from the two groups were significantly different (group A slope, $-0.033 \pm 0.012 \text{ Torr/}%$; group B slope, $-0.069 \pm 0.013 \text{ Torr/} %$; ANOVA, $P < 0.05$). However, there were no significant differences between the HA and SL subjects of either group A or group B.

For the data for $V\dot{E}$ in Table 2, there were no significant differences in the values for $V\dot{E}$ at $SaO₂ = 100\%$ between the HA and SL subjects in either group.

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Fig. 1. Relationships in group A subjects between ventilation ($V\dot{E}$) and calculated $O₂$ saturation ($SaO₂$) and between end-tidal $PCO₂$ (PETCO₂) and calculated $SaO₂$. Left: SL, subjects born at sea level. Right: HA, subjects born at $>3,000 \text{ m altitude}$. Thick lines, overall regressions. For SL subjects, $V\dot{E}$ vs. $SaO₂$, slope $=-0.65 \text{ l.min}^{-1}.\text{%}^{-1}$; PETCO₂ vs. $SaO₂$, slope $=-0.02 \text{ Torr/}%$. For HA subjects, $V\dot{E}$ vs. $SaO₂$, slope $=-0.74 \text{ l.min}^{-1}.\text{%}^{-1}$; PETCO₂ vs. $SaO₂$, slope $=-0.05 \text{ Torr/}%$.

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Fig. 2. Relationships in group B subjects between $V\dot{E}$ and calculated $SaO₂$ and between PETCO₂ and calculated $SaO₂$. Left: SL subjects; right, HA subjects (born and raised at $>3,500 \text{ m for } >20 \text{ yr, lived at SL } <5 \text{ yr}$). Thick lines, overall regressions. For SL subjects, $V\dot{E}$ vs. $SaO₂$, slope $=-0.52 \text{ l.min}^{-1}.\text{%}^{-1}$; PETCO₂ vs. $SaO₂$, slope $=-0.08 \text{ Torr/}%$. For HA subjects, $V\dot{E}$ vs. $SaO₂$, slope $=-0.48 \text{ l.min}^{-1}.\text{%}^{-1}$; PETCO₂ vs. $SaO₂$, slope $=-0.11 \text{ Torr/}%$. 

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or between groups A and B (ANOVA). For the slopes for the relationships between $V\dot{E}$ and $S_aO_2$ there were significant differences (ANOVA, $P < 0.005$) between the four sets of subjects (SL and HA subjects of groups A and B). On post hoc testing, no significant differences were found between the slopes for HA and SL natives within either group A or group B, confirming the impressions gained from Figs. 1 and 2, but there were significant differences between the slopes for groups A and B (group A slope, $-0.51 \pm 0.04 \text{l} \cdot \text{min}^{-1} \cdot \%^{-1} \cdot \text{m}^{-2}$; group B slope, $-0.34 \pm 0.02 \text{l} \cdot \text{min}^{-1} \cdot \%^{-1} \cdot \text{m}^{-2}$; ANOVA, $P < 0.001$). These analyses were then repeated in two slightly different ways. First, the data were reanalyzed without the normalization for body surface area. Second, the regressions between $V\dot{E}$ and $S_aO_2$ were recalculated by using the measured values for $S_aO_2$ from the oximeter, and the ANOVA was rerun on these data (after normalization for body surface area). In neither of these analyses were any of the statistical findings altered.

Finally, for the HA subjects of both group A and group B, linear regression was undertaken to determine whether there was any relationship between the durations of residence at HA and at SL and the magnitude of the ventilatory response to hypoxia. No such relationships were detected.

**DISCUSSION**

The major finding of this study is that we were unable to show a difference in ventilatory sensitivity to hypoxia between SL controls and HA natives resident at SL. For group A, the 95% confidence interval for the difference in slope (l min$^{-1} \cdot \%^{-1} \cdot$m$^{-2}$) between HA and SL was $[-0.27, 0.13]$, and for group B, the 95% confidence interval for the difference in slope was $[-0.09, 0.15]$. Taken with the mean values for the hypoxic sensitivities for groups A and B, these intervals indicate that in a statistical sense we can be 95% confident that the HA sensitivity was not $<75\%$ of SL sensitivity for group A and 95% confident that the HA sensitivity was not $<57\%$ of SL sensitivity for group B. Previous studies of blunting have reported the following hypoxic sensitivities for HA natives as a percentage of SL controls: 27% (18), 10% (15), 32% (7), and 10% (22). For the first two studies, the SL controls were studied at HA; for the second two studies, the SL controls were studied at lower altitude. The important point is that the degree of blunting reported in any one of these studies should have been detectable in our results.

**Critique of present study.** One problem associated with our study is that $P_{ETCO_2}$ on average increased slightly as the $P_{ETO_2}$ was reduced during the assessment of hypoxic sensitivity. Presumably, this occurred because we overestimated slightly the additional CO$\_2$ that needed to be introduced to maintain isocapnia when the $P_{ETO_2}$ was lowered. The hypoxic sensitivities we report may thus be an overestimate of the true isocapnic sensitivities. However, there were no statistically significant differences for this increase in $P_{ETCO_2}$ between the HA and SL subjects in either group A or group B. Thus the degree of overestimation should be similar for HA and SL subjects within each group.

A second problem associated with our study relates to the differences that we found between groups A and B. Group A generally had a higher sensitivity to hypoxia and a lower progressive elevation in $P_{ETCO_2}$ during the assessment of hypoxic sensitivity. This appears not to be related to the longer time spent at HA and the shorter time spent at SL by the HA subjects of group B compared with those of group A, because, if we pool all the HA subjects from groups A and B and compare them with all the SL subjects pooled from groups A and B, no significant difference is detected. Thus the difference between group A and group B suggests that something may have changed in the experimental conditions between the time study A was undertaken and the time study B was undertaken. In particular, we are suspicious that there may have been some deterioration in the functioning of the respiratory valve over time during the conduct of the experiments on group B. The reason for our suspicion is that the mean $V\dot{E}$ for both the HA subjects and the SL subjects in group B showed a statistically significant downward trend with subject number. Although this introduces a further degree of uncertainty in relation to the absolute hypoxic sensitivities reported, experiments were conducted on equal numbers of HA and SL subjects on each experimental day. Consequently, the development of a modest degree of incompetence associated with the respiratory valve should not invalidate the comparison between the HA and SL subjects within the group.

Comparison with previous results in literature. Most previous study results suggest that, when blunting is established, it is permanent. Sørensen and Severinghaus (19) found that a group of nine HA natives who had been resident at SL for 2–16 yr had hypoxic sensitivities that were on average only 4% of those of nine SL controls. Lahiri et al. (12) report three HA subjects who remained blunted after 10 mo of residence at SL, compared with two SL controls. Velasquez et al. (21) studied HA natives at altitude and then 1 yr after the HA natives had been living at SL. They found no
change in the HA natives’ modest or absent response to breathing a hypoxic gas mixture. In contrast to those results, Lahiri (9) has suggested from unpublished data that, in Andeans who have migrated from HA to SL, there may be some recovery of hypoxic sensitivity after 5–15 yr. With the exception of that report, it is quite difficult to reconcile our results with the earlier literature. However, the techniques used for assessing hypoxic sensitivity by Sørensen and Severinghaus (19) and by Lahiri et al. (12) were steady-state ones that involved breathing hypoxic gas mixtures for quite long periods of time (a complete set of measurements on 1 subject by Sørensen and Severinghaus took 2–4 h), and it is possible that the HA and SL natives could differ in the degree of hypoxic depression that developed during the test. The technique of Velasquez et al. (21) used 5 min of a hypoxic gas mixture, but there was no attempt to maintain isocapnia. This method results in responses that would be rather small even in SL subjects. In contrast to these studies, our technique sought to minimize the total exposure to hypoxia, so as to minimize the influence that hypoxic depression might have on the results, while, at the same time, we attempted to maintain isocapnia and allow time for a full hypoxic response to develop (16).

Another group of subjects who have been hypoxic from birth are those with certain congenital cardiac malformations. Sørensen and Severinghaus (20) have reported on a set of five patients who, >1 yr after surgical correction for tetralogy of Fallot, had hypoxic sensitivities markedly below normal. In contrast, Edelman et al. (6) reported on three subjects who had been operated on for cyanotic congenital heart disease and who had normal hypoxic ventilatory responses. Two of the subjects had been studied preoperatively while hypoxic; at that time, the subjects clearly had depressed ventilatory responses to hypoxia, as had two other congenitally cyanotic subjects who were studied. Similarly, Blesa et al. (1) report on a series of 13 children/adolescents who had been operated on for congenital cyanotic heart disease and in whom the hypoxic sensitivity was normal, some within a few weeks after operation. This was in contrast with eight children/adolescents who were hypoxic from cyanotic heart disease and who had very blunted ventilatory responses to hypoxia. These latter reports would seem to be consistent with the results from our study. Interestingly, there was a considerable difference in the techniques used to assess hypoxic sensitivity. Sørensen and Severinghaus (20) used a prolonged steady-state technique, whereas Edelman et al. (6) and Blesa et al. (1) used a few breaths of N₂ to assess hypoxic sensitivity. Thus, in the former study, substantial hypoxic ventilatory depression may have been induced by the experiment, whereas in the latter studies this should have been absent.

In conclusion, the absolute values for the ventilatory sensitivities to hypoxia that we report in the present study have some uncertainties associated with them. Nevertheless, it is clear that these migrants from HA had hypoxic sensitivities that were substantially greater than reported for HA subjects resident at HA. This was true not only for the subjects of group A but also for subjects of group B who had been resident at HA from birth for >20 yr and at SL for <5 yr. Particularly for these latter subjects, the evidence from prior studies is persuasive that they should have developed blunting while resident at HA.

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