Plasticity in Respiratory Motor Control

Selected Contribution: High-altitude natives living at sea level acclimatize to high altitude like sea-level natives

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Submitted 19 September 2002; accepted in final form 25 November 2002

Rivera-Ch, Maria, Alfredo Gamboa, Fabiola León-Velarde, Jose-Antonio Palacios, David F. O’Connor, and Peter A. Robbins. Selected Contribution: High-altitude natives living at sea level acclimatize to high altitude like sea-level natives. J Appl Physiol 94: 1263–1268, 2003. First published November 27, 2002; 10.1152/japplphysiol.00857.2002.—Sea-level (SL) natives acclimatizing to high altitude (HA) increase their acute ventilatory response to hypoxia (AHVR), but HA natives have values for AHVR below those for SL natives at SL (blunting). HA natives who live at SL retain some blunting of AHVR and have more marked blunting to sustained (20-min) hypoxia. This study addressed the question of what happens when HA natives resident at SL return to HA: do they acclimatize like SL natives or revert to the characteristics of HA natives? Fifteen HA natives resident at SL were studied, together with 15 SL natives as controls. Air-breathing end-tidal PCO2 and AHVR were determined at SL. Subjects were then transported to 4,300 m, where these measurements were repeated on each of the following 5 days. There were no significant differences in the magnitude or time course of the changes in end-tidal PCO2 and AHVR between the two groups. We conclude that HA natives normally resident at SL undergo ventilatory acclimatization to HA in the same manner as SL natives.

regulation of ventilation; human; Andean natives; chemoreflex; blunting

HIGH-ALTITUDE (HA) NATIVES residing at HA have certain characteristics in relation to respiratory control that distinguish them from sea-level (SL) natives. They have an end-tidal PCO2 (PETCO2) that has been described as below that for unacclimatized SL natives, but somewhat above the PETCO2 associated with SL natives after they have acclimatized to HA (3, 22, 25). HA natives residing at HA have ventilatory responses to hypoxia that are blunted compared with SL natives (8, 12, 14, 17, 24, 29, 30).

On moving to SL, HA natives develop a PETCO2 that is very similar to that of SL natives resident at SL (15). However, the blunting of the ventilatory response to hypoxia is thought to persist (13, 26, 29). More recently, the persistent blunting of the acute hypoxic ventilatory response (AHVR) of HA natives living at SL has been shown to be much less marked than previously thought (9, 28). However, the ventilatory response to sustained (20-min) hypoxia (i.e., after hypoxic ventilatory depression has had a chance to develop) of HA natives is much less than for SL control subjects (9).

These findings at SL raise the interesting question of what happens to HA natives, resident at SL, who are reexposed to HA. Do they develop the profile of a HA native resident at HA, with a blunted AHVR and a PETCO2 that is intermediate between unacclimatized and fully acclimatized SL natives? Alternatively, do they acclimatize as SL natives do, with a similar fall in PETCO2 and increase in AHVR? This study sought answers to these questions by exposing a group of HA natives resident at SL, together with a control group of SL natives, to 5 days of HA at Cerro de Pasco, Peru (4,300 m).

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METHODS

Subject Selection

Fifteen HA natives living in Lima at SL were selected for study. All had lived at >3,500 m for the first 20 yr of their lives. Fifteen SL natives living in Lima acted as controls. All subjects had taken part in a previous study that had involved determining their ventilatory sensitivities to hypoxia at SL (9). The SL controls were selected so as to have similar ages and values for AHVR as the group of HA natives.

Protocols

Preliminaries. The preliminaries to be conducted at SL on these subjects had been completed as part of our previous study (9). These included taking a brief residence history, noting their general physical characteristics, and conducting a brief medical history and examination to exclude major disease. In addition to this, the subjects’ air-breathing \(P_{ETCO2}\) and end-tidal \(P_{O2}\) (\(P_{ETO2}\)) were determined by using a fine nasal catheter to disturb ventilation as little as possible. Values for the instantaneous respiratory quotient were calculated from these measurements to check that the subjects were not hyperventilating. Finally, the subjects’ acute and sustained (20-min) ventilatory responses to hypoxia were determined at a \(P_{ETCO2}\) of 2 Torr above the subjects’ natural air-breathing value as detailed in Ref. 9. All SL measurements were made before any subject was taken to altitude.

Studies at HA. The first study was conducted on a group of six subjects (three HA natives and three SL natives). This was followed by two further studies with 12 subjects in each group (six HA natives and six SL natives on each occasion). Each group of subjects was transported from Lima to Cerro de Pasco on day 0 of the study, and the subjects were then accommodated at a local hospital in Cerro de Pasco for the duration of the study. Subjects were studied on 5 consecutive days in the laboratory (barometric pressure of 450 mmHg). Medical examination, personal communication, started on the first day after arrival at Cerro de Pasco.

Each subject was studied at the same time of day on each occasion. Air-breathing \(P_{ETCO2}\) and \(P_{ETO2}\) were measured by using a fine nasal catheter. This was followed by a measurement of \(P_{ETCO2}\) and \(P_{ETO2}\) after 3–10 min of breathing gas enriched with \(O_2\) through a face mask to bring \(P_{ETO2}\) to \(\sim 100\) Torr. After this, AHVR was measured by using the protocol of Mou et al. (18). For this protocol, \(P_{ETCO2}\) was held at 2 Torr above the value that had been obtained while the subject breathed the gas mixture that had been supplemented with \(O_2\) to bring \(P_{ETO2}\) to \(\sim 100\) Torr. \(P_{ETO2}\) was held at 100 Torr for 5 min and then at a series of seven decreasing levels of \(P_{ETO2}\), starting at a \(P_{ETO2}\) of 100 Torr and finishing at a \(P_{ETO2}\) of 45 Torr, with each level lasting 50 s. These levels were spaced so that there would be an approximately linear fall in arterial oxygen saturation and, consequently, an approximately linear rise in ventilation (\(V_E\)) over time.

Apparatus and Techniques

Respired gas concentrations were measured by using a Datex Normocap-Oxy gas analyzer in which the software had been modified to disable the automatic hourly zeroing of the instrument (this was done manually at appropriate times throughout the experiment). Respired gas volumes were measured by using a turbine volume-measuring device (10). Data were logged to a personal computer by using National Instruments interface cards (DAQCard-1200 and DAQCard-AO-2DC).

The protocol for assessing AHVR was implemented via the end-tidal forcing technique (19). In this technique, before an experiment starts, an estimate of the inspiratory \(P_{O2}\) and \(P_{PCO2}\) profile necessary to generate the desired \(P_{ETO2}\) and \(P_{ETCO2}\) values, respectively, for the protocol is made by using a respiratory model. During the experiment, the inspiratory gases are mixed via a fast gas-mixing system controlled by a computer. The composition of the mixed inspiratory gases is based on the profile calculated from the respiratory model, but the composition is also corrected by feedback of the actual \(P_{ETO2}\) and \(P_{ETCO2}\) values achieved on a breath-by-breath basis (using an integral-proportional controller). The real-time software for controlling the experiments was written in LabView (National Instruments, Austin, TX), and the fast gas-mixing system was constructed by using mass flow controllers (MKS Instruments, Altrington, UK).

In these experiments, the subjects sat upright and breathed the gases via a mouthpiece with their nose occluded with a clip.

Data Analysis

Values for AHVR were calculated from the data in two ways. In the first method, average values for \(V_E\) and \(P_{ETCO2}\) were calculated from the last 20 s of data from each of the seven levels of \(P_{ETO2}\). Calculated values for arterial saturation were obtained from the values for \(P_{ETO2}\) (23). A linear regression was then performed between the values for \(V_E\) and arterial desaturation to give a slope (\(S_{AHVR}\)) as a measure of AHVR and an intercept (\(K_{AHVR}\)) as a measure of hypoxia-independent \(V_E\). In the second method, a dynamic model of the respiratory response to acute hypoxia (model 3 of Clement and Robbins (5)) was fit to the entire data set from the seven levels of \(P_{ETO2}\). The gain term (\(Gp\)) gave an analogous measure of AHVR to \(S_{AHVR}\), and the intercept term (\(V_c\)), an analogous measure of hypoxia-independent \(V_E\) to \(K_{AHVR}\). The procedure also yielded a time constant (\(T\)) and pure delay (\(d\)) for the response.

Statistical significance was assessed by using repeated-measures ANOVA. For the various variables measured during acclimatization, a significant value for the interaction between subject type and time would indicate that the HA and SL natives differed in their acclimatization response. Statistical significance was taken at \(P < 0.05\).

RESULTS

Subjects

All 15 SL natives completed the full 5-day study at altitude. Of the 15 HA natives recruited, two withdrew from the study; one after 2 days at HA and the other after 3 days at HA. Both withdrew because they did not feel comfortable undertaking the protocol. It was not clear that either was suffering from acute mountain sickness. The results presented relate just to those subjects who completed the full study.

The physical characteristics for the subjects are given in Table 1. The HA natives did not differ significantly from the SL natives in any physical respect, but there was a tendency for the HA natives to have a higher vital capacity normalized to body surface area.

Responses at SL

The responses of these subjects at SL are a subset of the data previously reported in Ref. 9. SL values for
Table 1. General characteristics of the subjects

<table>
<thead>
<tr>
<th></th>
<th>SL</th>
<th>HA</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Age, yr</td>
<td>31.0 ± 6.8</td>
<td>32.9 ± 7.9</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>61.6 ± 9.8</td>
<td>68.3 ± 16.5</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.64 ± 0.06</td>
<td>1.64 ± 0.04</td>
</tr>
<tr>
<td>Surface area, m²</td>
<td>1.24 ± 0.16</td>
<td>1.34 ± 0.23</td>
</tr>
<tr>
<td>Vital capacity, l/m²</td>
<td>4.27 ± 0.67</td>
<td>4.54 ± 0.71</td>
</tr>
<tr>
<td>FEV₁, l/m²</td>
<td>3.57 ± 1.06</td>
<td>3.62 ± 1.15</td>
</tr>
<tr>
<td>Altitude of birth, m</td>
<td>150</td>
<td>3,871 ± 204</td>
</tr>
<tr>
<td>Age of migration to SL, yr</td>
<td>23.8 ± 3.8</td>
<td>23.8 ± 3.8</td>
</tr>
<tr>
<td>Time at sea level, yr</td>
<td>9.1 ± 6.8</td>
<td>9.1 ± 6.8</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of subjects. SL, sea-level natives; HA, high-altitude natives born and raised above 3,500 m but resident at SL; FEV₁, forced expiratory volume in 1 s.

There was an obvious drop in air-breathing \( \text{PETCO}_2 \) and \( \text{PETO}_2 \) on day 1 of HA in both HA and SL natives. There was a progressive further fall in \( \text{PETCO}_2 \) over the remaining 4 days of the exposure. These changes over time in air-breathing \( \text{PETCO}_2 \) were significant (\( P < 0.001 \), ANOVA), but there was no significant interaction between time and subject type (SL vs. HA natives). The fall in \( \text{PETCO}_2 \) over time appeared close to exponential, and fitting to the data provided a \( T \) of 1.3 ± 0.2 days (mean ± SE) and an asymptotic value for \( \text{PETCO}_2 \) of 26.0 ± 0.5 Torr. The pattern of response for \( \text{PETCO}_2 \) measured at \( \text{PETO}_2 \) of ~100 Torr was similar to that observed for air-breathing \( \text{PETCO}_2 \) (Table 2). During the acclimatization process, the average difference between \( \text{PETCO}_2 \) measured at a \( \text{PETO}_2 \) of ~100 Torr and \( \text{PETCO}_2 \) measured under air-breathing conditions was 0.53 ± 1.5 Torr (mean ± SD). This did not vary significantly, either with subject type or over time during acclimatization.

Numerical values for AHVR were obtained both by linear regression (\( S_{\text{AHVR}} \)) and from fitting a dynamic model (Gp). The results from both approaches were very similar, and so only the values for Gp are presented. There was a rise in Gp during acclimatization (\( P < 0.001 \)), but there was no significant difference with subject type and no significant interaction between time and subject type.

The calculated values for \( V_{\text{E}} \) in the absence of any hypoxic stimulus (parameter \( V_{\text{c}} \) from the dynamic model) appeared to decrease somewhat from the values

Table 2. End-tidal gases and ventilatory responses to acute hypoxia for SL natives and HA natives living at SL determined at SL and during a 6-day sojourn at 4,300 m

<table>
<thead>
<tr>
<th></th>
<th>SL</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SL natives</td>
<td></td>
<td>HA natives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air breathing (HX at HA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{PETCO}_2 ) Torr</td>
<td>38.2 ± 2.7</td>
<td>31.6 ± 3.2</td>
<td>28.7 ± 1.9</td>
<td>28.3 ± 1.9</td>
<td>26.9 ± 2.0</td>
<td>26.8 ± 1.6</td>
</tr>
<tr>
<td>( \text{PETO}_2 ) Torr</td>
<td>105.8 ± 2.8</td>
<td>50.7 ± 3.4</td>
<td>51.8 ± 2.4</td>
<td>52.9 ± 2.6</td>
<td>53.7 ± 2.5</td>
<td>53.8 ± 2.2</td>
</tr>
<tr>
<td>Inspired ( P_{\text{O}_2} ) = 150 Torr (EU)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{PETCO}_2 ) Torr</td>
<td>31.2 ± 4.2</td>
<td>29.4 ± 2.0</td>
<td>28.4 ± 2.8</td>
<td>27.9 ± 2.3</td>
<td>27.3 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>( \text{PETO}_2 ) Torr</td>
<td>100.9 ± 5.2</td>
<td>102.5 ± 8.2</td>
<td>101.9 ± 3.8</td>
<td>103.7 ± 3.2</td>
<td>104.2 ± 2.8</td>
<td></td>
</tr>
<tr>
<td>( \Delta \text{PETCO}_2 ) Torr (HX-EU)</td>
<td>0.46 ± 0.60</td>
<td>-0.63 ± 2.15</td>
<td>-0.16 ± 2.24</td>
<td>-1.01 ± 1.73</td>
<td>-0.48 ± 1.46</td>
<td></td>
</tr>
<tr>
<td>( G_{\text{p}}, \text{lmin}^{-1} \cdot %^{-1} )</td>
<td>0.86 ± 0.38</td>
<td>0.98 ± 0.71</td>
<td>0.98 ± 0.76</td>
<td>1.39 ± 0.85</td>
<td>1.77 ± 1.31</td>
<td>1.74 ± 1.39</td>
</tr>
<tr>
<td>( V_{\text{c}}, \text{l/min} )</td>
<td>9.3 ± 3.4</td>
<td>9.7 ± 4.9</td>
<td>8.0 ± 4.6</td>
<td>8.4 ± 4.3</td>
<td>7.5 ± 4.9</td>
<td>6.6 ± 3.7</td>
</tr>
<tr>
<td>( T_{\text{d}}, \text{s} )</td>
<td>17.0 ± 12.8</td>
<td>15.6 ± 11.0</td>
<td>11.9 ± 10.4</td>
<td>13.6 ± 10.7</td>
<td>14.5 ± 12.1</td>
<td>8.2 ± 8.6</td>
</tr>
<tr>
<td>( d_{\text{c}}, \text{s} )</td>
<td>7.2 ± 4.3</td>
<td>4.6 ± 2.7</td>
<td>7.9 ± 6.1</td>
<td>5.4 ± 4.0</td>
<td>4.7 ± 2.9</td>
<td>4.8 ± 2.0</td>
</tr>
</tbody>
</table>

Values are means ± SD. SL, sea level; HX, hypoxia; HA, high altitude; EU, euoxia; \( \text{PETCO}_2 \), end-tidal \( \text{P}_{\text{CO}_2} \); \( \text{PETO}_2 \), end-tidal \( \text{P}_{\text{O}_2} \); \( G_{\text{p}} \), model parameter for AHVR; \( V_{\text{c}} \), model parameter for ventilation in absence of hypoxic stimulus to breathe; \( T_{\text{d}} \), time constant; \( d_{\text{c}} \), pure delay. *\( \text{PETCO}_2 \) at SL for HA natives significantly lower than for SL natives, \( P < 0.05 \).
measured at SL. However, this did not reach significance. Again, there were no significant differences between subject type and no significant interaction between subject type and time.

In addition to Gp and V˙c, fitting the dynamic model to the data also provided values for T and d. There were no significant effects of acclimatization on T, whereas d fell with the hypoxic exposure (P < 0.05). The HA native and SL control groups did not differ in their values for these variables.

**DISCUSSION**

The major finding of this study is that HA natives resident at SL acclimatize to HA in a very similar manner to SL natives. There were no significant differences in time profile or in the magnitude of fall in PETCO2 between the two groups. AHVR increased in both groups in a very similar manner during the acclimatization process. These values should be contrasted with values for HA natives resident at HA, in whom values for AHVR would be expected to be well below the SL values for our subjects (8, 12, 14, 17, 24, 29, 30).

The SL controls were not perfectly matched with the HA subjects, although their ages were very similar. In particular, the HA natives had an air-breathing PETCO2 that was significantly lower than that of the SL natives. This difference does not appear to be a general finding (9, 15). Although not significantly different, the values for AHVR were not as perfectly matched as we had intended, with the average values for the HA natives being somewhat lower than those for the SL natives. Part of this arises because two HA natives did not complete the study. As we did not attempt to match the subjects for their sustained ventilatory response to hypoxia (Ve response to 20-min hypoxia), we might expect the HA natives to have a lower response in this respect than their SL controls (9). In fact, this did not reach significance (data from Ref. 9 for our subset of subjects), although numerically the average value for the HA natives was less than one-half that for the SL natives.

One of the biggest problems associated with assessing the change in AHVR during acclimatization is choosing the level of PETCO2 against which it should be measured. Sato et al. (21) adopted quite a sophisticated approach to this problem. They used 15–20 min of hyperoxia (PETO2 ~ 200 Torr) to reverse any hypoxic ventilatory depression that was present at altitude and then determined a level for PETCO2 that would produce a V˙E under hyperoxic conditions of 140 ml·kg⁻¹·min⁻¹. The rationale was that this would enable AHVR to be determined against a constant level of central chemoreflex stimulation. It is not clear that this rationale is correct. Indeed, although it remains unclear whether peripheral and central chemoreflexes interact (4, 6, 16, 27), it is very clear, at both neural (carotid sinus nerve) and reflex levels, that the magnitude of the acute response to hypoxia depends on the degree of arterial acidosis. The values for arterial pH from Sato et al. (21) suggest that their protocol results in an arterial pH that is more alkaline at HA than at SL, and, therefore, any increase in AHVR with HA would be underestimated.

In our study, we simply increased the PETCO2 to 2 Torr above the ambient value on each day before measuring AHVR. If anything, this should result in less...
disparity in arterial pH between the HA and SL measurements of AHVR than would have been present in the study of Sato et al. (21). This is because Sato et al. elevated PETCO2 less at HA when arterial pH was more alkaline and more at SL when arterial pH was more acid. With respect to central drive, our study differs from that of Sato et al. in two conflicting ways. First, we did not increase PETCO2 to −200 Torr for a 15- to 20-min period before our measurements of AHVR. Our protocol had a 5-min period of PETO2 20-min period before our measurements of AHVR. In acclimatizing humans.

It is certainly the case that measurements of AHVR do not persist under conditions of prolonged exposure to hypoxia (Abstract). FASEB J 14: A78, 2000. 20.

Sato et al. (20) did not have a 5-min period of PETO2 = 100 Torr before the measurement of AHVR. On its own, this would result in less central stimulation by hypoxia (or relief of central depression by hypoxia) in our study than in that of Sato et al. Second, at HA, we elevated PETCO2 by the same amount (2 Torr) as at SL, despite the fact that the acute ventilatory response to hypercapnia would have increased with exposure to HA. This should tend to result in more central stimulation at HA than in the study of Sato et al., in which PETCO2 was chosen to provide, under hypoxic conditions, the same level of ventilatory stimulation at HA as at SL. Experimentally, Vc provides a measure of what has happened to central drive in the absence of peripheral hypoxic stimulation, and the values for this variable appeared to decrease with exposure to altitude, although this observation failed to reach statistical significance. This decrease is surprising because, at HA, the combination of an increased VE in the absence of added CO2, coupled with a steeper Vc-PETCO2 response relation, might reasonably be expected to result in an increase in Vc.

There remains the question of whether Gp could have been suppressed at HA by inadequate preoxygenation before the measurements of AHVR were made. Although it is certainly the case that measurements of AHVR made after 20 min of hypoxia will be lower than those made without such exposure to hypoxia (1, 2, 11), Sato et al. (20) did not find the rapid change in ventilatory response in response to a rapid change in PETCO2 to be greatly increased by preoxygenation after the much longer exposure to hypoxia associated with acclimatization to HA. A similar finding has been made in relation to a 1-h exposure to room air after an 8-h exposure to hypoxia (7). These results suggest that, as long as AHVR is determined rapidly so that baseline changes in central drive do not have time to occur to any significant extent, substantial preoxygenation may not be necessary to obtain reasonable values for AHVR in acclimatizing humans.

This study was supported by the Wellcome Trust.

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