Carotid baroreflex control of heart rate during acute exposure to simulated altitudes of 3,800 m and 4,300 m

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THE CAROTID BAROREFLEX cardiac response plays an important role in regulating circulatory systems. It has been reported that responsiveness of the reflex is modified by a variety of physiological and pathological conditions, such as bed rest (3), spaceflight (10, 12), old age (13), heart failure (30), and hypertension (2, 24). An impairment of the reflex has been associated with a reduction of orthostatic tolerance after prolonged head-down bed rest (3) and spaceflight (10, 12). We have observed previously that orthostatic hypotension was evident during exposure to high altitude (28), in agreement with the reports of Malhotra and associates (22, 23). There are conflicting findings on the effect of hypoxia on carotid baroreflex control of heart rate (HR) in humans, because no impairment of carotid baroreflex sensitivity has been observed during mild to moderate hypoxia during inhalation of low PO2 air (4), asphyxia (1, 7), or exposure to a simulated altitude of 4,572 m (17), whereas Patakas et al. (25) reported a significant linear correlation between arterial PO2 and carotid baroreflex slope in patients with chronic pulmonary obstruction. Heistad et al. (14) have suggested an impairment of cardiac as well as vascular reflexes during exposure to a simulated altitude of 14,000 ft.

Thus the role of carotid baroreflex control of HR during hypoxia is still obscure.

We hypothesized that the mechanisms underlying the reduction of orthostatic tolerance during altitude exposure may involve a reduced sensitivity of the carotid sinus baroreflex. To investigate this hypothesis, we examined the stimulus-response curve, which is one of the most effective methods for analyzing the carotid sinus baroreceptor reflex (27). Hitherto we know there is no report of complete investigation of the carotid baroreflex responsiveness during altitude exposure. Our approach was to construct stimulus-response curves for the carotid sinus baroreflex using ramped neck pressure-suction sequences by serial R-wave trigger. Mild hypoxia (~50 mmHg PO2 in alveolar gas) and short exposure period to hypoxia (~10 min) in the previous studies (1, 4, 7, 17) might explain the lack of effect on the baroreflex. Therefore we tested the carotid baroreflex responsiveness at two levels of altitude, i.e., 3,800 m and 4,300 m, over 60 min of exposure. If the change in carotid baroreflex responsiveness was oxygen dependent, we would expect a more pronounced change at the higher altitude.

METHODS

Subjects

Seven healthy male subjects (27.0 ± 2.6 yr old, mean ± SE, 173.9 ± 2.7 cm height, 69.0 ± 2.3 kg body wt) participated in this study. None of the subjects were engaged in athletic exercise or had prior experience in mountain climbing. Each subject signed a written informed consent and passed comprehensive medical examinations. This research was approved by the Human Investigation Committees of the University of Occupational and Environmental Health.

Experimental Procedures

Each subject underwent two series of experiments conducted separately at two different altitudes. Subjects were allowed 2 wk between each experiment.

First experiment at 3,800 m. Each subject reported to the laboratory at 0900 and entered a climatic chamber at sea level. After a 30-min supine resting period, blood pressure, HR, and O2 saturation were measured for a 10-min control period (baseline data), and then measurement of baroreflex responsiveness using a neck chamber in a supine position followed. After completion of the test, end-tidal gas was collected for PO2 and Pco2 analyses, and then each subject relaxed for ~10 min. The altitude chamber was then decompressed to a simulated altitude of 3,800 m at a rate of 40 mmHg/min. Ambient temperature and relative humidity were maintained at 28°C and 60%, respectively, at sea level and high altitude. After reaching the designated pressure, the subject was allowed to relax for 60 min in a supine position; then the same experimental procedures as at sea level were followed.
Second experiment at 4,300 m. The same seven subjects underwent the identical time schedule as in the first experiment at a simulated altitude of 4,300 m.

Measurements

Carotid baroreflex cardiac responses were measured with the method described by Eckberg et al. (8) and Sprenkle et al. (31). Briefly, a Silastic neck chamber connected to a computer-controlled bellows (E 2000A; Engineering Development Laboratory, Newport News, VA) was strapped to the anterior neck of each subject. We asked the subject to stop breathing at normal expiration to avoid respiratory sinus arrhythmia (10). During held expiration, neck chamber pressure was kept to 0 mmHg for three heartbeats and then increased to 40 mmHg and kept there for two heartbeats. The pressure was then reduced to +20, 0, −10, −20, −30, −40, and −50 mmHg with each successive R-wave from the electrocardiogram signal and returned to ambient. This sequence was repeated eight times, and responses were averaged. Blood pressure was measured with an automated oscillometric blood pressure device (UA-751; Takeda Medical, Tokyo, Japan) before the neck pressure application. Mean blood pressure was calculated as one-third of pulse pressure plus diastolic pressure. End-expiratory gas was led to the outside chamber through a stainless tube (1 mm in diameter) for O2 and CO2 concentration by a mass spectrometer (WLCU-5201; Westron, Tokyo, Japan). O2 saturation measured by pulse oximeter (Biox 3740; Ohmeda, Tokyo, Japan) and HR obtained from an electrocardiogram were monitored throughout the experiment.

Data Analysis

R-R intervals were plotted against the neck chamber pressures and fitted to a four-parameter logistic function as originally described by Kent et al. (16) using the following equation

\[
R-R \text{ interval} = A_1 \times \left[1 + e^{A_2(\text{neck chamber pressure} - A_3)}\right]^{-1} + A_4 \tag{1}
\]

where \(A_1\) is the maximal range of the response, \(A_2\) is a slope coefficient that is a function of neck chamber pressure, \(A_3\) is centering point of the curve, and \(A_4\) is the minimum R-R interval. Maximal gain was calculated from the first derivative of the logistic function at the point where neck chamber pressure equals centering point using the following equation (16)

\[
\text{Maximal gain} = -A_1 \times A_2 / A_4 \tag{2}
\]

Fig. 1 is a representative baroreflex curve fit to the above equation.

Statistics

Statistical analysis for differences among average values between the different environmental conditions was used by one-way analysis of variance for repeated measures; further significance was tested by multiple-comparisons test (Fisher’s test). Data are expressed as means ± SE, with a value of P < 0.05 considered to be significant.

RESULTS

Baseline HR, Blood Pressure, and O2 Saturation

Effect of altitude on baseline HR, mean blood pressure, O2 saturation level, and PO2 and PCO2 in alveolar gas are summarized in Table 1. The average baseline HR was significantly higher at high altitude than at sea level (P < 0.05), and the magnitude of the increase was in proportion to altitude. An increase in HR was altitude dependent (P < 0.05). There was no altitude-related change in mean blood pressure. The reduction of O2 saturation, alveolar PO2, and alveolar PCO2 was inversely proportional to altitude (P < 0.05).

Baroreflex Responses at High Altitude

The mean stimulus-response curve at 3,800 m showed a parallel downward shift (Fig. 2A), whereas the curve at 4,300 m shifted downward greatly (Fig. 2B) but did not parallel that at sea level. Table 2 summarizes the sigmoideal parameters describing carotid baroreflex cardiac responses at 3,800 m and at 4,300 m. There were no significant differences in the sigmoideal parameters at 3,800 m except for a reduction of minimum R-R interval (\(A_4\)); however, maximal range (\(A_1\)), slope coefficient (\(A_2\)), minimum R-R interval (\(A_3\)), and maximal gain of the curve were significantly decreased (P < 0.05) compared with the corresponding sea-level values. There was no altitude-dependent change in the centering point (\(A_3\)).

Table 1. Effect of altitude exposure on heart rate, blood pressure, O2 saturation, and partial pressure of alveolar O2 and CO2 at rest

<table>
<thead>
<tr>
<th>Altitudes</th>
<th>HR, beats/min</th>
<th>MBP, mmHg</th>
<th>O2 Saturation, %</th>
<th>Alveolar PO2, mmHg</th>
<th>Alveolar PCO2, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sea level</td>
<td>60.9 ± 3.0</td>
<td>83.6 ± 3.3</td>
<td>96.1 ± 0.5</td>
<td>103.9 ± 2.0</td>
<td>42.8 ± 1.2</td>
</tr>
<tr>
<td>3,800 m</td>
<td>71.4 ± 3.0</td>
<td>86.7 ± 2.7</td>
<td>76.2 ± 2.5*</td>
<td>48.0 ± 1.5*</td>
<td>38.1 ± 1.1*</td>
</tr>
<tr>
<td>Sea level</td>
<td>62.5 ± 3.5</td>
<td>83.7 ± 3.2</td>
<td>96.3 ± 0.8</td>
<td>100.7 ± 2.1</td>
<td>43.0 ± 1.3</td>
</tr>
<tr>
<td>4,300 m</td>
<td>80.4 ± 3.3</td>
<td>83.9 ± 2.1</td>
<td>65.4 ± 2.1*</td>
<td>42.3 ± 2.3*</td>
<td>36.5 ± 1.5*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7. HR, heart rate; MBP, mean arterial blood pressure. *P < 0.05 vs. corresponding sea-level values. †P < 0.05 vs. values at 3,800 m.
DISCUSSION

The major finding of this study was that an acute exposure to a simulated altitude of 4,300 m (partial pressure of oxygen in inspired air ($P_{O2}$) = 82 mmHg) for 60 min resulted in the reduction of the maximal gain of the carotid baroreflex cardiac response curve, but not at 3,800 m ($P_{O2}$ = 90 mmHg). Our data may be the first example of a healthy human subject to demonstrate in healthy humans that an attenuation of the baroreflex was elicited by acute exposure to high altitude.

The single change observed at 3,800 m among the parameters of the stimulus-response curve was minimum R-R intervals; a parallel downward shift of the response curve (Fig. 2A and Table 2). This vertical shift may be a result of the baroreflex-independent change (20) and suggests a central resetting of the reference due to a central summation of inputs from the chemoreceptors and/or the pulmonary mechanoreceptors caused by hypoxia-induced hyperventilation (19, 20, 27).

At 4,300 m, we observed multiple changes in the parameters compared with sea level: a greater downward shift of the baroreceptor response curve and a reduction of the range of the response, slope coefficient, minimum R-R intervals, and maximal gain of the curves (Fig. 2B and Table 2). However, the centering point of the curve did not change in either altitude. This suggests that the baroreflex was not reset in the present experiment. Thus acute exposure to an altitude of 4,300 m resulted in a reduction in the sensitivity of baroreflex control of HR and a reduction of buffering capacity against blood pressure perturbation.

The present results from the exposure to 3,800 m confirmed previous findings (1, 4, 7) in which no impairment of the carotid baroreflex cardiac response was observed during mild hypoxia (~50 mmHg of alveolar $P_{O2}$); however, at 4,300 m (42 mmHg of alveolar $P_{O2}$, Table 1), a blunted baroreflex response was observed. On the contrary, Knudtzon et al. (17) have reported no change in the baroreflex slope at 4,572 m during a 10-min exposure. This discrepancy may be explained by a difference in the duration of exposure period (60 min vs. 10 min) and in sensitivity of assessment of the baroreflex. In the earlier reports, sensitivity of carotid baroreflex was not estimated from the complete stimulus-response curve, but only estimated by a single neck suction (7) or by an average slope during neck suction (17). A wide range of the neck pressure covering from positive to negative pressures is a good method for assessing the sigmoidal logistic parameters of the response curves. Therefore, the present results may have revealed a reliable estimation for the baroreflex responsiveness to the neck chamber pressures.

Because the duration of the neck chamber pressure ramp of the present experiment was short (entire sequence lasted ~15 s), the R-R interval response may be mainly mediated by vagal mechanisms (5). This viewpoint is supported by a study by Pisarri and Kendrick (26), who reported in dogs that the vagal component of the baroreflex bradycardia was suppressed during hypoxic gas breathing in proportion to the degree of hypoxemia.

Table 2. Logistic model parameters describing carotid sinus cardiac baroreflex response at various altitudes

<table>
<thead>
<tr>
<th>Altitudes</th>
<th>$A_1$, ms</th>
<th>$A_2$, mmHg</th>
<th>$A_3$, mmHg</th>
<th>$A_4$, ms</th>
<th>Max. Gain, ms/mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sea level</td>
<td>124.3 ± 16.2</td>
<td>0.146 ± 0.016</td>
<td>−15.8 ± 2.7</td>
<td>974.2 ± 50.4</td>
<td>−4.63 ± 0.81</td>
</tr>
<tr>
<td>3,800 m</td>
<td>121.5 ± 19.9</td>
<td>0.135 ± 0.019</td>
<td>−17.2 ± 3.6</td>
<td>907.7 ± 47.0*</td>
<td>−4.06 ± 0.81</td>
</tr>
<tr>
<td>4,300 m</td>
<td>116.3 ± 13.7</td>
<td>0.161 ± 0.020</td>
<td>−18.3 ± 2.8</td>
<td>949.5 ± 42.9</td>
<td>−4.63 ± 0.97</td>
</tr>
</tbody>
</table>

Values are means ± SE; $n = 7$. $A_1$, range of the response; $A_2$, slope coefficient; $A_3$, centering point; $A_4$, minimum R-R intervals; Max. gain, maximal gain of the curve. *P < 0.05 vs. corresponding sea-level values.

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early phase of acclimatization to an altitude of 3,500 m. Also, an impairment of cardiac and vascular reflexes during lower body negative pressure at a simulated altitude (14,000 ft, 4,267 m) was suggested by Heistad et al. (14). The present results suggest that acute exposure to hypoxia attenuates vagally mediated baroreflex control of HR; however, effects of hypoxia on sympathetic component of baroreflex control of HR were not examined in the present study. It is controversial whether systemic PCO2 alters baroreflex sensitivity in humans. Cunningham et al. (4) have shown that hyperoxic hypercapnia causes a reduced sensitivity of baroreflex cardiac responsiveness, whereas Bristow et al. (1) have observed no consistent change. The effect of hypocapnia in the present experiment is uncertain.

In the preliminary experiment, we examined an effect of hypobaria on the baroreflex in an additional seven subjects who were breathing normal partial O2 gas mixture (147 mmHg P1O2, 37% O2 and 0.05% CO2, N2 balanced) during exposure to 4,300 m. There was no change in the sigmoidal parameters between sea level and this hypobaric-normoxic environment (data not shown). Thus reduced atmospheric pressure per se may not be a mechanism responsible for the reduction of the baroreflex sensitivity.

Because the relationship between R-R interval and HR is a hyperbolic function, an increase in baseline HR results in a reduction of the baroreflex gain presented by R-R interval. The maximal baroreflex gain calculated from HR converted from R-R interval was significantly (P < 0.05) reduced at 4,300 m (data not shown). This suggests that the reduction of maximal gain at 4,300 m in the present study is partly responsible for that relationship. Although our study did not define the mechanisms by which altitude reduced carotid baroreflex sensitivity, a sympathetic augmentation and a parasympathetic withdrawal during acute altitude exposure (15, 18, 29) may be involved as one of the factors, because an increase in sympathetic tone in the heart may limit the cholinergic effects on the sinus node of the heart and vice versa (6, 32).

Thus we may reasonably speculate that one of the putative causes for reduced sensitivity of carotid baroreflex cardiac response at 4,300 m involves cardiac sympathetic activation and parasympathetic withdrawal, which probably makes the sinus node less responsive to parasympathetic baroreceptor modulation. However, central inhibitory interaction between the input from the baroreceptors and chemoreceptors in the carotid body and a direct effect of hypoxia on the central nervous system cannot be ruled out because a decrease in the carotid baroreflex sensitivity has been observed in dogs exposed to hypoxia (26).

In conclusion, the present study demonstrates that acute exposure to altitude (P1O2 = 82 mmHg) resulted in a reduction of maximal gain of the carotid baroreflex cardiac response and that the reduced maximal gain was probably dependent on severity of hypoxia. The mechanisms of a reduced orthostatic response during acute altitude exposure may be, in part, explained by this phenomenon.

Potential Limitations

Neck chamber technique. The neck chamber technique is a useful tool for studying human carotid baroreflexes; however, there are some limitations. Advantages and disadvantages of this technique are mentioned in the literature (9). A high reproducibility of the responsiveness has been tested by Eckberg et al. (8) by using a device similar to that in the present study. We used the neck chamber pressure as the abscissa instead of the estimated carotid sinus pressure (the difference of mean arterial pressure and neck chamber pressure), because the neck chamber pressure was not transmitted completely to the carotid sinus (21).

Experimental protocol. The order of experiments and the order of exposure to 3,800 m and 4,300 m were not randomized, because some subjects had headache or nausea briefly after they returned to sea level from 4,300 m. To avoid the effect of these stresses on the subsequent results, we did not examine the subject in reverse order, i.e., high altitude first and then sea level.

Effect of hyperventilation. Prior hyperventilation induced from hypoxia might have an effect on subsequent baroreflex sensitivity during held expiration because respiratory rate and volume were not controlled during altitude exposure. It is beyond our speculation whether the blunted carotid baroreflex control of HR was due to a direct effect of hypoxia per se and/or a secondary effect of hyperventilation or hypocapnia induced by hypoxia.

Perspectives

The present study did not provide evidence that individuals with impairment of baroreflex control of HR during exposure to high altitude would be predisposed to orthostatic compromise. Further work in this area is certainly warranted. A reduced orthostatic tolerance during the early stage of exposure to high altitude has been reported to improve after the second week at high altitude (22, 23); thus the dysfunction of blood pressure control may recover during an adaptation process in high-altitude environments. This may be examined by a different experimental design.

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