Cardiovagal regulation during combined hypoxic and orthostatic stress: fainters vs. nonfainters

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Halliwell, John R., and Christopher T. Minson. Cardiovagal regulation during combined hypoxic and orthostatic stress: fainters vs. nonfainters. J Appl Physiol 98: 1050–1056, 2005.—We tested the hypothesis that individual differences in the effect of acute hypoxia on the carotid arterial baroreflex would determine individual susceptibility to hypoxic syncope. In 16 healthy, nonsmoking, normotensive subjects (8 women, 8 men, age 20–33 yr), we assessed orthostatic tolerance with a 20-min 60° head-upright tilt during both normoxia and hypoxia (breathing 12% O2). On a separate occasion, we assessed baroreflex control of heart rate (cardiovagal baroreflex gain) using the modified Oxford technique during both normoxia and hypoxia. When subjects were tilted under hypoxic conditions, 5 of the 16 developed presyncopal signs or symptoms, and the 20-min tilt had to be terminated. These “fainters” had comparable carotid arterial baroreflex gain to “nonfainters” under both normoxic and hypoxic conditions (normoxia, fainters: −1.2 ± 0.2; nonfainters: −1.0 ± 0.2 beats·min−1·mmHg−1, P = 0.252; hypoxia, fainters: −1.3 ± 0.2; nonfainters: −1.0 ± 0.1 beats·min−1·mmHg−1, P = 0.208). Furthermore, hypoxia did not alter carotid arterial baroreflex gain in either group (both P > 0.8). It appears from these observations that hypoxic syncope results from the superimposed vasodilator effects of hypoxia on the cardiovascular system and not from a hypoxia-induced maladjustment in baroreflex control of heart rate.

METHODS

This study received Institutional Review Board approval, and each subject gave his or her informed, written consent before participation.

Subjects

Sixteen healthy, nonsmoking, normotensive subjects (8 women, 8 men) between the ages of 20 and 33 yr participated in this study [height 175 ± 10 cm, weight 69.6 ± 13.7 kg, body mass index 22.6 ± 3.3 kg/m2 (means ± SD)]. None of the subjects was taking medications other than oral contraceptives, and none had been at altitude (>1,500 m) for at least 5 mo. All female subjects had a negative serum pregnancy test within 12 h before participation. Subjects underwent investigations on two separate days, as shown in Fig. 1. On protocol day 1, we assessed orthostatic responses using a 20-min tilt test during both normoxia and hypoxia. On protocol day 2, we assessed baroreflex control of heart rate (cardiovagal baroreflex gain) using the modified Oxford technique during both normoxia and hypoxia. Protocol days 1 and 2 were separated by between 1 and 15 days. We did not control for menstrual cycle phase and phase of oral contraceptive use. However, each protocol day includes both a normoxia and hypoxia. Protocol days 1 and 2 were separated by between 1 and 15 days. We did not control for menstrual cycle phase and phase of oral contraceptive use. However, each protocol day includes both a normoxia and hypoxia trial such that comparisons are largely made by only scant experimental evidence.

Therefore, the goal of the present study was to provide insight into cardiovascular regulation during combined hypoxic and orthostatic stress. We tested the hypothesis that individual differences in the effect of hypoxia on the arterial baroreflex would determine individual susceptibility to hypoxic syncope. We also tested the alternative hypotheses that individual susceptibility to hypoxic syncope would be determined by the degree of arterial desaturation or the magnitude of peripheral vasodilation induced by hypoxia. Data were collected as part of a larger study, part of which has previously been published (9).

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acetylene, 9.0% helium, 20.9% O2, and balance N2 for 8–10 breaths. During measurement periods, subjects breathed either room air (normoxia) or 12% oxygen in N2 (hypoxia) via a two-way nonrebreathing valve attached to a custom-built pneumatic sliding valve that allowed periodic measurement of cardiac output via an open-circuit acetylene washin method (see below). Subjects breathed through a scuba mouthpiece while nasal breathing was prevented with a nose clip. Ventilation was measured via a pneumotach (model 3700, Hans Rudolph, Kansas City, MO, and end-tidal CO2 was measured at the mouth using a respiratory mass spectrometer (model MGA 1100, Perkin-Elmer). After instrumentation, subjects underwent two 40-min measurement periods (normoxia and hypoxia) separated by a 40-min rest period as depicted in Fig. 1. We continuously recorded heart rate, beat-by-beat arterial pressure, ventilation, and end-tidal CO2 during each measurement period. We measured standard arterial pressure and cardiac output at the end of every 5 min throughout each 40-min measurement period. Subjects were supine for the first 17 min of each 40-min period, and then they were tilted 60° head-upright for 20 min. Subjects were returned to supine for the final 3 min of each 40-min measurement period or if they became presyncopal.

Cardiac output. Cardiac output was estimated by using an open-circuit acetylene washin method as developed by Stout et al. (28) and modified by Gan et al. (8). This technique was recently validated in humans vs. the direct Fick approach (14). This method allows the noninvasive estimation of cardiac output and has several advantages over conventional rebreathing techniques, particularly in hypoxia studies. Most importantly, because rebreathing is not performed, subjects are exposed to stable O2 and CO2 levels throughout the measurement. An automatic three-way sliding-valve (Hans Rudolph) on the inspiratory side allowed measurement of cardiac output without interruption of the subject’s normal breathing pattern. Under normoxic conditions, subjects breathed a gas mixture containing 0.6% acetylene, 9.0% helium, 20.9% O2, and balance N2 for 8–10 breaths. When measurements were performed under hypoxic conditions, the gas mixture was modified to include an O2 percentage equivalent to the hypoxic condition (e.g., 12% O2). During the washin phase, breath-by-breath acetylene and helium uptake were measured by a respiratory mass spectrometer (model MGA 1100, Perkin-Elmer) and tidal volume was measured via a pneumotach (model 3700, Hans Rudolph) linearized by the technique of Yeh et al. (32) and calibrated using test gas before each study. The pneumotach and valve system had a combined dead space of 24 ml. We calculated cardiac output with the method of Stout et al. (28) and Gan et al. (8) as described previously (14). Total vascular resistance was calculated as mean arterial pressure/cardiac output, and it is expressed as arbitrary units.

Protocol Day 2

The purpose of this protocol day was to assess the effects of hypoxia on cardiovagal baroreflex control of heart rate. Throughout this protocol, subjects were instrumented in the supine position for measurement of heart rate (electrocardiogram), standard arterial pressure via an automated auscultometric device (Dinamap blood pressure monitor, model 1846SX, Critikon), beat-by-beat arterial pressure via finger photoplethysmography (Finapres blood pressure monitor, model 2300, Ohmeda), arterial O2 saturation via pulse oximetry of the earlobe (Biox 3740 pulse oximeter, Ohmeda), and forearm and calf blood flows via venous occlusion plethysmography. An intravenous catheter was placed in an antecubital vein for administration of vasoactive substances for the purpose of assessing baroreflex responses. During measurement periods, subjects breathed either room air (normoxia) or 12% O2 in N2 (hypoxia) via a two-way nonrebreathing valve. Subjects breathed through a scuba mouthpiece while nasal breathing was prevented with a nose clip. Ventilation was measured via a pneumotach (model VMM-2a, Interface Associates, Laguna Niguel, CA), and end-tidal CO2 was measured at the mouth via an infrared CO2 analyzer (model 1260, Novametrix Medical Systems, Wallingford, CT). After instrumentation, subjects underwent two 18-min measurement periods (normoxia and hypoxia) separated by a 20-min rest period. We continuously recorded heart rate, arterial pressure, and ventilation during each measurement period. We measured forearm and calf blood flow during minutes 11–13, and we assessed baroreflex control of heart rate during minutes 15–18 of each measurement period.

Forearm and calf blood flow. We used venous occlusion plethysmography with mercury-in-Silastic strain gauges to estimate forearm and calf whole limb blood flow under normoxic and hypoxic conditions. During these measurements, arterial occlusion cuffs around the wrist and ankle were continuously inflated to suprasystolic pressure.
Orthostatic Stress
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RESULTS

They are expressed as arbitrary units.

Blood flow measurements every 15 s. Forearm and calf vascular resistances were calculated as mean arterial pressure/blood flow, and they are expressed as arbitrary units.

Baroreflex control of heart rate. Baroreflex responses were assessed by measuring heart rate during arterial pressure changes induced by nitroprusside and phenylephrine as developed by Ebert and Cowley and others (5, 26). During both normoxia and hypoxia, 100 μg sodium nitroprusside were given intravenously as a bolus, followed 1 min later by 150 μg phenylephrine HCl. This paradigm decreases arterial pressure ~15 mmHg below baseline levels and then increases it ~15 mmHg above baseline levels, over a short time course.

Data Analysis

Data were digitized at 250 Hz with signal-processing software (WinDaq, Dataq Instruments, Akron, OH) and analyzed offline. Baroreflex control of heart rate was determined from the relation between heart rate and systolic pressure during vasoactive drug boluses (5, 26). The slope of this relation is used as an index of reflex sensitivity. The operating point for the relation in terms of resting arterial pressure and heart rate was determined as the average values over the 5-min period immediately preceding the nitroprusside bolus. Systolic pressure was used because heart rate correlates closely with systolic pressure but not with diastolic pressure (26, 29). To perform a linear regression between heart rate and pressure, values for heart rate were first pooled over 2-mmHg pressure ranges as described previously (5, 9, 10, 26). Consistent with our approach in the past, we have restricted our analysis to the linear region of the reflex response, which appears to be the region in which the human arterial baroreflex generally operates (6, 9, 10). This approach necessitates visual selection by the investigator to identify the linear region on each individual baroreflex trial.

Statistics

Baseline variables measured during normoxia and hypoxia were compared by paired t-tests. Responses to combined hypoxic and orthostatic stress were analyzed with a two-way repeated-measures ANOVA with factors for tilt and hypoxia. Significant effects were further tested with Fisher’s least significant difference test. Comparisons between “fainters” and “nonfainters” were analyzed with either a two-way mixed ANOVA with factors for group and hypoxia or by unpaired t-test as appropriate. Differences were considered significant when P < 0.05. All values are reported as means ± SE unless otherwise indicated.

RESULTS

Cardiovascular Responses to Combined Hypoxic and Orthostatic Stress

During exposure to hypoxia, arterial saturations were reduced from 96.5 ± 0.3 to 79.9 ± 1.4% (P < 0.001). This desaturation was associated with hyperventilation characterized by a rise in minute ventilation from 6.1 ± 0.4 to 6.6 ± 0.4 l/min (P = 0.027) and fall in end-tidal CO₂ from 5.5 ± 0.1 to 5.0 ± 0.1% (P < 0.001).

When subjects were tilted under hypoxic conditions, 5 of the 16 developed presyncopal signs or symptoms, and the 20-min tilt had to be terminated. Figure 2 shows representative data from one of these individuals. On average, mean arterial pressure fell 22.8 ± 5.0 mmHg at the time when the tilt was terminated in these subjects. We defined these 5 subjects as “fainters” and the remaining 11 subjects who were able to complete the 20-min tilt under hypoxic conditions as “non-fainters.” Characteristics of the fainters and nonfainters are presented in Table 1. Although the fainters included 4 women and only 1 man, the Fisher exact test (P = 0.282) and χ² test (P = 0.281) failed to detect any sex effect.

Figure 3 shows the group average hemodynamic responses to upright tilt under normoxic and hypoxic conditions in the fainters and nonfainters. In the supine position, hypoxia increased heart rate, mean arterial pressure, and cardiac output, with no effect on total peripheral resistance in the subjects who were nonfainters. In the upright tilted position, heart rate and mean arterial pressure were no longer different between normoxia and hypoxia, but cardiac output was still elevated with hypoxia compared with normoxia in the nonfainters. Total peripheral resistance was lower in the upright tilted position with hypoxia than with normoxia. Overall, the hemodynamic responses appeared similar in the fainters compared with the nonfainters.

Effect of Hypoxia on Baroreflex Control of Heart Rate

Figure 4 shows the slope of the arterial pressure-heart rate relationship, an index of cardiovagal baroreflex gain. There were no differences between fainters and nonfainters under either normoxic (P = 0.252) or hypoxic conditions (P = 0.252), and baroreflex gain did not change with hypoxia in either group (both P > 0.8).

Effect of Hypoxia on Arterial Saturation and Ventilation

Figure 5 shows the fall in arterial saturation and rise in ventilation induced by hypoxia in the fainters and nonfainters. There was a strong tendency for arterial saturation to fall more in the fainters (~19.4 ± 3.8%) than the nonfainters (~14.5 ± 1.0%; P = 0.080), despite similar increases in ventilation compared with nonfainters (P = 0.285).

Effect of Hypoxia on Vascular Tone

Figure 6 shows the forearm and calf vascular resistance during normoxia and hypoxia in the fainters and nonfainters. Both forearm and calf vascular resistance tend to decrease during hypoxia, but the vasodilation in the forearm was more variable than in the calf and thus did not reach significance (P = 0.195). Similarly, the vasodilation in the fainters did not reach significance (P = 0.271). Whereas forearm vascular resistance was lower under both normoxic and hypoxic conditions in fainters vs. nonfainters, there were no differences in the vasodilator response to hypoxia between groups (P > 0.8 for both calf and forearm response).

DISCUSSION

The present study attempted to identify individual differences in the effect of acute hypoxia on the arterial baroreflex that might underlie susceptibility to hypoxic syncope. It appears from our observations that hypoxic syncope is due to the superimposed vasodilator effects of hypoxia on the cardiovascular system and not from a hypoxia-induced maladjustment in cardiovagal control of heart rate. We did not find any indication of a differential arterial baroreflex response to hypoxia in individuals who were susceptible to hypoxic syncope. We also failed to demonstrate any clear evidence that the vasodilator response to hypoxia is greater in susceptible individuals. How-
ever, it appears that the degree of arterial desaturation in these individuals might explain some of the differences in orthostatic tolerance during exposure to hypoxia.

**Hypoxic Syncope is a Vasovagal Response**

Early work by Henderson and Seibert (12) and Anderson et al. (1) demonstrated that vasovagal-like syncope could be produced in most individuals by having them breathe low O2 levels (<8%). Surprisingly, these early studies (12) found that some individuals will become syncopal while breathing only moderately hypoxic O2 mixtures (13–14% O2), similar to the O2 levels at altitudes of 3,000 – 4,000 m. It should be noted that these vasovagal responses occurred in supine subjects. The effect is more striking (and occurs at more modest levels of hypoxia) in upright subjects. More recent studies have documented reduced tolerance to orthostatic stress at altitude (4,000 m) and during hypoxic breathing at sea level that simulated altitude (2,500 – 4,300 m) (19, 20, 25, 27). These cases of hypoxic syncope are clearly differentiated from the effects of central nervous system hypoxia, known as hypoxic coma, in which profound central nervous system hypoxia leads to a depression of higher center functioning, producing stupor and subsequent coma (1, 12). In contrast to hypoxic coma, hypoxic syncope appears to be a form of vasovagal syncope because vasodilation, bradycardia, and hypotension are observed. Hypoxic coma occurs without these concomitant vasovagal signs. The incidence rate of hypoxic syncope among visitors to altitude remains unknown, but it is probably significant.

Early hemodynamic studies highlighted a potential role of exaggerated circulating epinephrine levels in precipitating hypoxic syncope (23, 31). In one recent study, Dinenno et al. (4) were able to obtain an arterial blood sample from a hypoxic individual at the onset of hypotension and bradycardia and found fourfold higher epinephrine than other subjects exposed to the same degree of hypoxia. This observation is consistent with the notion of exaggerated circulating epinephrine in hy-

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**Table 1. Characteristics of “fainters” vs. “nonfainters”**

<table>
<thead>
<tr>
<th></th>
<th>Nonfainters</th>
<th>Fainters</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>7 male, 4 female</td>
<td>1 male, 4 female</td>
<td>0.282</td>
</tr>
<tr>
<td>Age, yr</td>
<td>25.1±1.0</td>
<td>24.0±2.5</td>
<td>0.596</td>
</tr>
<tr>
<td>Height, cm</td>
<td>178±10</td>
<td>169±7</td>
<td>0.083</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74.2±13.3</td>
<td>59.6±9.1</td>
<td>0.044</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.4±3.5</td>
<td>20.8±2.3</td>
<td>0.161</td>
</tr>
</tbody>
</table>

Values are means ± SE.
poxic syncope. In this individual, high epinephrine was associated with progressive skeletal muscle vasodilation, but part of the hypotension may have been linked to hypoxic vasodilation of the splanchnic circulation (23, 31). In further support of this “working hypothesis,” one case report suggests that β-adrenergic blockade may prevent hypoxic syncope. (7).

Role of Sympathetic Nervous System

It has long been postulated that hypoxia impairs blood pressure regulation, increasing the incidence of orthostatic intolerance. With respect to the sympathetic nervous system, these hypoxia-associated impairments have been thought to be due to an inhibition of norepinephrine release from sympathetic nerve endings (24), a reduction in postjunctional α-adrenergic vasoconstrictor responsiveness (11), a reduction in baroreflex-mediated increases in sympathetic outflow to reductions in central blood volume and arterial blood pressure (13, 22), or an interaction between these determinants of peripheral vasoconstrictor tone. However, recent studies have demonstrated that elevated sympathetic activity does evoke norepi-
nephrine release during hypoxia (17) and that sympathetic-baroreflex gain is not impaired during systemic hypoxia in healthy humans (9). Furthermore, Dinello et al. (4) recently demonstrated that postjunctional α-adrenergic responsiveness is not blunted during hypoxia. Taken together, these observations support the notion that peripheral vasoconstrictor responses and arterial blood pressure regulation are not impaired during exposure to hypoxia in most subjects. It appears as if the vasodilator effects of hypoxia and the vasoconstrictor effects of increased sympathetic nerve activity summate at the level of the vascular smooth muscle without interference or interaction between these influences (4, 17). Within the context of the present study, we observed vasodilation during hypoxia in terms of calf, forearm, and total vascular resistance in the supine position. Subsequently, we observed vasoconstriction when we superimposed orthostatic stress on the subjects, yet total vascular resistance remained lower during orthostatic stress with hypoxia.

Role of Superimposed Vasodilation

If hypoxic syncope is the result of superimposed hypoxia-mediated vasodilation on orthostatic stress, why did we not observe any evidence that the vasodilator response to hypoxia was greater in individuals susceptible to hypoxic syncope? One possible explanation is that the vasodilation is largely occurring in the splanchnic circulation, and we focused our efforts on measuring changes in the limbs, which predominantly reflect changes in skeletal muscle vascular beds. If this were the case, however, we suspect that we would have observed differences in terms of the total peripheral resistance response to hypoxia between individuals who developed hypoxic syncope and those who did not (Fig. 3). Another possible explanation is that the vasodilation that precedes vasovagal syncope is transient or abrupt in nature and thus may have been missed by our measurements. This would be consistent with the notion of a sudden surge in epinephrine release in the individuals who developed hypoxic syncope. Finally, it is possible that the degree of vasodilation was, in fact, similar between those individuals who developed hypoxic syncope and those who did not but that the fainters are inherently less tolerant to orthostatic stress. In other words, the modest hypoxic vasodilation overwhelms an already compromised cardiovascular system’s ability to respond to orthostatic stress. Along these lines, it would have been interesting to test whether an alternative
stressor, such as passive body heating, might have equally reduced orthostatic tolerance in the same individuals. Thus we have considered several plausible explanations for why certain individuals developed hypoxic syncope while others did not, but we are not able to provide strong evidence to support any of the possible explanations. On the basis of our observations, we can exclude from the list of possible explanations a hypoxia-induced deficit in cardiovagal baroreflex regulation.

Role of Ventilation

It should not be unexpected that one of the differences between subjects who developed hypoxic syncope and those who did not was the level of arterial O2 saturation (Fig. 5). What is unexpected is that this greater degree of desaturation during exposure to hypoxia does not produce a greater ventilatory response. In fact, there was a tendency for the ventilatory response to be blunted in the individuals who developed hypoxic syncope. This raises the possibility that chemoreflex control of ventilation may be blunted in these individuals. This set of observations is in contrast with what has been suggested by others (2), that the hyperventilation associated with hypoxia produces hypocapnia-mediated vasoconstriction of the cerebral circulation and that individuals with the greatest ventilatory response are the most susceptible to hypoxic syncope.

Conclusions

We explored individual differences in the response to combined hypoxic and orthostatic stress. It appears from these observations that hypoxic syncope results from the superimposed vasodilator effects of hypoxia on the cardiovascular system and not from a hypoxia-induced maladjustment in cardiovagal control of heart rate.

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