Effect of acute exposure to 3,660 m altitude on orthostatic responses and tolerance

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Blaber, A. P., T. Hartley, and P. J. Pretorius. Effect of acute exposure to 3,660 m altitude on orthostatic responses and tolerance. J Appl Physiol 95: 591–601, 2003. First published April 25, 2003; 10.1152/japplphysiol.00749.2002.—Orthostatic reflexes were examined at 375 m and after 60 min of exposure in a hypobaric chamber at 3,660 m using a 20-min 70° head-up tilt (HUT) test. Mean arterial blood pressure, R wave-R wave interval (RRI), and mean cerebral blood flow velocity (MFV) were examined with coarse-graining spectral analysis. Of 14 subjects, 7 at 375 m and 12 at 3,660 m were presyncope. Immediately on arrival to high altitude, breathing frequency and MFV increased, and end-tidal PCO₂, RRI, RRI complexity, and the parasympathetic nervous system indicator decreased. MFV was similar in HUT at both altitudes. The sympathetic nervous system indicator increased with tilt at 3,660 m, whereas parasympathetic nervous system indicator decreased with tilt at both altitudes. Multiple regression analysis of supine variables from either 375 or 3,660 m and the time to presyncope at 3,660 m indicated that, after 1 h of exposure, increased presyncope at altitude was the result of 1) ineffective peripheral vasoconstriction, despite increased cardiac sympathetic nervous system activity with HUT, and 2) insufficient cerebral perfusion owing to cerebral vasoconstriction as the result of hypoxic hyperventilation-induced hypocapnia.

head-up tilt; heart rate variability; transcranial Doppler; spontaneous baroreflex sensitivity; cerebrovascular reactivity

The effect of high altitude, or hypoxia, on human physiology is complex, involving the cardiovascular, respiratory, and cerebrovascular systems and their associated autonomic control. As the body responds to systemic hypoxia, it increases ventilation to improve arterial oxygen saturation and attempts to redistribute blood flow to maintain oxygen delivery to the vital organs. These adjustments and adaptations start immediately on exposure; however, the interaction of the various systems may evolve over several hours, days, or months (27). Initially, with moderate to high-altitude hypoxia, equivalent to 15–10% normobaric oxygen, chemoreceptor stimulation results in an increase in ventilation (51). The cardiovascular chemoreflex response to hypoxia should decrease heart rate and increase sympathetically mediated peripheral vasoconstriction as seen with breath holding (apnea) (19, 50). However, the hyperventilation response to the same chemoreceptor stimulation results in an increase in heart rate, cardiac output, and epinephrine with little change in blood pressure (for review, see Ref. 37). The sympathetic activation is modulated by the degree of hyperventilation during hypoxia, possibly through stimulation of pulmonary afferents and respiratory alkalosis due to ventilatory induced hypocapnia (54, 55). Over several days, as the oxygen-carrying capacity of the blood improves and pH is reduced toward normal, hyperventilation decreases, resulting in a gradual increase of sympathetic nervous system (SNS) activity (26, 39).

Changes in cardiovascular control due to environmental or pathological reasons can be observed through the application of an orthostatic stress such as head-up tilt (HUT) or lower body negative pressure (46). It is generally accepted that orthostasis in normal subjects results in an initial decrease of cardiac output, slight to moderate elevated heart rate, decrease in cerebral blood flow, and slight changes in blood pressure (16, 34, 46). Despite the gravitational effects of increased blood pooling in the lower body and a plasma shift from the vascular to the interstitial space, parasympathetic withdrawal and increased sympathetic activity compensate through increased heart rate, stroke volume, and vasoconstriction (46).

Reduced orthostatic tolerance with acute hypoxemia, induced by normobaric hypoxia, has been widely documented and has been associated with an inhibition of sympathetic vasoconstriction (for review, see Ref. 46). Reduced orthostatic responses in heart rate and blood pressure have been reported (20, 36, 47), yet direct measurement of muscle sympathetic nerve activity with acute exposure to altitude showed an increase in SNS activity (48). Reduced orthostatic tolerance with acute (1 h) exposure to altitude was associated with no change (47) or a decrease (20) in total peripheral resistance with HUT. These groups (20, 47) did not observe any differences in altitude-related changes in cutaneous vasoconstriction to orthostatic stress, and it was suggested that vasodilation must have occurred in skeletal muscle and/or in the splanchnic regions of the body.

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body. A number of authors have speculated that the vasodilatory effect of epinephrine, released in response to hypoxia (37), on skeletal muscle may be responsible for this decrease in total peripheral resistance (46), dominating over the SNS vasoconstriction. Indeed, epinephrine has recently been suggested as an important factor in orthostatic intolerance under normoxic conditions (18).

As the organ of consciousness, the brain has its own system of blood flow regulation, “cerebral autoregulation,” for matching oxygen delivery (perfusion) with demand, in the face of changes in the systemic circulation. The cerebral autoregulation vessels respond to changes in blood pressure and arterial CO$_2$ and O$_2$ partial pressures (Pa$_{CO_2}$ and Pa$_{O_2}$, respectively) (33, 43), all of which are affected by altitude. If, during orthostatic stress, any combination of cerebral autoregulation, cardiovascular, or ventilatory effects result in insufficient delivery of oxygen to the brain, loss of consciousness (syncope) will occur.

During HUT, the brain is at a negative hydrostatic pressure with respect to the heart, resulting in a decrease in the perfusion pressure at the level of the brain. As well, a transient decrease in mean arterial blood pressure (MAP) at the beginning of tilt will occur. In these situations, cerebral autoregulation ensures that cerebral blood flow remains relatively constant despite fluctuations in blood pressure. With a decrease in blood pressure, cerebral vessels dilate; with an increase in pressure, they constrict. Exposure to moderate or high altitude results in both hypoxia, due to the decrease in air pressure, and hypocapnia, due to hyperventilation. These will affect cerebral blood flow because hypoxia is a vasodilator and hypocapnia is a vasoconstrictor (45). Several authors (28, 29, 53) describe the outcome of these opposing factors as a net increase of cerebral blood flow at high altitude. Although cerebral blood flow may be elevated during the acute phase of exposure to high altitude, this increase does not appear to be sufficient to maintain arterial oxygen delivery to the brain at sea level values (24, 25, 32, 57).

Cerebral syncope, or presyncope, may also occur in some subjects due to a blood pressure independent decrease in cerebral blood flow (9, 10, 23, 34). Middle cerebral artery mean blood flow velocities (MFV), used as a measure of cerebral blood flow (1), have been observed to fall during orthostatic stress while MAP was maintained (9, 23, 34). This has led to the suggestion that, during orthostatic stress, cerebral vasoconstriction rather than vasodilation may occur owing to either a sympathetic cerebral vasoconstriction that overrides compensatory vasodilation or a downward shift in the cerebral autoregulation set point (9, 10).

Clearly, the orthostatic tolerance during hypobaric hypoxia may be affected not only by changes in cardiovascular control (47) but also by the cerebrovascular response to hypocapnic hypoxia and elevated sympathetic activity. Furthermore, because limits in both the dilation and constriction of the cerebral vessels, cerebral autoregulation must still depend on the cardiorespiratory system to maintain arterial blood pressure and Pa$_{O_2}$ within this range (33, 43).

The purpose of this study was to investigate the effect of orthostasis (HUT) and altitude (3,660 m) on the interaction of cerebrovascular, respiratory, and cardiovascular control and its relation to presyncope in healthy subjects. We used noninvasive methods to evaluate changes in autonomic control of heart rate [heart rate variability (HRV)], blood pressure [blood pressure variability (BPV)] (4), and spontaneous baroreflex sensitivity (SBS) (3, 7). HRV is the most common and accepted method used to provide noninvasive indicators of the autonomic nervous system (56). Given the distribution of sympathetic and parasympathetic nervous system activity with frequency at the sinus node, indicators of parasympathetic (PNS) activity and of sympathetic (60, 61) activity, or sympathovagal balance (42), control of heart rate can be estimated. Spectral analysis of HRV from high altitude has provided results consistent with those found with traditional measures of autonomic activity: SNS activity increased over several days of adaptation (26) and SNS activity was augmented during exercise at altitude (58). In addition to cardiovascular measurements, measures of cerebral blood flow velocity, respiratory frequency, and end-tidal CO$_2$ were also determined during HUT at low (375 m) and at high altitude (3,660 m). We hypothesized that reduced orthostatic tolerance at high altitude would be associated with low autonomic indicators and high cerebrovascular sensitivity to hypocapnia.

**METHODS**

**Subjects.** Fourteen subjects (6 men and 8 women: 63.5 ± 2.6 kg, 167.9 ± 3.7 cm, 24.2 ± 1.0 yr) participated in the study. Subjects were all nonsmokers and did not ingest caffeinated or alcoholic beverages or perform heavy exercise 24 h before the tests. Each subject signed a consent form approved by the Office of Human Research (Simon Fraser University) after reading a complete description of the procedures and potential risks involved.

**Experimental procedure.** The general experimental protocol is described in Fig. 1. Each subject was observed during a HUT test, consisting of 60 min supine followed by up to 20 min of 70° HUT, in the Aerospace Physiology Laboratory (altitude 375 m) and at a simulated altitude of 3,660 m in the hypobaric chamber at the School of Kinesiology, Simon Fraser University (Burnaby, British Columbia, Canada). A tilt bed, with a footplate, was used. In the Aerospace Physiology Laboratory, subjects were instrumented in the supine position during a period of ~20 min. A number of adaptations were made when testing in the hypobaric chamber. For convenience, subjects were usually instrumented in the upright position and then tilted supine. The chamber was then closed for the ascent to the simulated altitude of 3,660 m. The ascent, at 300 m/min, took ~11 min (elapsed time 11:00).

Ten minutes of supine data were collected after the subject had been in the supine position for 30 and 60 min (19 and 50 min after arrival at 3,660 m). After the 30-min supine data collection, the subject was asked to hyperventilate to an end-tidal CO$_2$ (PETCO$_2$) of 25 Torr. This procedure was no more than 3 min in duration and was used to calculate the cerebrovascular reactivity to decreases in CO$_2$ (percent
change in cerebral blood flow velocity per Torr change in CO₂. After the 60-min supine measurement, the subject was tilted within 3 s to a 70° HUT position and remained there for up to 20 min before being returned to the supine position. Any subject who became presyncopeal during the HUT protocol was returned immediately to the supine position.

A subject was deemed to be presyncopeal if the subject indicated symptoms such as dizziness or nausea or if any of the following were observed during HUT: 1) a decrease in heart rate of >15 beats/min; 2) a decrease in systolic blood pressure (SBP) of >25 mmHg in 1 min; 3) a decrease in diastolic blood pressure of >15 mmHg in 1 min; 4) a decrease in MFV of >15 cm/s in 1 min; or, 5) a change in the Doppler velocity envelope topology similar to that described by Bondar et al. (11).

Data collection. Instrumentation was the same for measurements at 375 and 3,660 m. R wave-R wave interval (RRI) was obtained continuously from a standard three-lead electrocardiograph (LifePak-8 Cardiac Monitor, Physio-Control, Redmond, WA). Percent end-tidal CO₂ was monitored continuously via a sample line inserted into the facemask (Hans Rudolph, St. Louis, MO) using a quadrupole mass spectrometer (RAMS M100, Marquette Electronics, Milwaukee, WI) calibrated with medical-grade precision-measured gas mixtures. This was then converted to partial pressure PETCO₂ by multiplication with the ambient air pressure.

Blood pressure was obtained by the noninvasive tonometry method (NIBP 7000, Colin Medical, San Antonio, TX). Compared with intra-arterial measures, this device has been shown to provide continuous beat-to-beat blood pressure monitoring with low artifact rating and high accuracy during reactivity testing (40). To provide beat-to-beat estimates of arterial blood pressure in the supine and 70° HUT positions, the arm of the subject was supported at the level of the left ventricle. A customized arm and wrist support attached to the arm of the subject was supported at the level of the left ventricle. A customized arm and wrist support attached to the support, and the wrist immobilized so that the blood pressure wrist sensor would not move out of position during the procedure. All parameters used by the device remained within acceptable limits, as communicated by the manufacturer, throughout the experiment, and the device did not have to be reset during HUT.

MFV of the middle cerebral artery (MCA) was measured noninvasively by using transcranial Doppler (TCD) ultrasound (MultiFlow, DWL Elektronische Systeme, Sipplingen, Germany). A Doppler probe (2 MHz) was positioned over the right temporal bone window and anchored by use of a head harness so that the angle of insonation remained constant. Doppler signals from the right MCA were identified (2) and measured at a depth of 45–50 mm, and the probe was fixed in place. The same operator performed all TCD measurements.

Doppler ultrasound was used because it is the only noninvasive method that can provide beat-to-beat data on cerebral blood flow dynamics; however, it does not measure blood flow directly but instead measures flow velocity. The relationship between velocity changes measured and changes in actual cerebral blood flow depends on the diameter of the insonated vessel. An increase in diameter would result in a decrease in the velocity measured (assuming constant flow), and a decrease in diameter would have the opposite effect. The MCA is used because, as a major cerebral artery, it supplies blood to a larger portion of the brain and is not a functional component of the autoregulation system. That is, no change in diameter has been detected during tests to cerebral autoregulation (21, 52), and a number of previous studies have validated the use of TCD under a variety of conditions known to affect cerebral perfusion (22, 41). Smaller vessels downstream change diameter with autoregulation, which in turn affects flow, and hence flow velocity upstream in the MCA varies inversely with downstream resistance. For example, during hyperventilation, vasoconstriction of the autoregulation vessels results in a decrease in flow and a decrease in MFV measured by TCD.

Analog signals were recorded simultaneously at 10 kHz per channel by using a computer strip chart recorder. Beat-by-beat analysis of these data was performed off-line. All signal tracings were manually reviewed for anomalies and movement artifact. The pressure and velocity envelope tracing between the initial increases in blood pressure or velocity after successive ECG R-waves described a single beat for each beat. Any unusable blood flow velocity or blood pressure data were removed, and the time series was adjusted by interpolating new values from the two valid points surrounding the excluded segment. If >10% of any 256-beat segment required for spectral analysis was interpolated, the results were deemed invalid.

Variability and complexity. The beat-by-beat variability and fractal complexity of MFV, blood pressure, and RRI were...
evaluated by coarse-graining spectral analysis (59). This method has the ability to extract fractal and harmonic components from physiological time series (59). Previous observations of heart rate, cerebral blood flow velocity, and BPV have indicated that underlying the harmonic components analyzed by spectral analysis there is a pattern of fractal variability (6). The algorithm has been described in detail, along with a demonstration of its efficiency in extracting harmonic (linear) from fractal (complex) components (59). The total power (P_{TOT}) can be divided into fractal (P_{FRAC}) and harmonic (P_{HARM}) components. The harmonic component can be divided into two frequency regions: high frequency (>0.15 Hz) and low frequency (0–0.15 Hz). The high-frequency region is respiratory related, whereas the low-frequency region is a consequence of several factors. From the harmonic component, the total harmonic power (P_{HARM}), and the integrated power in 0.0–0.15 Hz (P_{LO}) and 0.15–0.50 Hz (P_{HI}) can be calculated.

In this study, the square root was used as a normalizing function of the harmonic power values (P_{HARM}, P_{LO}, P_{HI}) for RRI, SBP, and MFV. This gave the amplitude of the harmonic variations (A_{HARM}, A_{LO}, A_{HI}; in units of ms, mmHg, and cm/s for RRI, SBP, and MFV, respectively). In addition, because of the distribution of SNS and PNS activity with frequency at the sinus node, PHI/PTOT was used as an indicator of PNS activity and PLO/PHI was used as an indicator of SNS activity (60, 61).

The fractal component has linear scaling across a wide range of frequencies when the data are plotted as log spectral power vs. log frequency. This is what is commonly called the 1/β relationship (44, 59), where β is the positive value of the slope of the linear regression applied to these data. When the value of β is close to 1, there is a high level of complexity because the data frequently change direction toward or away from the mean. In contrast, a value of β close to 2 represents a low level of complexity with less complex changes of the measured data (59). In a less complex system, feedback control is probably dominated by a reduced number of inputs (38).

Spontaneous baroreflex slope. Recordings of RRI and SBP were analyzed for spontaneous baroreflex events (3, 7). Baroreflex events were defined by at least three consecutive beats in which the SBP and the RRI of the same, following, or preceding event (lags 0, 1, 2) beat both either increased or decreased (8). A linear regression was then calculated for each baroreflex event. The mean of all the slopes was computed for each data segment to represent the SBS. The total number of spontaneous baroreflex sequences was recorded for each 256-beat data segment, and the average number of sequences per minute was computed.

Statistical analysis. The JMP-IN statistical package (SAS Institute) was used. All cardiovascular and cerebrovascular values were calculated from 256-beat segments starting after 30 and 60 min supine and after 1 min of HUT. Respiratory data were analyzed by breath by breath and averaged over the first 2 min of each of the same data segments. Statistical analysis of these variables was performed across the HUT protocol (supine: 30th and 60th minute, and 70° HUT) and altitude (Aerospace Physiology Laboratory at 375 m, simulated chamber altitude of 3,660 m) by using a two-way repeated-measures analysis of variance (ANOVA). A two-way ANOVA was also used to compare the effects of hyperventilation (eupnea, hyperventilation) and altitude (375 m, 3,660 m) on heart rate, blood pressure, and cerebral blood flow velocity. If main effects or interactions (P < 0.05) were detected, subsequent post hoc analysis using a Student-Newman-Keuls test was performed (P < 0.05). All data are given as means ± SE.

Subject supine ventilatory, cardiovascular, and cerebrovascular 30-min data at 375 and 3,660 m were compared with their times to presyncope at 3,660 m to determine significant pre-HUT predictors of orthostatic intolerance. A mixed stepwise multiple regression, which alternated forward and backward steps, was used. It included the most significant term that satisfied the probability to enter (0.250) and removed the least significant term satisfying the probability to leave (0.100). Terms were removed in order of least significance (backward steps) until the remaining terms in the model were significant. At this point, the stepwise process would change to the forward direction, bringing in terms that most improved the fit. When terms were added, they were checked for collinearity with existing terms in the model. Terms with a correlation coefficient with an existing term in the model >0.85 were excluded as well as terms with a variance inflation factor >10. Two criteria were used for selecting the best model: the Mallows’s Cp criterion (Cp) and Akaike’s information criterion. The model where the calculated Cp first approached the number of terms entered into the model and which had the smallest value of Akaike’s information criterion was considered the best. All regression coefficients are quoted as the adjusted r², which uses the degrees of freedom in its computation, for comparison over models with different numbers of parameters.

RESULTS

Incidence of presyncope. The increase in simulated altitude to 3,660 m in the hypobaric chamber caused an increase in the total number of subjects, from 7 to 12, who reported signs of presyncope and/or had heart-rate, blood pressure, or cerebral blood flow values indicative of presyncope during 70° HUT (Table 1). One subject who was presyncopal in the Aerospace Physiology Laboratory (375 m) was not presyncopal at 3,660 m. All the remaining subjects who were presyncopal at 375 m were presyncopal earlier in HUT at 3,660 m. The average time spent in HUT was greater (P < 0.001) at 375 m (15.1 ± 1.6 min) compared with 3,660 m (10.6 ± 1.5 min).

Table 1. Subject physical characteristics and times to presyncope at 375 and 3,660 m

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>375 m Presyncope Time, min:sec</th>
<th>3,660 m Presyncope Time, min:sec</th>
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<tr>
<td>1</td>
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<td>23</td>
<td>158</td>
<td>52</td>
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<td>22</td>
<td>161</td>
<td>55</td>
<td>2:00</td>
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</table>

F, female; M, male.
**MFV.** MFV and MFV-β decreased with HUT (Fig. 2). At 30 min, MFV was higher at 3,660 m compared with at 375 m. By 60 min and during HUT, MFV was similar at both altitudes (Fig. 2). MFV-β decreased (i.e., increase in MFV complexity) from supine to HUT at 375 m but not at 3,660 m (Fig. 2).

**MAP.** MAP was unaffected by altitude and was not reduced after 1 min of HUT compared with measurements immediately before HUT (Fig. 3). MAP-AHI (not shown) was reduced (*P < 0.05) at 3,660 m (1.41 ± 1.88 mmHg) compared with 375 m (5.74 ± 1.87 mmHg). MAP-ALO increased from supine to HUT; however, the increase was greater at 375 m compared with at 3,660 m (Fig. 3).

**RRI.** Overall, RRI decreased with altitude (*P < 0.001) as well as with HUT (*P < 0.001) (Fig. 4). Mean RRI was lower in the supine (30 and 60 min) and HUT positions at 3,660 m compared with at 375 m. At both altitudes there was a decrease with HUT (Fig. 4). RRI total power, fractal power, AHARM (not shown), and AHI (Fig. 4) at 3,660 m showed similar effects as mean RRI with tilt and altitude (Fig. 4). The SNS indicator increased with HUT only at 3,660 m (Fig. 4, *P < 0.001). The PNS indicator decreased with HUT at both altitudes (Fig. 4, *P < 0.001). Overall, the spectral exponent, β, increased with tilt (30 min: 1.15 ± 0.08; HUT: 1.57 ± 0.08, *P < 0.05) and altitude (375 m: 1.04 ± 0.06; 3,660 m: 1.3 ± 0.06, *P < 0.001), indicating a decrease in the complexity of heart rate control.

**Spontaneous baroreflex.** SBS was affected by both altitude (*P < 0.001) and HUT (*P < 0.001) with a significant altitude by tilt test interaction (*P = 0.0002) (Table 2). The supine SBS increased from 30 to 60 min at 375 m but not at 3,660 m. Supine SBS at altitude was close to one-half its 375-m value. During HUT, at both 375 and 3,660 m, SBS decreased to a similarly low value (Table 2). No difference was observed in the number of sequences per 256 beats over all conditions (Table 2). Main effects (*P < 0.05) but not interactions...
for altitude and the tilt test on the number of sequences per minute were observed (Table 2). Overall, the sequence rate increased from 9.5 ± 0.5 min⁻¹ at 375 m to 11.6 ± 0.5 min⁻¹ (P = 0.011) at 3,660 m. The sequence rate also had an overall decrease from 30 min (10.3 ± 0.6 min⁻¹) to 60 min (8.3 ± 0.6 min⁻¹) supine and an increase to 12.4 ± 0.7 min⁻¹ during HUT.

Respiratory changes. There was a main effect for breathing frequency (fB) with altitude but not with the tilt test (Table 2). The fB increased from an average of 12.5 ± 0.3 breaths/min at 375 m to 13.9 ± 0.3 breaths/min at 3,660 m (P < 0.01). There was not an interaction between the tilt test and altitude. PETCO₂ decreased with altitude (P < 0.001) and from supine to HUT (P < 0.001). There was no tilt test-by-altitude interaction (Table 2).

Responses to hyperventilation. The response of MFV to a decrease in PETCO₂ was found to increase from 2.7 CRU [cerebrovascular reactivity units: (% change MFV/1Torr of CO₂)] at 375 m to 5.0 CRU at 3,660 m (P < 0.01). Heart rate increased with hyperventilation at low and high altitudes (Table 3). Despite a higher baseline heart rate at 3,660 m, heart rate during hyperventilation was not different between the two altitudes. Supine MAP was not affected by hyperventilation at either low or high altitude (Table 3). MFV was reduced with hyperventilation, but, similar to heart rate, this value was not different between 375 m and 3,660 m despite a higher 30-min MFV at high altitude (Table 3).

Physiological associations with presyncope. At 375 m, there were equal numbers of presyncopal (n = 7) and nonpresyncopal (n = 7) subjects. Gender distribution, height, and weight were not different between the two groups. A two-way repeated-measures ANOVA, with the presyncopal and nonpresyncopal categories nested within subjects, was used to determine differences between the cardiorespiratory and cerebrovascular variables after 30 and 60 min supine and during HUT at 375 m. The only differences found between the two groups were in the low-frequency components of RRI and BPV. Over all conditions, the nonpresyncopal subjects had higher (P = 0.039) low-frequency variability (RRI-ΔLO = 21.8 ± 3.7 ms) compared with the presyncopal subjects (RRI-ΔLO = 9.8 ± 3.9 ms). MAP-ΔL0 was not different in nonpresyncopal and presyncopal subjects in the supine position (30 and 60 min); however, with HUT, MAP-ΔL0 increased (P = 0.001) in the nonpresyncopal but not the presyncopal group. Non-presyncopal MAP-ΔL0 was significantly greater (P = 0.019) than presyncopal MAP-ΔL0 with HUT (Fig. 5).

A similar test could not be performed at altitude because there were only two subjects who did not become presyncopal during 20 min of HUT. To test the hypothesis that cerebrovascular, ventilatory, and cardiovascular interactions are important in susceptibility to presyncope at altitude, a multiple-regression analysis was performed using the 375 and 3,660 m supine data from the subjects who were presyncope at 3,660 m. Because of difficulties in the data collection with some of the subjects just before HUT at 3,660 m, we chose to use the data collected when the subjects were 30 min supine (Fig. 1, Sup-1) to maximize the physiological data available. On the basis of our hypotheses and the current literature on syncope and responses to altitude, the following terms were entered

<table>
<thead>
<tr>
<th>Table 2. Effects of tilt and altitude on spontaneous baroreflex variables</th>
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<td>375 m Altitude</td>
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<tr>
<td>30 min</td>
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<td><strong>Baroreflex</strong></td>
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<td>Seq rate, min⁻¹</td>
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<td><strong>Respiratory</strong></td>
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<td>fB, min⁻¹</td>
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<td>PETCO₂, Torr</td>
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Values are means ± SE. HUT, head-up tilt; SBS, spontaneous baroreflex sensitivity in number of sequences per 256 beats (seq/256) and number of sequences per minute (seq rate). Respiratory variables: breathing frequency (fB) and partial pressure of end-tidal CO₂ (PETCO₂).

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<th>Table 3. Effects of altitude and hyperventilation on HR, MAP, and MFV</th>
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<tbody>
<tr>
<td>375 m Altitude</td>
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<tr>
<td>Eupnea</td>
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<tr>
<td>HR, beats/min</td>
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<td>MAP, mmHg</td>
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<td>MFV, cm/s</td>
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Values are means ± SE. HR, heart rate; MAP, mean arterial blood pressure; MFV, middle cerebral artery mean flow velocity. *Significant altitude (375 m, 3,660 m) main effect; †significant ventilation (eupnea, hyperventilation) main effect; ‡significant altitude by ventilation interaction with post hoc analysis (§different from eupnea; ¶different from 375 m).
into the multiple-regression model: MFV, MFV-H9252, MAP, PETCO2, CO2 reactivity, RRI, PNS, SNS, and RRI-H9252.

By use of a mixed stepwise multiple regression, these terms were entered into, or removed from, the model. The results from these analyses are presented in Fig. 6. Of the data from 375 m, MFV, CO2 reactivity, SNS, and fB were found to be the most significant predictors of presyncope at 3,660 m (Table 4). Subjects who had lower MFV and SNS activity and higher CO2 reactivity and fB at low altitude were the fastest to reach conditions of presyncope at high altitude. Of the supine data collected at 3,660 m, SNS, PNS, PETCO2, and RRI-H9252 were found to be the most significant predictors of presyncope at 3,660 m (Table 4). After 20-min exposure to 3,660 m, subjects with lower SNS and PNS activity, lower PETCO2, and higher RRI-H9252 were the fastest to reach conditions of presyncope during HUT after 60-min supine exposure to high altitude.

DISCUSSION

The aim of this study was to investigate the dynamics of acute cardiorespiratory and cerebrovascular adaptations in the first few hours of exposure to hypobaric hypoxia and their relationship to decreased orthostatic responses (20, 36, 47) and tolerance (47). The major finding of this study was that, along with previously implicated autonomic factors, ventilatory interaction with cerebrovascular control played a significant role in rate of onset of presyncope at altitude: subjects with lower resting MFV and PETCO2 and higher CO2 reactivity had lower orthostatic tolerance at altitude.

Cerebrovascular. As expected, we observed a decrease in PETCO2 with exposure to high altitude due to increased ventilation, as indicated by the increase in fB. There was also a further decrease in PETCO2 with tilt that was the same at both high and low altitude. The decrease in MFV commonly observed on tilt has previously been found to be highly correlated with this decrease in PETCO2, and cerebral vasomotor reactivity to CO2 (5, 15). In this study, reactivity to a decrease in CO2 was almost doubled at 3,660 m compared with the control at 375 m, consistent with previous work by Jansen et al. (28), who found an increase of 1.7 when comparing sea level with 4,243 m altitude. MFV was not secondarily affected by blood pressure because MAP was constant overall under all eucapnic and hyperventilation conditions (Table 3). These reactivity values may have been inflated because they were calculated after only 25 min of exposure to 3,660 m altitude when MFV was high, whereas, at 50 min when HUT took place, MFV was not different from 375 m. Although the significance of this increase in cerebral reactivity should be viewed with caution, the CO2 reactivity, when corrected for supine MFV just before HUT, would still be increased by ~1.4, because eupneic PETCO2 was significantly lower at 3,660 m. Despite the effects of reduced PO2 on the cerebral vasculature with altitude, the cerebral vessels were more sensitive to decreases in PCO2 compared with low altitude. This may be due to an interaction between the effects of PO2 and PCO2 at altitude; compared with low altitude, hyperventilation-induced hypocapnia at high altitude is associated with a larger increase in blood oxygen content.

We observed only a transient, 12% increase in cerebral blood flow velocity after 20 min of exposure to hypobaric hypoxia at 3,660 m. After 50 min of exposure, MFV returned to low-altitude levels (Fig. 2).
Many studies have shown similar increases in cerebral blood flow at the onset of hypoxia (12, 57) as well as after several hours of exposure (53); however, we are not aware of a single study that has systematically observed MFV over several hours. Because MFV was not measured past 2 h, the decline in MFV at 1 h before the tilt may represent a previously unreported transient decrease, possibly associated with the time course of ventilatory adaptation to hypoxia and the interaction of ventilation with cerebral blood flow. During hypoxia, the increase in cerebral blood flow is smaller under hypocapnic conditions compared with normocapnic conditions (32). With ascent to altitudes over 3,000 m (51), PaO2 drops below 60 Torr (12), which produces an acute increase in ventilation. This increase in ventilation peaks within 15 min of exposure and slowly declines over several hours before increasing to a plateau over a number of weeks (51). It is possible that the significant effects seen here with respect to MFV and presyncope may be confined to the time over which we conducted the HUT test.

Similar changes in spectral analysis components in cerebral blood flow to HUT were observed at both 375 and 3,660 m with one exception, MFV-β. The expected decrease in MFV-β with HUT (6), and hence an increase in the complexity of cerebral blood flow velocity, was observed at 375 m but not at 3,660 m (Fig. 2). The fractal component represented by MFV-β is thought to be related to the complexity of the overall blood flow velocity variability. An increase in the number of mechanisms involved with cerebral blood flow variability during orthostatic stress is a normal response. That is, under normal resting conditions, the number of mechanisms involved with cerebral blood flow regulation is minimal (e.g., blood pressure, PCO2, and PO2) because blood pressure is well regulated and maintained at a level optimal for cerebral perfusion. At high altitude, the lack of change in β with HUT may indicate that the number of mechanisms involved with autoregulation was not increased. It is possible that reduced PACO2 due to hypoxic hyperventilation impaired local cerebral vasomotor control during HUT. A blunted vasomotor response to hypoxia could lead to a reduced ability to react to changes in blood pressure and increased susceptibility to presyncope during orthostatic stress.

The addition of CO2 to inspired air during HUT has also been found to delay the onset of presyncope in susceptible subjects (5), suggesting that the effect of CO2 on MFV may be a moderating factor of presyncope (5). Similar effects could be seen in the responses of our subjects. At altitude where hyperventilation significantly reduced PETCO2, the incidence of presyncope increased and the time to presyncope decreased from low altitude in those subjects who were presyncopal at both low and high altitude.

Cardiovascular. The effect of HUT at altitude on autonomic nervous control of the heart is shown by changes in the spectral components of RRI (Fig. 4) and reduced spontaneous baroreflex sensitivity (Table 2). Mean RRI was significantly decreased with altitude and tilt. Total power and the high-frequency component of RRI (RRI-PTOT, RRI-AHI) were also significantly reduced. These, as well as the significant decrease in parasympathetic (PNS-indicator) and increased sympathetic activation (SNS-indicator) with HUT show that, with altitude, autonomic influences on the sinoatrial node of the heart are shifted toward more sympathetic and less parasympathetic tone. Other authors have also found increased sympathetic activity during high altitude through direct measurement of sympathetic nerve activity via microneurography (17, 30) and HRV (26).

Spectral analysis of heart rate in a variety of physiological settings has been shown to provide indicators of PNS and SNS activities. This method relies on the respiratory frequency residing above 0.15 Hz. Although we were not able to measure ventilation in these subjects, an attempt was made to control this variable (56) by requesting that the subjects breathe at 15 breaths/min (0.25 Hz). Analysis of HRV revealed a frequency peak above 0.15 Hz in all subjects. Depth of breathing will also influence HRV, with HRV increasing with tidal volume. We did not measure tidal volume, but it could be assumed that at 3,660-m altitude tidal volume was increased. This would have had the effect of increasing HRV in the respiratory region. Because RRI-AHI was found to decrease with altitude, this decrease may have been underestimated, resulting in an overestimation in PNS and underestimation of SNS activity. In normal subjects, a change from supine to standing causes a shift to greater SNS over PNS regulation of cardiac function with a corresponding increase in sympathovagal balance, PLO/PHI (42). HRV analysis, although a recognized technique for autonomic assessment (56), is still an indirect method.
and therefore may not be as sensitive as direct measurements. This is most likely reflected in our inability to detect the shift to higher cardiac SNS vs. PNS activity during HUT at 375 m.

There was an overall decrease in RRI complexity from low to high altitude (increased β), as well as the expected decrease with tilt (4, 13, 14). It has been proposed that RRI-β represents the complex interactions of different nervous as well as local metabolic and humoral factors. Because β is inversely related to complexity, an increase is indicative of less complex interactions of autonomic nervous control mechanisms over heart rate during acute exposure to high altitude as well as with tilt. Dramatically reduced parasympathetic control with both altitude and tilt may be the reason (Fig. 4).

In the supine position, SBS, RRI, and RRI spectral power values showed significant decreases with acute exposure to 3,660 m altitude with no significant difference between 375 m and 3,660 m values during HUT. Supine SBS was reduced at altitude but number of sequences per 256 beats was unchanged, and the activation rate (sequences/min) was greater, at 3,660 m (Table 2). This is evidence of an active arterial baroreflex with reduced control of BPV at altitude. Although MAP did not decrease in the first few minutes of HUT, there was an increase in the MAP low-frequency component (MAP-ALO) at both altitudes. However, this increase in MAP-ALO with HUT was less at high altitude (Fig. 3). Low-frequency variation in blood pressure is thought to be related to sympathetic regulation and has been found to be reduced in patients with peripheral sympathetic neuropathy (4). Reduced MAP-ALO during HUT at 375 m was also associated with presyncope subjects (Fig. 5). Note the similarity between Fig. 5 (presyncope vs. nonpresyncope) and Fig. 3 (3,660 vs. 375 m). As well, presyncope at 375 m was associated with an overall lower RRI-ALO. This reduction of R-R variability to altitude and decreased MAP variability in response to tilt at high altitude, despite increased cardiac SNS activation, represents a blunting of autonomic cardiovascular control.

Multiple regression analysis. The individual cerebrovascular and cardiovascular components strongly suggest that, after 1 h of hypocapnic hypoxia, cerebral blood flow and cardiovascular responses to HUT are attenuated. These may be contributing factors to increased incidence of presyncope at high altitude. It was not possible for direct comparison of presyncope and nonpresyncope groups at high altitude because of this high incidence of presyncope. However, an analysis through multiple regressions may provide insight into the possible contributing factors to presyncope.

We used information from data recorded after the subjects were supine for 30 min rather than information from the HUT position. These data represent the baseline physiological state of each subject. Two comparisons were made: one from 375 m and one from 3,660 m (Fig. 6). The former was conducted to determine which factors associated with the transition to altitude were responsible for presyncope. The latter was performed to indicate which factors after 30 min of adaptation were still associated with presyncope.

The SNS indicator was common to both analyses, third and first in level of significance at 375 m and 3,660 m, respectively (Table 4). In both cases, the effect was positive with higher levels of sympathetic activity associated with longer times to presyncope. This result is consistent with the hypothesis that presyncope during acute altitude exposure was related to ineffective SNS regulation of blood pressure (47). However, our analysis revealed other precipitating factors.

Analysis of low-altitude data indicated that three other factors were important: MFV, CO2 reactivity, and Fb (Table 4). MFV was positively correlated whereas CO2 reactivity and Fb were negatively correlated with presyncope. A comparison of low and high altitude revealed significant changes in all three. Consistent with our hypothesis that the hypocapnia associated with hypoxic hyperventilation blunts the cerebrovascular response to hypoxia, subjects at low altitude with higher supine resting MFV and lower CO2 reactivity and Fb had the longest times to presyncope at high altitude. Previous research has shown that PETCO2 may play a moderating role in the onset of presyncope through elevation of MFV at the onset of HUT (5). Similarly, in our subjects, a higher initial MFV before going to altitude was associated with longer times to presyncope. With the decrease in PETCO2 at high altitude due to hyperventilation, a greater low-altitude sensitivity of cerebral blood flow to decreases in PACO2 coupled with higher initial respiratory frequency would have contributed to shorter times to presyncope.

Although interindividual differences in absolute values of MFV with respect to altitude and the HUT test are minimized in a repeated-measures ANOVA design, this is not the case when performing multiple regression analysis. Of major concern was the possibility that anatomic differences in vessel diameter might bias the results. Although MCA diameter could not be measured, it is not unreasonable to assume that the size of a subject may be associated with the diameter of the MCA and thereby influence the absolute value of MFV. No correlation of height or weight with MFV (all P > 0.4 and r < 0.5) was present with these subjects. We also calculated cerebrovascular reactivity as a percent change of MFV from eucapnia to hypocapnia.

At high altitude, PNS activity, the cardiovascular complexity estimate, RRI-β, and PETCO2 were found to be important factors. The first two, like the SNS indicator, are related to autonomic nervous system regulation of cardiovascular homeostasis (4, 14, 31, 35, 49) associated with orthostatic tolerance. Normal responses to orthostatic stress involve PNS withdrawal to increase heart rate and SNS activation to increase heart rate and peripheral vasoconstriction. These mechanisms serve to maintain MAP. If PNS activity is low and SNS activity high before the orthostatic stress, there is less cardiovascular reserve for increasing heart rate and vasoconstriction. Although MFV was an initial input to the multiple regression, unlike at low altitude, it was not present in the final model. Instead,
PETCO2 was found to be a significant contributor to presyncope. The variable PETCO2 is related to MFV and two other low-altitude predictors, fB and CO2 reactivity. A higher PETCO2 would be associated with lower fB and CO2 reactivity and higher MFV.

Of the two multiple-regression analyses, the data from 375 m when applied to the nonpresyncope subjects gave the longest time to presyncope estimates (Fig. 6). The lower estimate of presyncope time for these same subjects when using the data from 3,660 m may indicate that, by 30 min, the results at altitude were influenced by the individual differences in the rates and magnitude of adaptation to altitude in the presyncope subjects. The significant variables at 375 m give a strong indication of the components involved with susceptibility to presyncope at altitude, whereas the analysis at 3,660 m may give insight into the acute adaptive changes that occur at altitude and their influence on orthostatic tolerance.

We further investigated the importance of the interaction of these variables on our results by performing the data analysis with respiratory data and then cerebral blood flow data removed. The latter would be similar to the study by Sagawa et al. (47). When ventilatory parameters were removed (PETCO2 and fB) from the low-altitude analysis (Table 4), no significant multiple regression was found. This would suggest that low-altitude baseline cardiorespiratory and cerebrovascular interaction plays a major role in the susceptibility to presyncope after 1 h of exposure to 3,660 m. When high-altitude baseline data were examined, significant multiple regression was found when ventilatory or ventilatory and cerebrovascular data were removed (Table 7). MFV replaced PETCO2 as a contributing variable when ventilatory data were removed, confirming the significant interaction of ventilation and cerebral blood flow regulation on orthostasis at altitude. Finally, when both ventilatory and cerebrovascular components were removed, a significant regression still remained. The level of autonomic activity (SNS and PNS), as previously reported (47), and cardiovascular complexity before HUT remained strong determinants of orthostatic tolerance.

In conclusion, these results highlight the fact that syncope is a multifactor event. Any one of a number of physiological factors can trigger symptoms of presyncope; however, a number of associated factors may modify the rate at which presyncope occurs. Acute exposure to high altitude increases the interaction of factors that contribute to decreased orthostatic tolerance. The increased ventilation and reduced PETCO2 resulted in hypoxic hypocapnia and a possible insufficient cerebral oxygen perfusion. Furthermore, at altitude there was an observed withdrawal of parasympathetic activity and a blunted sympathetic response to HUT; these effects may have also been exacerbated by the interactive effects of hypoxia and hypocapnia on cardiovascular control.

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DISCLOSURES

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