Initial orthostatic hypotension is unrelated to orthostatic tolerance in healthy young subjects

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The key question arises: are individuals who experience more IOH also more prone to syncope? To address this question, cardiorespiratory and cerebrovascular responses associated with IOH were monitored continuously following standing and compared with those responses leading up to and during presyncope as provoked by an orthostatic tolerance test combining head-up tilt and progressive lower body suction. Since individual variability in orthostatic tolerance may be partly determined by vasoconstrictor reserve (6), we indirectly examined whether a diminished vasoconstrictor capacity underlies both pronounced IOH and a tendency to faint during the common symptoms of light-headedness, dizziness, and nausea upon standing. These symptoms are characterized by their time of onset (5–10 s after standing up) and short duration (disappearance within 30 s), and they occur especially following standing from prolonged supine rest (44). Indeed, this initial orthostatic challenge of standing represents a critical time in which cerebral hypoperfusion and syncope may occur and therefore an important period in which homeostatic mechanisms must operate properly. Yet, cerebral autoregulation lags by ~10 s (54), and blood pressure is not fully restored until ~30 s after standing (39). It has been reported that initial orthostatic hypotension (IOH) is a frequent cause of orthostatic intolerance (51); however, because monitoring of beat-to-beat blood pressure is necessary for the objective assessment of IOH, a procedure normally unavailable in routine clinical assessment, detailed assessment of IOH and related symptomatology has not been clearly established (51).

Symptoms and loss of consciousness before impending syncope are fundamentally due to cerebral hypoperfusion (49). Continuous tracking of cerebral blood flow (CBF) velocity by transcranial Doppler ultrasound, and oxygenation by near-infrared spectroscopy, has contributed to further understanding of the cerebrovascular adjustments to postural stress; e.g., arterial blood pressure does not necessarily reflect the cerebrovascular phenomena associated with syncope (49). It is not known, however, if the IOH associated with standing is related to the occurrence of syncope (51). The importance of this question is apparent in the initial diagnosis of orthostatic hypotension; that is, persons with frequent orthostatic hypotension and related syncopal symptoms, which normally occur when resuming the upright position, are often referred for clinical assessment using upright tilt as a means to reproduce the symptoms associated with the suspected vasovagal syncope (16). Despite this apparent linkage between IOH and syncope, it should be noted that the hemodynamic alterations associated with IOH and syncope are likely to differ. For example, IOH differs from general orthostatic hypotension in that decreases in blood pressure are immediate and temporary, due to a mismatch between arterial inflow and outflow as seen by the large drop in systemic vascular resistance and an increase in cardiac output (51). The speed and magnitude of the fall in blood pressure exceed baroreflex control adjustments of vascular resistance. In contrast, syncope during prolonged orthostatic stress is reported to be dependent on the neural vasoconstrictor reserve (6). In addition, excessive hyperventilation and related cerebral vasoconstriction during orthostatic stress may lead to a reduction in orthostatic tolerance (12, 31).
prolonged orthostatic stress. Since IOH reflects immediate and temporary adjustments, compared with the sustained adjustments during orthostatic stress, it would seem unlikely that the severity of IOH would be unrelated to orthostatic tolerance expressed as time to presyncope. Surprisingly, this issue has not been previously addressed. Numerous authors have reported that hyperventilatory-induced hypocapnia leads to a reduction in cerebral perfusion at presyncope in patients with orthostatic intolerance (12, 31); therefore, we also anticipated that, because of the sustained nature, such hyperventilation and related reductions in CBF would further exacerbate imminent syncope in otherwise healthy individuals. In contrast, because of the transient nature of IOH and related time course of action of hypocapnia on the cerebrovascular bed (53), we reasoned that such hyperventilation would not have a major influence on cerebral perfusion.

METHODS

Forty-six apparently healthy individuals ([24 men; 22 women] aged 25 ± 5 yr (mean ± SD); body mass index (BMI) 24.4 ± 3.4 kg/m²] volunteered for this study, which was approved by the Human Ethics Committee of the University of Otago and conformed to the standards set by the Declaration of Helsinki. Eight of these subjects (4 men, 4 women) were used as a separate subgroup to verify the use of noninvasive beat-to-beat blood pressure (BP) and end-tidal gases (see Validation of noninvasive beat-to-beat BP and end-tidal PCO₂). Subjects were informed of the experimental procedures and possible risks involved in the study, and written informed consent was obtained. Subjects were not taking any medication, all were nonsmokers, and none had any history of syncope, or cardiovascular, cerebrovascular, or respiratory diseases. The majority of the subjects were recreationally active, typically engaging in low-intensity (e.g., walking) and moderate-intensity (e.g., jogging, stationary bike) aerobic activities (2–3 days/wk); none were competitive athletes. None of the subjects had been previously clinically diagnosed with IOH, and none of them reported frequent recurrent episodes of IOH and/or related symptoms in their daily lives.

Experimental design. Subjects were instructed to abstain from exercise, alcohol, and caffeine 12 h before, and to not eat a heavy meal 4 h before experimental testing. Subjects attended the laboratory on two occasions. The first was to familiarize with the physical maneuvers (tilt table and lower-body negative pressure) and related experimental apparatus. The second visit was for the main experimental testing, which was conducted at the same time of day, at least 2 days later. The room temperature was maintained between 22 and 24°C.

Measurements of CBF velocity, cerebral oxygenation, arterial blood pressure, and end-tidal gases. During each session CBF velocity, cerebral oxygenation, arterial BP, end-tidal carbon dioxide partial pressure (PETCO₂), and electrocardiography (ECG) were recorded continuously. Blood flow velocity in the right middle cerebral artery (MCAv) was measured using a 2-MHz pulsed Doppler ultrasound system (DWL Doppler, Sterling, VA). The Doppler probe was maintained in position, at a fixed angle, using a commercial headpiece. Cerebral oxygenation was monitored using a commercially available near-infrared spectroscopy system (NIRO-200; Hamamatsu Photonics KK; Hamamatsu, Japan). A probe holder containing an emission probe and detection probe was attached at the right side of the forehead with a distance of 5 cm between the probes, as previously described (29). Beat-to-beat BP was measured by finger photoplethysmography (Finapres Medical Systems, Biomedical Instruments) or, in an additional subgroup (n = 8), intra-arterially (see Validation of noninvasive beat-to-beat BP and end-tidal PCO₂). In addition, following 5–10 min of supine rest, manual BP recordings were intermittently used to confirm the accuracy of the finger photoplethysmography measurements; if the BP at baseline differed markedly between the manual and finger photoplethysmography, the finometer cuff was replaced (or, if needed, the hand was warmed) until adequate agreement between the two methods was apparent. During both the supine rest and stand, subjects were instructed to keep their hand at waist level. Before each experiment and during each maneuver, we confirmed that an adequate arterial pulse pressure profile was evident. If movement artifact or loss of signal in the Finometer BP waveform did occur, the experiment was repeated. The Finometer uses a height correction system, whereby any changes in vertical displacement of the finger cuff relative to the heart are corrected for by a reference probe placed on the chest at the fourth intercostal space in the midclavicular line (heart level), and reconstructed brachial arterial pressure is reported. Although the influence on reconstruction of the brachial artery pressure (from the finger pressure) on altering the BP recording is clear, our manual confirmation and comparison with intra-arterial measurements (see RESULTS) would indicate that there is little drift. Stroke volume (SV) and cardiac output (Q) were calculated from the blood pressure waveform obtained from the finger photoplethysmography using the Modelflow method, incorporating age, sex, height, and weight (BeatScope 1.0 software; TNO TPD; Biomedical Instruments). As used in other studies, MCAv and BP were expressed as the percentage change from this baseline to enable the same relative comparisons and to reduce interindividual variability unrelated to the experimental manipulation. Because the Modelflow method was not validated against a gold standard reference, relative changes of both Q and total peripheral resistance (TPR) are presented in arbitrary units (aU).

Participants breathed through a respiratory mask (Hans-Rudolph 8980, Kansas City, MO) attached to a one-way nonrebreathing valve (Hans-Rudolph 2700). PETCO₂ was sampled continuously and measured using a gas analyzer (model CD-3A, AEI Technologies, Pittsburgh, PA). Heart rate (HR) was also recorded using three-lead electrocardiogram via a Bio Anp (model ML132, ADInstruments, Colorado Springs, CO). All data were sampled continuously at 200 Hz using an analog-to-digital converter (Powerlab/16SP ML795; ADInstruments) interfaced with a computer and displayed in real time during testing. Data were later analyzed using commercially available software (Chart version 5.4.2, ADInstruments). Cerebrovascular resistance (CVR) was calculated as mean arterial pressure (MAP) divided by MCAv. Pulsatility index was calculated as the difference between the systolic and diastolic MCAv divided by the mean MCAv (10).

IOH. Following between 25 and 30 min of supine rest, participants quickly (within ~3 s) assumed a standing posture on verbal command, which they maintained for 3 min; t = 0 was taken to be the moment they started rising from the supine position. The bed was adjusted for each individual so that it was at a suitable height to ease their transition from supine to standing. Subjects were asked to sit up, swing their legs round, and stand up in one smooth motion. They were also instructed to not use their left hand for support as they stood up, so as to avoid disturbing the Finometer recording. During the stand participants were requested not to speak and to breathe normally and were advised to remain as still as possible to reduce any influence of the skeletal muscle pump. IOH associated with standing was defined as a decrease in systolic blood pressure (SBP) of >40 mmHg and/or a decrease in diastolic blood pressure (DBP) of >20 mmHg within the first 15 s of standing (51). As described previously (52), two main phases of each orthostatic response were considered: the initial response (during the first 30 s) and the “steady-state” alterations (2–3 min). MCAv, cerebral oxygenation, BP, HR and ECG were monitored continuously. The identification of the nadir of each of the monitored variables during the first 30 s after standing was used to best represent the comparison with the other key physiological changes associated with initial standing.

Head-up tilt and lower body negative pressure. Following the postural maneuvers, subjects were placed on the combined tilt-lower body negative pressure (LBNP) table and rested supine for at least 15
min. Subjects were then tilted to 60° for 5 min where they remained until termination of the subsequent LBNP protocol. Lower body suction was applied in −10-mmHg incremental steps for 5 min each (21). Testing was terminated on participants’ request due to subjective symptoms of presyncope (feelings of dizziness, nausea, faintness), or when a continuous drop in SBP below 80 mmHg for more than 10 s was observed. Although previous studies have used the <80 mmHg as the cut-off point (21), data from our laboratory indicate that respiratory-induced swings in BP occur, especially at lower blood pressures between 75 and 85 mmHg. These less conservative criteria of termination of the syncope protocol allowed better monitoring of physiological changes immediately before syncope. All related values presented in Table 1 and Figs. 2–5 were obtained at the moment the BP nadir was reached, which occurred in the last 2–3 s before terminating the tilt test.

Validation of noninvasive beat-to-beat BP and end-tidal $\text{PCO}_2$. In a subgroup of the 46 subjects (n = 8), following local anesthesia (1% lidocaine), arterial pressure was measured with a radial arterial catheter (Abbott Critical Care System) together with the noninvasive finger photoplethysmography method to corroborate changes in arterial pressure. Arterial blood gases were measured at baseline, during the last minute of 60° upright tilt, and close to presyncope, from 2-ml samples of arterial blood drawn into chilled heparin syringes and analyzed immediately in duplicate (NPT Series, Radiometer, Copenhagen, Denmark). Before the samples, 1 ml of dead-space blood was discarded. Commercial standards were used to calibrate the blood gas analyzer before starting the tests. PETCO$_2$ was averaged over the 20-s period during the arterial blood draws.

Presyncope symptoms. Presyncope symptoms were recorded following the 3-min stand and following presyncope, using a validated questionnaire containing seven posture-related symptoms rated on a visual analog scale from 0 to 10, with a maximum score of 70 (1, 11, 37). Specifically, 36 of the 38 participants were technically classified as “orthostatically hypotensive” during the supine to stand maneuver (Fig. 1). Importantly, no subject was classed as orthostatically hypotensive during the steady-state (2–3 min) standing, reflected in a maintained arterial blood pressure [MAP = 80 ± 8 mmHg during the last 30 s of the stand, compared with 83 ± 8 mmHg in the supine baseline (P > 0.05)].

Altered respiration in response to the initial, transient systemic hypotension of the active stand are reported in Fig. 2, A and B, respectively; t = 0 was taken to be the actual start of rising from the supine into the standing position, and the variables were considered to have returned to baseline when they reached the baseline values on the way up from the nadir. MAP decreased ~44% within 11 ± 2 s of standing from supine before returning to baseline within ~20 ± 5 s of standing in the majority of the participants. HR increased by 37 ± 9 beats/min, and this peak occurred at 12 ± 2 s after standing. During the last 30 s of standing the HR had declined to 21 ± 11 beats/min above the baseline. MCAv decreased ~35% within 9 ± 2 s of standing before returning to baseline in 14 ± 3 s for all but two participants. There was no relationship between the change in MAP and the change in MCAv on standing ($R^2 = 0.1; P > 0.05$). On standing, cerebral oxygenation decreased by 4% (Fig. 2C) within 13 ± 3 s; this drop showed no association with MAP and MCAv. PETCO$_2$.

### Table 1. Cardiorespiratory and cerebrovascular changes from baseline during IOH and at presyncope

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>IOH</th>
<th>Δ from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>64 ± 11</td>
<td>37 ± 9* (60 ± 18%)</td>
<td>44 ± 25* (68 ± 11%)</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>83 ± 8</td>
<td>−36 ± 11* (−44 ± 14%)</td>
<td>−33 ± 10* (−40 ± 11%)</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>123 ± 11</td>
<td>−42 ± 16* (−34 ± 13%)</td>
<td>−52 ± 12* (−43 ± 8%)</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>64 ± 7</td>
<td>−34 ± 9* (−53 ± 14%)</td>
<td>−24 ± 11* (−37 ± 16%)</td>
</tr>
<tr>
<td>Q, aU</td>
<td>6.8 ± 1.5</td>
<td>3.0 ± 1.4+ (49 ± 29%)</td>
<td>−2.9 ± 1.2* (−42 ± 14%)</td>
</tr>
<tr>
<td>TPR, aU</td>
<td>13 ± 4</td>
<td>−8 ± 3* (−61 ± 10%)</td>
<td>0.4 ± 3 (5 ± 21%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PETCO$_2$, mmHg</td>
<td>39.4 ± 4.5</td>
<td>−4.2 ± 2.9* (−12.1 ± 8.8%)</td>
<td>−7.3 ± 6.0+ (−21.4 ± 19.6%)</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCAv, cm/s</td>
<td>66 ± 12</td>
<td>−24 ± 10* (−35 ± 13%)</td>
<td>−24 ± 12* (−36 ± 18%)</td>
</tr>
<tr>
<td>sMCAv, cm/s</td>
<td>110 ± 20</td>
<td>−12 ± 11* (−11 ± 11%)</td>
<td>−28 ± 19* (−27 ± 18%)</td>
</tr>
<tr>
<td>dMCAv, cm/s</td>
<td>45 ± 11</td>
<td>−34 ± 10* (−76 ± 18%)</td>
<td>−23 ± 13* (−50 ± 30%)</td>
</tr>
<tr>
<td>Pulsatility index, %</td>
<td>109.7 ± 20.5</td>
<td>13.1 ± 20.1 (11.7 ± 20.9)</td>
<td>−26.5 ± 16.4+ (−24.9 ± 14.4%)</td>
</tr>
<tr>
<td>CVR, mmHg cm²/g</td>
<td>13.3 ± 0.4</td>
<td>−0.1 ± 0.6 (−7 ± 40%)</td>
<td>−0.01 ± 0.4 (−11 ± 31%)</td>
</tr>
<tr>
<td>Oxygenation, absolute %</td>
<td>69 ± 4</td>
<td>−3 ± 2+ (−4 ± 2%)</td>
<td>−4 ± 4 (−6 ± 5%)</td>
</tr>
</tbody>
</table>

* Values are expressed as absolute means ± SD; percentage changes from baseline value (± 2 SD) are denoted in parentheses. HR, heart rate; MAP, mean arterial blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; Q, cardiac output; TPR, total peripheral resistance; PETCO$_2$, partial pressure of end-tidal carbon dioxide; MCAv, middle cerebral artery velocity; sMCAv, systolic MCAv; dMCAv, diastolic MCAv; pulsatility index = (sMCAv − dMCAv)/MCAv; CVR, cerebral vascular resistance. * Differences when compared with baseline. † Difference between initial orthostatic hypotension (IOH) and presyncope. Presyncope values were taken as a 1-s average around the blood pressure (BP) nadir, which was reached in the 2-3 s before terminating the tilt test. aU, arbitrary units; Δ, change. For oxygenation, parenthetical value is relative % change.

### RESULTS

**IOH.** The majority of participants experienced IOH moving from a supine to standing position, as defined previously (51). Specifically, 36 of the 38 participants were technically classified as “orthostatically hypotensive” during the supine to stand maneuver (Fig. 1). Importantly, no subject was classed as orthostatically hypotensive during the steady-state (2–3 min) standing, reflected in a maintained arterial blood pressure [MAP = 80 ± 8 mmHg during the last 30 s of the stand, compared with 83 ± 8 mmHg in the supine baseline (P > 0.05)].
decreased by \( -4 \pm 3 \text{ mmHg} \) (Fig. 2D) and also had no correlation with MAP, MCAv (Fig. 3A), or cerebral oxygenation. As outlined in Table 1, \( \dot{Q} \) increased by \( 3.0 \pm 1.4 \text{ aU (} \sim 49\% \) due to an instantaneous and pronounced increase in HR and a stable stroke volume. TPR, estimated by instantaneous MAP divided by \( \dot{Q} \), was decreased by \( 8 \pm 3 \text{ mmHg} \cdot \text{l}^{-1} \cdot \text{min (} \sim 61\% \) during IOH.

Figure 4 illustrates the typical changes in BP (Fig. 4A), HR (Fig. 4C), MCAv (Fig. 4E), cerebral oxygenation (Fig. 4G), and cardiac output (Fig. 4I) in one representative individual on standing. These graphs typify the responses seen in the majority of the group. The traces in Fig. 4 represent the 30 s before and after standing, clearly illustrating the extent of the drop in BP, MCAv, and cerebral oxygenation and the increase in HR resulting from the change in posture. Interestingly, during IOH, when compared with presyncope, there was a preferential decrease in diastolic MCAv (dMCAv) whereas systolic MCAv (sMCAv) was relatively well maintained, i.e., pulsatility of MCAv tended to increase (\( P = 0.08 \)). In contrast to IOH, however, there was a greater fall in sMCAv during presyncope, which was reflected in a reduction in MCAv pulsatility (\( P < 0.05 \) vs. baseline and IOH). The averaged group responses are presented in Fig. 5.

Head-up tilt and LBNP. All of the participants experienced presyncope as defined by a drop in SBP below 80 mmHg for more than 10 s, the manifestation of presyncopal symptoms, or both. The reductions from baseline in MCAv, MAP, cerebral oxygenation, and PETCO\(_2\) at presyncope are shown in Fig. 2 (in Fig. 2B, \( n = 36 \); data from 2 participants were lost due to poor Doppler signals). Immediately before termination of the test, MAP dropped below our cutoff criteria and reached its nadir, and a 1-s average around this nadir was taken to be the time point of presyncope, from which all the related data were obtained. Figure 4 illustrates typical beat-to-beat traces for BP (Fig. 4B), HR (Fig. 4D), MCAv (Fig. 4F), cerebral oxygenation (Fig. 4H), and cardiac output (Fig. 4J) obtained from one participant in the 30 s preceding tilting, followed by the final 30 s before the termination of the tilt test during which time presyncope occurred. Within the group MAP was reduced by \( -40 \pm 11\% \), MCAv by \( -36 \pm 18\% \), and cerebral oxygenation by \( -6 \pm 5\% \) at presyncope (\( P < 0.05 \) vs. baseline). There was no association between time to presyncope and the extent of...
the drop from baseline within IOH for MCAv, MAP (Fig. 6), or cerebral oxygenation, or between the time to presyncope and the baseline values of any of the measured variables. $P_{ETCO_2}$ had decreased by $\sim 7 \pm 6$ mmHg at presyncope and was related to the reduction in MCAv ($R^2 = 0.4; P < 0.05$; Fig. 3B). There was a correlation between the percentage change in MAP with the percentage change in MCAv at presyncope ($R^2 = 0.1; P < 0.05$); no relationships were evident with cerebral oxygenation, or with related changes during IOH.

There was a nonsignificant elevation from baseline in estimated TPR at presyncope ($5 \pm 21\%$), with no evident correlation between the change in TPR and time to presyncope ($R^2 < 0.1$). Likewise, there were no relationships between age, height, weight, or BMI with time to presyncope.

Presyncopal symptoms. Presyncopal symptoms were identified in 16 of the 38 participants during the IOH trial (mean symptom score $3.2 \pm 1.9$; range 1–7 of a possible 70) and in 28 of the 38 participants during the progressive test to presyncope (mean score $11.2 \pm 7.0$; range 2–25). The major symptom experienced during IOH was described as dizziness, as opposed to other commonly experienced prodromal symptoms during presyncope such as visual or hearing disturbances, sweating, nausea, neck, back or precordial discomfort, palpitations, and fatigue. Importantly, there were no related symptoms between IOH and those at presyncope, i.e., those who experienced symptoms during IOH did not necessarily experience them at presyncope and vice versa. Interestingly, in both conditions, there were no differences between the magnitude of the change in HR (Fig. 7A), MAP (Fig. 7B), MCAv (Fig. 7C), or $P_{ETCO_2}$ (Fig. 7D) between the symptomatic and asymptomatic groups ($P > 0.05$). Furthermore, there were no associations between the magnitude of these changes in aforementioned physiological variables and the severity of the symptoms.

Reliability of noninvasive measurements of BP and end-tidal $PCO_2$. For comparative purposes, arterial pressure was measured with a radial arterial catheter in eight subjects during the IOH and head-up tilt and LBNP interventions. In these subjects, at supine rest, small absolute differences of $\sim 3$ mmHg in MAP ($P < 0.05$) were found between the measurements of radial and finger arterial pressure. However, the magnitude of decline in arterial pressure monitored using the Finometer and direct intra-arterial line were comparable during IOH (MAP: 44% by Finometer, 41% by catheter; $P > 0.05$) and at presyncope (MAP: 41% by Finometer, 42% by catheter; $P > 0.05$). Moreover, during both IOH and at presyncope, the absolute difference in the MAP between the noninvasive Finometer and direct intra-arterial line did not differ ($P > 0.05$). These data confirm the validity of using finger photoplethysmography to measure changes in arterial pressure during the conditions imposed in the present study. In addition, at rest, during head-up tilt, and at presyncope, the declines in $P_{ETCO_2}$ tracked ($\pm 1.4$ mmHg) the declines in arterial $PCO_2$ ($P > 0.05$). Although it has been suggested that intra-arterial instrumentation affects orthostatic blood pressure control (40), on comparison, the volunteers who had the intra-arterial instrumentation had “normal” responses to both the extent of IOH tolerated and time to presyncope that fitted well within the mean response to those found in the subjects without the direct instrumentation.

**DISCUSSION**

The four main novel findings of this study are as follows:

1. Significant transient IOH and cerebral hypoperfusion associated with resuming the upright posture are both common and physiologically acceptable insults that can be well tolerated in otherwise healthy young subjects.

2. Comparable decreases in MAP, MCAv, and cerebral oxygenation were evident during IOH and at presyncope; however, because of the differential changes in vascular resistance (as estimated from MAP/$Q˙$) and hypocapnia during IOH and at presyncope, it seems unlikely that a diminished vasocostrictor capacity per se may result in a more pronounced IOH and a tendency to faint during prolonged orthostatic stress.

3. At presyncope, MCAv pulsatility was markedly reduced whereas it was well maintained during IOH.

4. A relative intolerance to sustained orthostatic stress and syncope is not related to the severity of IOH and cerebral hypoperfusion. These findings indicate that, during standing, the transient nature of physiological changes can be well tolerated; however, potentially mediated by a reduced MCAv pulsatility and greater degree of hypocapnic-induced cerebral vasoconstriction, when comparable changes are sustained, the development of syncope is imminent. Collectively, our data underscore the notion that IOH and presyncope should be considered as two very separate clinical entities.

**IOH.** IOH is a transient decrease in BP observed within 15 s of standing, and it is characterized by the aforementioned decrease in BP with symptoms of cerebral hypoperfusion (51).
It has been well reported that IOH is a frequent cause of orthostatic intolerance (51); however, monitoring of beat-to-beat BP is critical for the objective assessment of IOH. Although the relationship between the initial and sustained adjustment during orthostatic stress and between IOH and a tendency to faint have been addressed previously (34, 41), to the best of the authors’ knowledge, this study is the first to provide a comprehensive study in “healthy” subjects, with the addition of key respiratory and cerebrovascular monitoring alongside the detailed comparison with the tilt-LBNP protocol, which provides a greater orthostatic stress than previously used. The findings indicate that the majority of participants experienced IOH, reflected also in considerable reductions in MCAv while moving from supine to stand. Although this initial orthostatic challenge of standing represents a critical time in which cerebral hypoperfusion occurs, participants managed to remain upright and syncope did not occur. Therefore, it seems that IOH is both a common and physiologically acceptable insult that can be well tolerated in otherwise healthy young subjects. The IOH differs from general orthostatic hypotension in that decreases in BP are immediate and temporary, due to a mismatch between arterial inflow and outflow.

Fig. 4. Traces obtained from 1 representative participant in response to standing for BP (A), heart rate (HR; C), MCAv (E), cerebral oxygenation (G), and cardiac output (I). The final 30 s of baseline before standing and the 30 s after the posture change are shown. B, D, F, H, and J, respectively, illustrate the same variables during the tilt test. The final 30 s of baseline before tilting are shown, followed by the final 30 s of the tilt test, during which time presyncope occurred. These traces represent the typical response seen in most participants. Note the marked respiratory-induced swings in BP and MCAv at termination of tilt and the differential changes in MCAv pulsatility during IOH with those at presyncope. bpm, beats/min; aU, arbitrary units.
as seen by the large drop in TPR and an increase in $\dot{Q}$ on standing (51). Proposed mechanisms governing this initial fall in arterial pressure, on standing, involve the complex interactions of an instantaneous mechanical decrease in vascular resistance (18, 19, 35); a venous emptying-mediated increase in the local arteriovenous pressure gradient (46); rapid, locally mediated vasodilatation effects; and a cardiopulmonary receptor-mediated systemic sympathetic withdrawal in response to sudden increases in right atrial pressure (2, 39, 50). The challenge during IOH is that the speed and magnitude of the drop in MAP exceed baroreflex control adjustments of vascular resistance (i.e., sympathetically mediated vasoconstricor ef-
effects with a latency of 1–3 s and a time constant of ~10 s cannot correct a fall in pressure with a nadir around 7–10 s). This timing is particularly important as the related drops in BP during IOH are likely to be at the lower limit of cerebral autoregulation; thus, because of this, and the related delay in cerebral autoregulation of ~10 s (54), the brain is likely to be at its limit of oxygen reserve during this time point.

Orthostatic tolerance is not related to the severity of IOH and cerebral hypoperfusion. Our findings indicate that orthostatic intolerance, expressed as time to presyncope during combined head-up-tilt with progressive LBNP, is not related to the severity of IOH and cerebral hypoperfusion. Moreover, it was apparent that those subjects who developed symptoms during IOH did not necessarily experience them at presyncope and vice versa. These findings indicate that the integrated cardiorespiratory and cerebrovascular responses to resuming the upright posture and at presyncope reflect different physiological and symptomatic changes and adjustments.

Specifically, it seems that the transient nature of the physiological changes with standing can be well tolerated; however, when comparable changes are sustained the development of syncope is imminent. It seems that the individual variability in orthostatic tolerance may be partly determined by vasoconstrictor reserve, which is the intrinsic limit on sympathetically mediated vasconstriction (6). For example, Fu et al. (6) found that time to presyncope was positively correlated with muscle sympathetic nerve activity, an indicator of neural sympathetic reserve, and that those who had greater increases in muscle sympathetic nerve activity also had greater increases in TPR and time to presyncope. In this study, however, there was no direct correlation between TPR and time to presyncope. Indeed, changes in TPR at presyncope varied widely and were both positive and negative compared with the baseline values, potentially explained by both the normal response to orthostatic stress in which increased sympathetic activity results in vasoconstriction in skeletal muscle, and also a gradual withdrawal in sympathetic innervation as syncope impends (6). Taking into consideration the fact that our values of TPR are estimated, and the lack of assessment of sympathetic activity, a comparable conclusion about the sympathetic control of orthostatic tolerance cannot be ascertained in the present study. Nevertheless, because of the differential changes in vascular resistance (as estimated from TPR) and hypocapnia during IOH and at presyncope, it seems unlikely that diminished vasoconstrictor capacity per se may result in a more pronounced IOH and a tendency to faint during prolonged orthostatic stress. Another critical point is that, although TPR is always calculated as the quotient of mean BP and Q, we cannot be sure that this quotient is a true expression of the arterial tone. For example, systemic vascular resistance and Q interact (36, 38); thus a fall in systemic vascular resistance in the splanchnic bed (42) might result in translocation of blood to the venous system and thereby in a decrease in Q. Nevertheless, although our estimated TPR cannot differentiate between different vascular beds (e.g., a decrease in splanchnic resistance and a simultaneous increase in pulmonary resistance will not be picked up), because the relative change in Q and MAP can be accurately monitored, it would seem likely that the calculated TPR is valid (i.e., MAP = Q × TPR). Regardless of the underlying mechanism(s), the occurrence of syncopal episodes with assuming the upright posture, the rationale for using upright tilt testing as a means to reproduce the symptoms associated with the suspected vasovagal syncope (16), seems to be at odds with the inherent differences in the hemodynamic reflexes and symptomatic responses between IOH with those at presyncope.

Differential influence of hypocapnia during IOH and presyncope. One striking finding was the very comparable decreases in MAP, cerebral oxygenation, and MCAv during IOH with those found at presyncope. The key difference at presyncope, in contrast with IOH, was the greater degree of hypocapnia that was related to the reduction in MCAv. It is well established that hypocapnia reduces cerebral perfusion due to cerebral vasoconstriction (22). It has been well reported that hyperventilatory-induced hypocapnia and subsequent reduction in cerebral perfusion occur during presyncope in patients with orthostatic intolerance (12, 31). While acknowledging the limitations of correlational analysis in establishing cause and effect, our findings would seem to confirm and extend this result to show that such changes can occur in the absence of pathology. The likely reason for the lack of influence of hypocapnia on cerebral perfusion during IOH is the transient nature of the change and related time course of action on the cerebrovascular bed (i.e., nadir and recovery all occurring within ~20 ± 5 s). For example, because of the CO2 transportation time from the lungs to the brain (53), the MCAv response to step changes in PETCO2 has a reported time delay of ~5–7 s (27, 32); moreover, following a step change in arterial PCO2, at least 45 s is required before a steady-state change in CBF occurs. Furthermore, Gisolf et al. (9) showed that during the first 25 s after a change in posture, the mechanisms responsible for regulating PETCO2 are very different compared with those involved in a steady-state upright posture. Therefore, during IOH, the drop in MCAv is more likely to be due to the initial hypotension and
related time delay (~10 s) before cerebral autoregulation becomes effective and helps regulate MCAv (54). Additionally, there is some suggestion that the oxygen reserve time for the brain (~5–10 s) is progressively reduced when SBP drops to <80 mmHg (45); therefore, in contrast to the sustained orthostatic stress of combined LBNP and head-up tilt, the length of time BP is below 80 mmHg systolic with initial standing is likely within the oxygen reserve time. Thus it seems reasonable to speculate that different physiological mechanisms might underlie and result in the comparable reductions in MCAv during IOH and at presyncope.

**Differential changes in CBF velocity pulsatility during IOH and presyncope.** A relevant and novel observation was that during IOH, despite a preferential decrease in dMCAv, sMCAv...
was relatively well maintained, i.e., pulsatility of MCAv tended to increase. In contrast to IOH, however, there was a greater fall in sMCAv during presyncope, reflected in a marked reduction in MCAv pulsatility. Although the etiology of the differential changes in pulsatility with IOH and at presyncope are not known, elevations in pulsatility have been interpreted as a compensatory maneuver that is associated with CBF preservation despite falling perfusion pressure by promoting pulsatile flow (23). It has also been suggested, at least in patients with head injury, that pulsatile flow requires less energy expenditure to maintain forward flow (3). At least in the animal model, this compensatory mechanism maintains CBF until further dilatation and fall in diastolic MCAv is exhausted; once that point is surpassed CBF diminishes rapidly (23). It seems reasonable to speculate that the differential alterations in pulsatility between IOH and presyncope may partly explain why the initial but not sustained changes can be well tolerated.

Interindividual variability to orthostasis. Although it is well known that there is a large interindividual variability in the HR and BP responses to an orthostatic stress, such variability appears to be a fundamental part of cardiovascular regulation (for recent report, see Ref. 33). Our findings are consistent with such variability in the previously reported cardiovascular responses, which is also reflected in variability in the cerebrovascular responses to orthostatic stress. We feel that our findings of the marked IOH (and related variability) do not necessarily reflect a "special population" as such, but rather they reflect a "normal" continuum of these cardiovascular responses to orthostasis. The end of this continuum, (33) may well represent and be classified clinically by autonomic disorders such as the postural tachycardia syndrome, in which patients experience exaggerated increases in HR responses (≥30 beats/min) to head-up tilt. These patients also present with symptoms of heart palpitations, dizziness, and headaches in the upright posture even when arterial BP appears well maintained, i.e., pulsatility of MCAv is relatively well maintained, i.e., pulsatility of MCAv

vasovagal syncope despite the fact that their cerebral hemodynamics followed similar patterns (20). Future studies conducted in patients with orthostatic intolerance during IOH, with inclusion of detailed prodromal symptoms, are needed to extend our findings and to determine whether the occurrence of symptoms can be used as a clinical predictor, or if, as it appears with vasovagal syncope (20), there is no such relevant link.

One possibility that underlies these unremarkable differences between symptomatic and asymptomatic groups is that a more severe degree of cerebral ischemia would be required to produce universal symptoms and a potential link between these variables. For example, a classical early report (5) indicated that syncope and symptoms of cerebral ischemia developed when CBF was reduced below a critical level (−35 ± 11%), irrespective of a wide variation in BP (−19% to −64%). Thus, because of effective cerebral autoregulation at presyncope, arterial BP does not necessarily reflect the cerebrovascular phenomena at this time point (49). Thus it would seem likely that, although the decline in BP was comparable at presyncope, between-subject variation in the degree of cerebral hypoperfusion, especially to the ascending reticular activating system or the cerebral cortex, or both (15), might explain why there was no link between symptoms and MCAv or cerebral oxygenation. Further studies exploring the linkage between symptomatology and blood flow distribution to the ascending reticular activating system and/or the cerebral cortex would seem warranted.

It should be noted that our findings can only be directed to young healthy volunteers and that the regulation of CBF may differ in patients with orthostatic hypotension during IOH or at presyncope. Nevertheless, to be able to interpret the pathophysiological significance of these observations, a clear understanding of the normal responses of the cerebral circulation to IOH and at presyncope must be obtained. Although none of our participants had a reported history of symptoms related to postural tachycardia syndrome, our findings provide additional insight into the notion that normal healthy individuals show marked cardiovascular responses to orthostatic stress that are broadly similar to patients with postural tachycardia syndrome. For example, in the present study, HR was initially increased by 37 ± 9 beats/min within 12 ± 2 s after standing after which it remained elevated by ~20 beats/min. There exists some discrepancy between values observed in earlier reports. For example, our reported change in HR with standing is comparable with some studies (43, 44), but higher than others (24, 25, 39); however, in this case, the elevated HR response seems appropriate to attempt to compensate for the greater magnitude of the drop in BP that was experienced. The duration of supine rest in the present study, which was extended compared with others (4, 9, 39), and the greater number of younger participants may explain the reported differences in HR and BP on IOH. The changes in MCAv with standing and at presyncope are consistent with previous reports (28, 49). Although future work is required to address the intriguing question about what is an appropriate and inappropriate HR response to an orthostatic stress, such interindividual variability is clearly advantageous for our experimental design and related examination of our hypothesis using correlational analysis.

Technological considerations. Although we used Doppler ultrasound to measure flow velocity, rather than blood flow, in the middle cerebral artery, previous reports indicate that
MCAv is a reliable index of CBF (8, 17, 30, 37, 47). To rule out the potential uncertainty about the use of noninvasive photoplethysmography to estimate arterial pressure, we confirmed the adequacy of these noninvasive measures with direct intra-arterial measurements in a subgroup of eight subjects who completed our experimental protocol. Although previous studies have shown that the tracking of finger arterial pressure of the changes in arterial pressure is valid (13, 14), comparisons were made for only 30 s before and 120 s after the active stand (13) and during 30 min of 70° head-up tilt (14) and therefore reflect different experimental conditions to that in the present study. Thus our comparison between noninvasive and direct intra-arterial measurements is the first to provide additional insight into the validity of this method for testing during IOH and syncope. Moreover, our data also highlight good agreement between PETCO2 measurements and direct arterial PCO2. It should be noted that, intentionally, our experiments were conducted on otherwise healthy young subjects without history of syncope; as such, our results can only be generalized to this population. The possibility that IOH and syncope is more closely related in patients with orthostatic hypotension warrants further research.

In summary, at presyncope, marked postural-induced hypocapnia, reductions in MCAv pulsatility, and related hyperventilatory-induced hypocapnia further exacerbate cerebral hypoperfusion, facilitating the onset of syncope. Such hypocapnia seems to be less important during the initial adjustment to the perfusion, facilitating the onset of syncope. Such hypocapnia further exacerbate cerebral hypo-tension, reductions in MCAv pulsatility, and related hyperventilation.

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REFERENCES


