Increased vasoconstriction predisposes to hyperpnea and postural faint

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Taneja I, Medow MS, Glover JL, Raghunath NK, Stewart JM. Increased vasoconstriction predisposes to hyperpnea and postural faint. Am J Physiol Heart Circ Physiol 295: H372–H381, 2008. First published May 23, 2008; doi:10.1152/ajpheart.00101.2008.—Our prior studies indicated that postural fainting relates to splanchnic hypervolemia and thoracic hypovolemia during orthostasis. We hypothesized that thoracic hypovolemia causes excessive sympathetic activation, increased respiratory tidal volume, and fainting involving the pulmonary stretch reflex. We studied 18 patients 13–21 yr old, 11 who fainted within 10 min of upright tilt (fainters) and 7 healthy control subjects. We measured continuous blood pressure and heart rate, respiration by inductance plethysmography, end-tidal carbon dioxide (ETCO₂) by capnography, and regional blood flows and blood volumes using impedance plethysmography, and we calculated arterial resistance with patients supine and during 70° upright tilt. Splanchnic resistance decreased until faint in fainters (44 ± 8 to 21 ± 2 mmHg·l⁻¹·min⁻¹) but increased in control subjects (47 ± 5 to 53 ± 4 mmHg·l⁻¹·min⁻¹). Percent change in splanchnic blood volume increased (7.5 ± 1.0 vs. 3.0 ± 11.5%, P < 0.05) after the onset of tilt. Upright tilt initially significantly increased thoracic, pelvic, and leg resistance in fainters, which subsequently decreased until faint. In fainters but not control subjects, normalized tidal volume (1 ± 0.1 to 2.6 ± 0.2, P < 0.05) and normalized minute ventilation increased throughout tilt (1 ± 0.2 to 2.1 ± 0.5, P < 0.05), whereas respiratory rate decreased (19 ± 1 to 15 ± 1 breaths/min, P < 0.05). Maximum tidal volume occurred just before fainting. The increase in minute ventilation was inversely proportionate to the decrease in ETCO₂. Our data suggest that excessive splanchnic pooling and thoracic hypovolemia result in increased peripheral resistance and hyperpnea in simple postural faint. Hyperpnea and pulmonary stretch may contribute to the sympathoinhibition that occurs at the time of faint.

Splanchnic resistance; total peripheral resistance; minute ventilation; regional blood flow

SYNCOPE (FAINTING) is defined by a sudden transient loss of consciousness and postural tone due to cerebral hypoperfusion (7). Simple postural faint is identified with upright vasovagal syncope in which vasodilation causing hypotension and bradycardia are relieved by recumbency (24).

Upright positioning ordinarily produces subdiaphragmatic gravitational blood pooling primarily within the venous system (41). As a result, venous return and cardiac output decrease in all upright subjects. In healthy subjects, baroreceptors sense the postural decrease in arterial and cardiopulmonary stretch, which maintains blood pressure (BP) by a compensatory increase in total peripheral resistance (TPR) and associated elastic recoil of venous blood and by an increase in heart rate (HR). This is the normal reflex response to orthostasis (35).

Is postural faint related to increased peripheral vasoconstriction? The pathophysiology of postural faint is less well defined. Increased (16), decreased, (26) or unchanged (34) sympathetic activity and TPR compared with control subjects have been reported. BP often begins to fall well in advance of loss of consciousness, indicating inadequate compensatory sympathetic vasoconstriction or reduced venous return, or both. Ultimately, sympathetic withdrawal, vasodilation, hypotension, and vagotonic bradycardia supervene, precipitating loss of consciousness (24, 40).

Our prior work suggested that excessive central thoracic emptying and splanchnic filling occur in simple faint, although the time course was not specified (48). Such segmental blood volume shifts should increase baroreflex unloading, increase sympathetic stimulation, and increase TPR during early orthostasis. Thus our first aim was to determine the time course of regional blood volume and peripheral arterial resistance changes in fainters compared with control subjects. We hypothesized that TPR is increased during early upright tilt in those patients with simple faint because of excessive splanchnic blood pooling and resulting thoracic hypovolemia.

Is the hyperpnea and hypocapnia of postural faint related to vasoconstriction? We and others (19, 39) have observed respiratory changes that have their onset well in advance of loss of consciousness and often begin soon after the onset of upright tilt. Typically, hyperpnea (increased tidal volume) without tachypnea (increased respiratory rate) produces hyperventilation (increased minute ventilation) and hypocapnia [decreased end-tidal carbon dioxide (ETCO₂)]. Decreased cerebral perfusion as an effect of hypocapnia is well known and may have a role in fainting (20). Less is known about the causes of hyperpnea and hypocapnia. Potential mechanisms of hyperpnea include reduced blood flow to the carotid body (stagnant hypoxemia) and excessive carotid body sympathoexcitation (6, 32). These produce hyperpnea without tachypnea (42), which is qualitatively different from the hyperventilation of anxiety in which tachypnea predominates. Therefore, our second aim was to investigate any relationship between peripheral vasoconstriction, used as a measure of sympathoexcitation, and the onset of hyperpnea. We hypothesized that the onset of hyperpnea is produced by increased sympathoexcitation in fainters compared with healthy control subjects.

Is the pulmonary stretch reflex a mechanism for hypotension and bradycardia in simple faint? Hyperpnea activates pulmonary stretch afferents, resulting in marked sympathoinhibition and bradycardia via the pulmonary stretch reflex (45). Therefore, our final aim was to investigate whether hyperpnea is related to the vasodilation and bradycardia of the vasovagal
response. We hypothesized that an abrupt increase in hyperpnea is linked to peripheral vasodilation and bradycardia at the time of faint.

METHODS

The current study was designed to investigate the respiratory and hemodynamic changes during fainting. The study was approved by the Institutional Review Board of New York Medical College, and informed consent was obtained from all subjects. The authors have full access to the data and take responsibility for its integrity. All authors have read and agree to this article as written.

Subjects

We studied 11 patients ages 13–21 yr (median age 16 yr, 5 men, 6 women) who were referred after more than three episodes of postural fainting during the past 6 mo and who had a vasovagal response within 10 min of head-up tilt (HUT) at 70° in the laboratory. We refer to these subjects as “fainters” throughout the remainder of the article. We also studied seven comparably aged healthy control subjects who did not have a vasovagal response to 10 min of HUT and had no history consistent with orthostatic intolerance. All subjects were free of systemic illness. There were no trained competitive athletes or bedridden subjects. Subjects were not taking any medication. There were no smokers. All subjects had normal electrocardiograms (ECG) and echocardiograms.

Prolonged upright positioning may induce fainting in healthy volunteers. To avoid this problem, we restricted the time of upright tilt to 10 min and retained for study only those fainters who fainted during this 10-min tilt. We compared fainters with control subjects who did not faint or develop presyncopeal symptoms during 10 min of HUT at 70°.

Protocol

Tests began at 10:00 AM after 4 h of fasting. Subjects refrained from beverages containing xanthine and caffeine for at least 72 h before testing. Subjects were familiarized with the procedures used in the study. Subjects were instrumented for ECG, respiratory plethysmography, impedance plethysmography (IPG), continuous BP recording, and capnography. After a 30-min supine acclimatization period, we assessed HR, BP, respiratory rate, ETCO2, and minute ventilatory volume during a baseline period of at least 5 min. We used IPG to continuously measure regional blood volumes and beat-to-beat changes in regional blood flows of thoracic, splanchnic, pelvic, and leg segments (4).

After supine data collections were complete, the subjects were tilted upright to 70° for a maximum of 10 min. Continuous BP, HR, respirations, and impedance measurements were recorded. Subjects were tilted back if fainting ensued. Postural vasovagal fainting was defined as a tilt-induced decrease in systolic blood pressure (SBP) to <60 mmHg or a decrease in SBP to <80 mmHg associated with symptoms of impending loss of consciousness, severe lightheadedness, nausea, or diaphoresis. All the fainters developed a classic vasovagal faint while upright, with hypotension and bradycardia at the onset of fainting (Fig. 1).

Details of Method

Defining fiducial event markers. Orthostasis results in gravitational pooling, leading to neurovascular adjustments. Immediately following upright tilt, there are transient changes in HR and BP that reach a quasi-stable state within the first minute. Thereafter, the time course of HR and BP in fainters and control subjects diverges. As described by Julu et al. (17), there is an intermediate phase during which BP gradually decreases while HR increases, followed by a later phase during which both HR and BP fall precipitously with the onset of fainting. The time between these events, the early start of gradual decrease in BP and increase in HR and the onset of fainting, varies among individual fainters. However, the events (i.e., the quasi-stable events during the first minute of HUT, the early BP fall, the late BP fall, and the faint itself) and the physiology behind these events do not vary. Therefore, we regarded the events as fiducial markers of the pathophysiology and chose to compare changes in HR and BP, regional blood flow, regional blood volume, and thoracic impedance at these fiducial points that define an ordinal scale of events. These fiducial event markers are defined as shown in Fig. 1: 1) “baseline” (before tilt); 2) “1 min” HUT, “early” onset of the gradual decrease in BP, “mid” decrease in BP, “late” decrease in BP, and “faint” are indicated. After a gradual decrease in BP, marked hypotension and bradycardia occurred.

Fig. 1. Heart rate (HR; top), mean arterial pressure (MAP; middle), and thoracic impedance (bottom) of a representative fainting patient during head-up tilt (HUT) to 70°. The fiducial points “baseline,” “1 min” HUT, “early” onset of the gradual decrease in BP, “mid” decrease in BP, “late” decrease in BP, and “faint” are indicated. After a gradual decrease in BP, marked hypotension and bradycardia occurred.
decrease in BP; 4) “mid” fall in BP, which occurred midway between the onset of the gradual BP decrease and the rapid late BP decrease; 5) “late” in the gradual fall in BP, just before the onset of the rapid decrease in heart rate and BP directly preceding the faint; and 6) “faint.” Since healthy control subjects do not have a fall in BP and do not faint, we defined equivalent fiducial time points for healthy control subjects by averaging the actual time of occurrence of each fiducial marker event in the fainters. Thus control subjects and fainting subjects were compared at the same average times, and we chose to compare their responses to tilt at equivalent times to allow for a uniform evaluation of cardiorespiratory parameters across groups.

**HR and BP monitoring.** HR was monitored by a single-lead ECG. Upper extremity BP was continuously monitored with a finger arterial plethysmograph (Fionimeter; FMS, Amsterdam, The Netherlands) placed on the right middle or index finger. Finometer data were calibrated to a brachial artery oscillographic pressure. The Finometer contains software permitting height correction during positional changes.

**Heart rate variability.** We analyzed beat epochs, free of ectopy. Epochs were linearly detrended. An autoregressive model was used to calculate the power spectrum using the methods of Montano et al. (27) and Pagani et al. (37). In brief, RR intervals were acquired as a sequence of discrete point events. The RR intervals were transformed into an equivalent impulse train in which pulses were arranged at equal intervals (equal to the mean RR interval) with impulse heights equal to the RR intervals. Autoregression was performed and digital power spectra calculated. The Levinson-Durbin algorithm on the Yule-Walker equations was followed by Anderson’s test, choosing the order of the model that minimized Akaike’s final prediction error. The interval spectrum was converted to the spectrum of counts by dividing by the mean RR interval of the sequence. The spectral power within a given band was computed by taking the power in the actual frequency band. For present purposes, spectral power was partitioned into low- (LF; 0.04–0.15 Hz) and high-frequency (HF; 0.15–0.40 Hz) power bands. The total power (THRV) was also calculated.

Heart rate variability (HRV) data were calculated during supine rest (5 min pretilt), after 1 min of HUT at 70° (for 2 min), and during end HUT (for 2 min) preceding faint. These time points were chosen to inform on the HRV events before HUT, after the initial adjustment to tilt, and just before faint. LF HRV and the ratio of LF and HF variability (LF/HF) have been used as an index of sympathetic activity, and HF HRV as an index of parasympathetic activity, to evaluate cardiovascular baroreflex regulation (37).

**Changes in regional blood volumes.** IPG with the use of a tetrapolar high-resolution impedance monitor four-channel digital impedance plethysmograph (UFI, Morro Bay, CA) used to measure changes in segmental blood volumes and segmental blood flows (28, 29). These quantities were obtained within four anatomic segments operationally defined by electrode placement on anatomic landmarks that delimit respective regional circulations. These were designated the thoracic segment (supraclavicular area to xiphoid process), the splanchnic segment (xiphoid process to iliac crest), the pelvic segment incorporating lower pelvis to the knee (iliac crest to knee), and the leg or calf segment (upper calf just below the knee to the ankle). Ag-AgCl ECG electrodes were attached at these segmental boundaries and also to the left foot and left hand, where they served as current injectors. Electrical resistance values were measured by using the segmental pairs as sampling electrodes. The midline distance between the sampling electrodes (L) was measured. We also measured the circumferences of calf, thigh, hips, waist, and chest to obtain approximate volume contents of each anatomic segment. We estimated postural changes in blood volume in each segment during HUT from the formula $\Delta V_{\text{segment}} = \rho L^2/(R_1 R_2 \Delta R)$, where $\rho$ is the electrical conductivity of blood, estimated as 53.2 $\times$ $10^{-3}$ as given by Geddes and Kidder (12), $R_0$ is the resistance of a specific segment before change in the HUT angle or degree of pressure, $R_1$ is the resistance after change in the HUT angle or degree of pressure, and $\Delta R$ is the change in resistance ($R_1 - R_0$) in a specific segment during each incremental HUT. $\rho$ was regarded as constant during all maneuvers.

**Regional blood flows.** IPG was also used to measure segmental or regional blood flows. (30) Methods have recently been validated against the reference standard indocyanine green dye technique in our laboratory for the detection of leg, thoracic, and splanchnic blood flow (49, 50). Pulsatile changes in electrical resistance for each segment were employed to compute the time derivative $\partial R/\partial t$, which we used to obtain the blood flow responses of each body segment during HUT. Blood flow was calculated for an entire anatomic segment from the formula $\Delta F = (HR \rho_{\text{ipg}} L^2 T \Delta R_{\text{max}})/R_0^2$, where $HR$ is heart rate, $T$ is the ejection period, $R$ is the pulsatile resistance, and $R_0$ is the baseline resistance. Respiratory artifact was removed from the signal using a custom, Fourier-based filtering technique. IPG flows were expressed in milliliters per minute for each anatomic segment and could be normalized by dividing by the estimated segmental volume. Thoracic blood flow measurements correspond to impedance cardiography measurements of cardiac output (CO). Cardiac index (CI) was calculated as CO/body surface area.

**EKG, respiratory, Finometer, ETCO2, and impedance data.** EKG, respiratory, Finometer, ETCO2, and impedance data were interfaced to a personal computer through an analog-to-digital converter (DI-720 DataQ Ind, Milwaukee, WI). Mean arterial pressure (MAP) was calculated from SBP and DBP from the formula MAP = (SBP + 2DBP)/3. Peripheral resistance was estimated as MAP/segmental blood flow. Thus, for example, TPR was calculated as MAP/thoracic blood flow.

**Respiratory volumes.** Relative respiratory volumes were obtained by respiratory inductance plethysmograph (Respitrace; NIMS Scientific) as follows: on startup, Respitrace volumes were normalized to an internal scale; once normalization was complete and with the subjects remaining supine, we calibrated normalized Respitrace volumes against a pneumotachograph (model RSS100-HR; Hans Rudolph, Kansas, MO), which also yielded tidal volumes recorded for the fainters and control subjects alike. This enabled the unobtrusive use of the Respitrace as a comparative quantitative measure of relative changes in tidal volume throughout supine and upright testing. Data for assessment of relative changes in ventilation were obtained offline. After taking absolute values of Respitrace excursions, we integrated these values and calculated slopes to obtain a quantity proportional to total minute ventilation volume (MVV) normalized to baseline. We measured ETCO2 with a capnograph (Tri-anim Health Services).

**Upright tilt table testing.** An electrically driven tilt table (Colin Medical, San Antonio, TX) with a footboard was used. After supine measurements were complete, the table was tilted up within 6 s to 70° and remained at this angle for 10 min. The HUT was concluded before 10 min if a subject fainted.

**Data Analysis and Statistics**

Data were digitalized and stored in a computer and analyzed off-line with custom software. Data were analyzed by two investigators blind to the subject type (control vs. fainter), and both reached similar results. This was used to validate the correct placement of fiducial points. HR, BP, respiration, and segmental blood flows and blood volumes were determined at each fiducial point. Data are expressed as averages over 15-s intervals centered at these time markers. We used repeated-measures analysis of variance (ANOVA) to compare changes obtained from the baseline over time, and if significant, a Bonferroni test was used as a post hoc test for multiple comparisons. To compare data between fainters and control subjects, we used Student’s t-test. Any relationship between variables was determined using Pearson’s correlation value. Results were calculated using SPSS (Statistical Package for the Social Sciences) software.
version 14.0 and graphed using GraphPad Prism software version 4. All tabular and graphic results are means ± SE.

RESULTS

All the control subjects completed 10 min of 70° HUT.

Baseline Hemodynamics

Baseline supine hemodynamic characteristics of subjects undergoing HUT protocols are shown in Table 1. There were no significant differences in SBP or DBP or in HR or respiratory rate between fainters and control subjects.

HR is Increased While BP and CI are Decreased in Fainters During HUT

HR, MAP, and CI changes during HUT are shown in Fig. 2. HR. Although HR was similar between groups before HUT, it was significantly greater (P < 0.01) during HUT in fainters compared with control subjects until fainting occurred. HR increased from 67 ± 2 beats/min at baseline to 87 ± 51 beats/min at 1 min postilt and reached a maximum of 106 ± 2 beats/min (P < 0.001) at the late BP marker in fainters. Thereafter, it decreased to 69 ± 7 beats/min at the time of faint. HR increased from 65 ± 5 to 83 ± 6 beats/min in healthy control subjects (P < 0.05) at 1 min of tilt and thereafter did not change significantly.

BP. The MAP increased from 84 ± 2 to 93 ± 2 mmHg in fainters at 1 min of upright tilt and then started gradually falling to reach a minimum of 52 ± 3 mmHg (P < 0.001) at the time of faint. There was no significant change of MAP in healthy control subjects during HUT (86 ± 4 to 84 ± 3 mmHg).

CI. In fainters, CI decreased from 3.9 ± 0.3 l·min⁻¹·m⁻² at baseline to 1.75 ± 0.2 l·min⁻¹·m⁻² (~55%) at mid tilt in fainters (P < 0.05) compared with control subjects in which it decreased from 4.2 ± 0.2 l·min⁻¹·m⁻² at baseline to 2.9 ± 0.2 l·min⁻¹·m⁻² (~33%) (Fig. 2, P < 0.05). Minutes before the onset of faint, at the late fall in BP, the CI increased in fainters such that there was no significant difference in CI between fainters and control subjects.

HRV. LF HRV and LF/HF were higher in fainters than in controls (P < 0.05) when supine, as shown in Fig. 3. HUT at 70° resulted in a reduction in THR, but there was a significant increase in the LF component of HRV in both fainters and controls (P < 0.05). Toward the time of faint, fainters had a significant blunted increase in the LF component (LF/HF) compared with controls (P < 0.05) and an increase in HF (P < 0.05).

Timing of Fiducial Points

The average times to the early, mid, and late fall in BP for fainters were 5.5 ± 0.86, 6.9 ± 0.85, and 8.6 ± 0.9 min, respectively. The average time to fainting was 8.69 ± 0.85 min.

IPG Measurements in Segmental Blood Flows Show Increase Splanchnic Blood Flow in Fainters

Thoracic blood flow. Thoracic blood flow impedance measurements are the same as impedance cardiography measures of CO as shown in Fig. 2. There was an initial marked decrease

<table>
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<tr>
<td>Resting RR, min⁻¹</td>
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Values are means ± SE; n = no. of subjects. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; RR, respiratory rate.
in CI in fainters compared with control subjects. CI increased to baseline just before faint.

**Splanchnic blood flow.** As shown in Fig. 4, splanchnic blood flow during HUT was always greater in fainters compared with controls ($P < 0.05$).

**Pelvic blood flow.** There was an initial decrease in pelvic blood flow ($P < 0.05$ compared with baseline) in all subjects (Fig. 4). Thereafter, there were no significant differences in pelvic or leg blood flows in fainters and control subjects.

**Leg blood flow.** Leg blood flow decreased similar to pelvic flow during the earlier parts of HUT and was not different for fainters and control subjects (Fig. 4). However, there was a significant increase in leg blood flow late, just before syncope ($P < 0.05$) in fainters.

**IPG Measurements of Segmental Blood Volumes Show Thoracic Hypovolemia and Splanchnic Hypervolemia in Fainters**

Changes in fractional segmental blood volumes comparing fainters and control subjects are shown in Fig. 5.

**Thoracic blood volume.** Thoracic blood volume was decreased in all subjects with tilt but was more markedly decreased in fainters compared with control subjects ($P < 0.05$).

**Splanchnic blood volume.** There was a corresponding reciprocal increase in splanchnic blood volume that was increased in fainters compared with control subjects ($P < 0.05$).

**Pelvic and leg blood volumes.** Both the pelvic and leg volumes increased uniformly with upright tilt. There were no significant differences ($P = NS$) between fainters and control subjects.

**IPG Shows Biphasic Changes in Segmental Arterial Resistances in Fainters Compared With Control Subjects**

As shown in Fig. 6, splanchnic resistance began to decrease in fainters soon after HUT while increasing throughout HUT in controls. Thoracic, pelvic, and leg arterial resistances exhibited a biphasic response in fainters. Resistances initially increased in fainters and control subjects but were significantly greater in fainters during the earlier parts of HUT. Thereafter, all segmental resistances decreased until the time of faint (all $P < 0.05$). Control subjects maintained the initial increase in arterial resistances until the end of HUT.

**Respiratory Measurements Show Increased Tidal Volume, Increased MVV, and Decreased $ET_{CO_2}$ in Fainters**

Respiratory changes are shown in Fig. 7.
MVV increased significantly in fainters from baseline to faint (1 ± 0.2 to 2.1 ± 0.5, P < 0.05) but did not increase in control subjects (1 ± 0.2 to 1.3 ± 0.2; P = NS).

ETCO₂. Both groups had a decrease in ETCO₂ during HUT that was significantly greater in fainters, decreasing from 39 ± 1 to 32 ± 1.4 mmHg (P < 0.05). ETCO₂ and MVV data for fainters and controls are shown in Fig. 7.

Tidal volume. Normalized tidal volume increased steadily in fainters from 1 ± 0.08 at baseline to 2.6 ± 0.24 at late BP fall and to 2.3 ± 0.28 at faint (P < 0.05). Tidal volume did not significantly increase in control subjects.

Respiratory rates. Respiratory rate decreased in fainters from 19 ± 1 breaths/min at baseline to a minimum of 15 ± 1 at late BP fall (P < 0.05) and then increased to 18.7 ± 1.2 (P = NS compared with baseline) at faint. Respiratory rates did not change significantly in control subjects during tilt.

Correlations

HR at baseline was inversely correlated to the fractional change in splanchnic filling at faint ($r^2 = 0.578$, $P < 0.05$). The normalized change in thoracic volume following HUT in fainters was correlated to the normalized change in minute ventilation ($r^2 = 0.495$, $P < 0.05$), and the change in splanchnic arterial resistance was correlated to ETCO₂ ($r^2 = 0.473$, $P < 0.05$).

DISCUSSION

Interpretation and Synthesis of Data

Patients with postural fainting have increased splanchnic blood pooling and a greater reduction of central thoracic blood volume compared with healthy control subjects as shown by current data and as we previously published (48). There are no
differences in the change of pelvic or leg volume between fainting subjects and control subjects, but there is increased splanchnic pooling due to increased splanchnic vasodilation in fainters throughout upright tilt. Increased splanchnic pooling results in decreased central blood volume in fainters. This facilitates baroreceptor unloading, causing increased reflex vagal withdrawal and sympathetic activation. HR and TPR therefore increase while CO decreases, because of reduced preload and increased afterload compared with controls. Increased sympathoexcitation in fainters increases pelvic and leg vasoconstriction, although the splanchnic vasculature remains vasodilated. Increased renal resistance should also contribute to increased TPR. HRV data support the hypothesis of higher sympathetic activation in fainters soon after HUT with sympathetic withdrawal and parasympathetic activation just before fainting.

Progressive hyperventilation is due to increased tidal volume, rather than tachypnea, and upright respiratory rate actually decreased. One explanation for such hyperventilation is increased sympathetic excitation of the chemoreflexes through the indirect effect of ischemic or “stagnant” hypoxemia (32) and the direct effect of sympathetic stimulation of the carotid body (25). Progressively increasing tidal volume increases lung stretch, evoking the pulmonary stretch reflex (3, 45). The reflex produces sympathoinhibition, contributing to subsequent decreased vascular resistance and increased vagal activity starting from the early onset of BP fall through the late period of faint as tidal volume reaches its maximum.

Fig. 6. Arterial resistance in fainters and healthy control subjects during upright tilt. Total peripheral resistance (TPR) is shown at top left, splanchnic resistance at top right, pelvic resistance at bottom left, and leg resistance at bottom right. Fainters demonstrated biphasic change in TPR, pelvic, and leg resistances in which an initial increase in TPR was followed by a decrease in resistance until faint occurred. This was not observed in healthy control subjects. Splanchnic resistance never increased in fainters. $P < 0.05$ compared with baseline. $P < 0.05$ compared with 1 min. *$P < 0.05$, between-group comparison.

Fig. 7. Changes in respiratory parameters during HUT70 in fainters and healthy control subjects. Respiratory rate (Resp) is shown at top left, relative tidal volume (TV) at top right, relative minute volume ventilation (MVV) at bottom left, and end-tidal partial pressure of carbon dioxide (PETCO$_2$) at bottom right. Respiratory rate decreased while TV increased, reaching a maximum just before faint. MVV increased and PETCO$_2$ decreased monotonically in fainters. $P < 0.05$ compared with baseline. *$P < 0.05$, between-group comparison.
Alternative Explanations for Fainting and Comparison with the Literature

Alternative explanations for our findings are suggested by the work of others. For example, early exaggerated cardiac sympathetic activity and an underfilled left ventricle might elicit a Bezold-Jarisch-like vagal inhibitory reflex (31), leading to hypotension and bradycardia in animals (36) and humans (11, 47). However, heart transplant patients lacking this form of innervation remain capable of simple faint (44).

Decrease in plasma volume due to filtration loss as well as sex-related differences in plasma volume may contribute to orthostasis (9, 22). However, decreased plasma volume should be less important during the brief tilts studied presently. MAP = TPR \times CO. Our results confirm the work of investigators who stress the preeminent importance of reduced venous return to the heart rather than a reduction in arterial resistance as the main determinant of the hypotension of syncope (10, 51). Their findings are consistent with our work. Others also have reported a rise of TPR during orthostasis (34), as we observed.

A delayed or otherwise altered baroreceptor response could also play a part in fainting (14). Enhanced chemoreflex activity blunts baroreflex gain (18). This may in part account for the biphasic arterial resistance response in fainting subjects with an initial increase in TPR followed by a significant decrease as syncope supervenes.

Causes of Selective Splanchnic Vasodilation

Selective splanchnic vasodilation is a common occurrence during eating, where it is related to the elaboration of cholecystokinin and serotonin (43). Splanchnic vasodilation also occurs in abnormal hemodynamic states such as sepsis, where it is related to the increased release of nitric oxide by inducible nitric oxide synthase and inflammatory mediators (53), and in portal hypertension, where it may relate to excessive nitric oxide production. To date, however, there is no adequate explanation for splanchnic vasodilation in simple faint.

Orthostasis and Respiration

Orthostasis often results in changes in respiration related to redistribution of blood within the pulmonary vasculature (13). This is associated with lowering of the diaphragm and adjustment of the ventilated lung volumes, which could by themselves reduce venous return. Decreased venous return results in sympathetic vasoconstriction with hyperpnea consistent with our data. Therefore, mechanical changes in ventilation when upright may lead to sympathoexcitation.

Modest increases in ventilation and decreases in ET\textsubscript{\text{CO}}\textsubscript{2} are consistently observed during upright positioning (2, 15). These findings have been attributed to a rise in tidal volume with smaller contributions from changes in the functional residual capacity and in the amount and distribution of CO within the lungs (13). In the current study, healthy control subjects had a decrease in ET\textsubscript{\text{CO}}\textsubscript{2} from a supine value of 41 mmHg to an upright value of 38 mmHg, similar to our earlier experience (46). This contrasts with findings in fainters, in whom ET\textsubscript{\text{CO}}\textsubscript{2} decreased from a supine value of 39 mmHg to an upright value of 32 mmHg. At every fiducial point, ET\textsubscript{\text{CO}}\textsubscript{2} was decreased due to hyperventilation in fainters compared with control subjects.

Postural hyperventilation is often explained by teleology in that it might theoretically benefit the fainter by increasing venous return and thoracic blood volume (38). There is no evidence for such an increase in our data, and upright voluntary hyperventilation with increased tidal volume does not increase thoracic blood volume. Consistent with our data and hypotheses, autonomic modulation of the peripheral chemoreflexes, particularly the carotid chemoreflex, has been offered as a reason for increased ventilation during physical and emotional stress (1, 18, 25). LeLorier et al. (23) produced consistent and large reductions in ET\textsubscript{\text{CO}}\textsubscript{2} using combined upright tilt and lower body negative pressure even in healthy control subjects. Most often, investigators ignore the cause of postural hyperventilation in deference to its effect, focusing primarily on the hypocapnia resulting from hyperventilation. There is no doubt that hypocapnia causes a reduction in cerebral blood flow that could contribute to orthostatic intolerance (33). However, hypocapnia fails to explain the stimulus for hyperpnea and does not account for the precipitous decrements of HR and BP at faint (21).

Limitations

The use of fiducial time markers enabled comparison of subjects undergoing similar physiological phenomena at different times (e.g., the onset of rapid decrease in HR and BP late, just before faint). However, it removes the absolute time dependence of the observed phenomena.

The use of IPG as a measure of fractional change in volumes and resistance is semiquantitative and can only assess relative changes in blood volume. However, prior studies (49, 50) provide validation for the use of impedance methods to continuously assess the changes in segmental blood flow and blood volume.

Hypotension and bradycardia of syncope were attributed to sympathetic withdrawal potentially related to the pulmonary stretch reflex. We did not measure sympathetic activity, pulmonary stretch vagal afferent activity, or efferent activity, and we did not seek to block these actions. These attributions are therefore conjecture. Measurement of catecholamine spillover also could have added to estimates of sympathetic activity, although some authors have questioned the role of epinephrine in fainting (52) whereas others have seen a positive association (5). However, it is most probable that changes in vasoconstriction are attributable to changes in sympathetic activity during HUT. Also, Jardine et al. (16) suggested that muscle sympathetic nerve activity was increased by tilt and decreased just before syncope.

We did not measure plasma volume, which can play an important role in inducing vasovagal syncope (22), in these subjects. We studied the subjects during 10 min of HUT, which was considered an appropriate time based on prior studies (16). Increasing the time of HUT may give different information; different times (e.g., the onset of rapid decrease in HR and BP early, just before faint). However, it removes the absolute time dependence of the observed phenomena.

We did not measure cerebral blood flow, which is known to be affected by ET\textsubscript{\text{CO}}\textsubscript{2}. However, other researchers have debated whether changes in cerebral blood flow alone could precipitate faint (7, 8, 21).
In conclusion, excessive splanchic pooling and thoracic hypovolemia drive increased peripheral resistance and hyperpnea in simple postural faint. Hyperpnea and pulmonary stretch may contribute to the sympathoinhibition that occurs at the time of faint.

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