Relation of Postural Vasovagal Syncope to Splanchnic Hypervolemia in Adolescents

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Background—The mechanisms of simple faint remain elusive. We propose that postural fainting is related to excessive thoracic hypovolemia and splanchnic hypervolemia during orthostasis compared with healthy subjects.

Methods and Results—We studied 34 patients 12 to 22 years old referred for multiple episodes of postural faint and 11 healthy subjects. Subjects were studied in the supine position and during upright tilt to 70° for 30 minutes and subgrouped into S+, historical fainters who fainted during testing (n=24); S−, historical fainters who did not faint during testing (n=10); and control subjects. Supine venous occlusion plethysmography showed no differences between blood flows of the forearm and calf in S+, S−, or control. Cardiac index, total peripheral resistance, and blood volume were not different. Using impedance plethysmography, we assessed blood redistribution during upright tilt. This demonstrated decreased thoracic blood volume and increased splanchnic, pelvic, and leg blood volumes for all subjects. However, thoracic blood volume was decreased in S+ compared with control volume, correlating well with the maximum upright heart rate. Splanchnic volume was decreased in the S+ and S− groups, correlating with the change in thoracic blood volume. Pelvic and leg volume changes were similar for all groups and uncorrelated to thoracic blood volume.

Conclusions—Enhanced postural thoracic hypovolemia and splanchnic hypervolemia are associated with postural simple faint. (***Circulation***. 2004;110:2575-2581.)

Key Words: syncope ■ blood volume ■ hypovolemia

S imple faint is common, with estimates up to 15% to 25% of young people experiencing the disorder.[1] Apparently healthy volunteers who do not faint during ordinary life can be induced to faint by provocative testing or physiological maneuvers.[2]

The fainting response, comprising increased bradycardia caused by vagal tone[3] coordinated with peripheral vasodilation with the withdrawal of muscle sympathetic nerve activity,[4] may be a reflex consequence of thoracic hypovolemia[5], as observed during the second stage of hemorrhagic shock.[6]

Mosqueda[7] subclassified fainting by clinical criteria into central, situational, and postural variants. Situational syncope is relatively uncommon in adolescents. Central vasovagal syncope is typically independent of body position[8,9] and is fairly common in the young. However, the most common variant in adolescents is postural syncope, which occurs when upright and is relieved by recumbency. Upright positioning produces thoracic hypovolemia by a caudal shift of blood volume[10] that is affected by splanchnic vasoconstriction[11] and potentiated by hypovolemia of any pathogenesis.[12] Increased fainting risk has been attributed to excessive orthostatic redistribution of blood to the lower extremities, but data from our laboratory[13] and others[14] suggest that lower-limb pooling is not different between fainters and control subjects.

We hypothesized that enhanced thoracic hypovolemia occurs during postural faints related to dependent pooling in the splanchnic circulation.

Methods

Subjects and Experimental Outline

We studied 34 patients 12 to 22 years old (median, 16.2 years; 13 male, 21 female) referred for 3 or more episodes of simple faint within a period of 3 months with no other cause established on testing. Patients with posturally related syncope who were well between episodes, free of systemic illnesses, and free of heart disease were included. None were taking medications.

We also studied 11 healthy volunteers 14 to 21 years old (median, 17.0 years; 4 male, 7 female). Subjects with a history of syncope or orthostatic intolerance were excluded. Only those free of systemic illnesses and heart disease were eligible to participate. There were no trained athletes.

Subjects were categorized by the results of head-up tilt-table testing at 70°. Significant hypotension was defined as a decrease in systolic blood pressure (BP) >20 mm Hg. Significant bradycardia was defined as a decrease in heart rate >20 bpm. Vasovagal syncope was defined as a transient loss of consciousness and postural tone

Hemodynamic Data

	Control (n=11)	Syncope S+ (n=24)	Syncope S− (n=10)
Normalized blood volume, mL/kg	70±5	68±4	74±4
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	4.3±0.4	4.1±0.3	4.8±0.6
Total peripheral resistance, $mm\ Hg \cdot L^{-1} \cdot min^{-1} \cdot m^{-2}$	19±6	23±5	17±5
Heart rate, bpm			
Supine	70±11	69±9	67±10
Upright 3 minutes	79±11	95±14†*	89±10†*
Maximum upright heart rate	90±10	112±16†*	102±11†*
Mean arterial pressure right arm, mm Hg			
Supine	73±6	75±5	77±12
Upright 3 minutes	76±7	77±6	79±7
Maximum upright heart rate	79±7	75±9	83±10
Venous pressure arm, mm Hg	10±2	13±3	12±6
Venous pressure calf, mm Hg	14±3	12±5	12±6
Forearm blood flow, $mL \cdot 100\ mL^{-1} \cdot min^{-1}$	2.6±0.6	2.3±0.4	2.9±0.3
Calf blood flow, $mL \cdot 100\ mL^{-1} \cdot min^{-1}$	2.8±0.4	2.6±0.4	2.8±0.5
Forearm arterial resistance, $mL \cdot 100\ mL^{-1} \cdot min^{-1} \cdot mm\ Hg^{-1}$	24±7	29±3	28±6
Calf arterial resistance, $mL/100\ mL^{-1} \cdot min^{-1} \cdot mm\ Hg^{-1}$	35±12	31±12	28±8
Forearm venous capacity, mL/100 mL	4.4±0.4	4.5±0.3	4.6±0.5
Calf venous capacity, mL/100 mL	5.2±0.4	4.3±0.7	4.6±0.4

*$P<0.05$ vs control; †$P<0.05$ vs supine.

relieved by recumbence associated with significant bradycardia and hypotension. Vasovagal presyncope was defined as transient significant bradycardia and hypotension relieved by recumbence but without loss of consciousness. Patients who experienced syncope or presyncope during testing were designated S+. Patients who did not experienced syncope or presyncope during testing were designated S−.

Informed consent was obtained, and the Committee for the Protection of Human Subjects (IRB) of New York Medical College approved all protocols.

Protocol

Tests began in a temperature-controlled room after an overnight fast. After a 30-minute acclimatization period, we measured blood volume and cardiac output by dye dilution technique. We measured BP continuously by arterial tonometry; measured heart rate by ECG; and estimated thoracic, splanchnic, pelvic, and calf blood segmental blood volumes by impedance plethysmography (IPG). We assessed peripheral blood flow, peripheral resistance, venous pressure, and peripheral venous capacity while supine by venous occlusion plethysmography for consistency with previous experiments.[13]

Supine hemodynamic measurements were performed. When these were complete, subjects were tilted upright to 70° while impedance measurements continued for 30 minutes or until syncope or presyncope occurred. Patients with syncope were returned immediately to the supine position, and the test was terminated.

Details of the Method

Strain Gauge Measurements: Peripheral Blood Flow, Venous Pressure, Peripheral Arterial Resistance, Venous Capacitance

We used venous occlusion strain-gauge plethysmography to measure forearm and calf blood flow. Measurements were made with occlusion cuffs placed around the upper and lower limbs ≈10 cm above a strain gauge attached to a strain-gauge plethysmograph (Hokanson, Inc). Supine arterial inflow in units of $mL \cdot 100\ mL\ tissue^{-1} \cdot min^{-1}$

was estimated as the rate of change of rapid increase in limb cross section using rapid cuff inflation to 40 mm Hg.[15] A secondary cuff prevented wrist and ankle blood flow. BP of the contralateral arm and leg were determined by oscillometry. Capacitance vessel pressure (venous pressure, P_v) was assessed by gradually increasing the occlusion cuff pressure until an increase in limb volume occurred. Peripheral resistances in forearm and calf were calculated using the formula [(mean arterial pressure−P_v)/resting flow].

We measured venous capacitance using our previously documented techniques.[16] This involved elevating the limb above heart level until no further decrease in volume was obtained and then using 4-minute-long, 10-mm Hg pressure steps to a maximum of 60 mm Hg. At lower pressures, limb size reaches a plateau representing venous filling, whereas at higher pressure, a linear component representing microvascular filtration[17] and a vascular component are superimposed. These are extracted by least-squares methods,[18] and capacitance is calculated from the sum of supine venous volume and vascular increments.[16]

Heart Rate and BP Monitoring

The ECG and right arm BP by arterial tonometer (Colin Instruments) were monitored continuously. Leg BP was measured intermittently by oscillometry on the calf contralateral to the strain gauge and used to calculate the calf mean arterial pressure. The ECG and tonometric pressure were interfaced to a computer through an A/D converter (DataQ Inc) and synchronized with strain-gauge and impedance data.

Dye Dilution Measurement of Blood Volume, Cardiac Output, and Total Peripheral Resistance

Indocyanine green dye dilution technique[19] using a noninvasive spectrophotometric finger photosensor (DDG, Nihon-Kohden Inc) was used to estimate blood volume, cardiac output, and total peripheral resistance. The dye decay curve is a monoexponential representing liver clearance. Once the hematocrit is measured, we extrapolated dye decay to the time of dye injection, yielding estimated blood volume. Total peripheral resistance was estimated
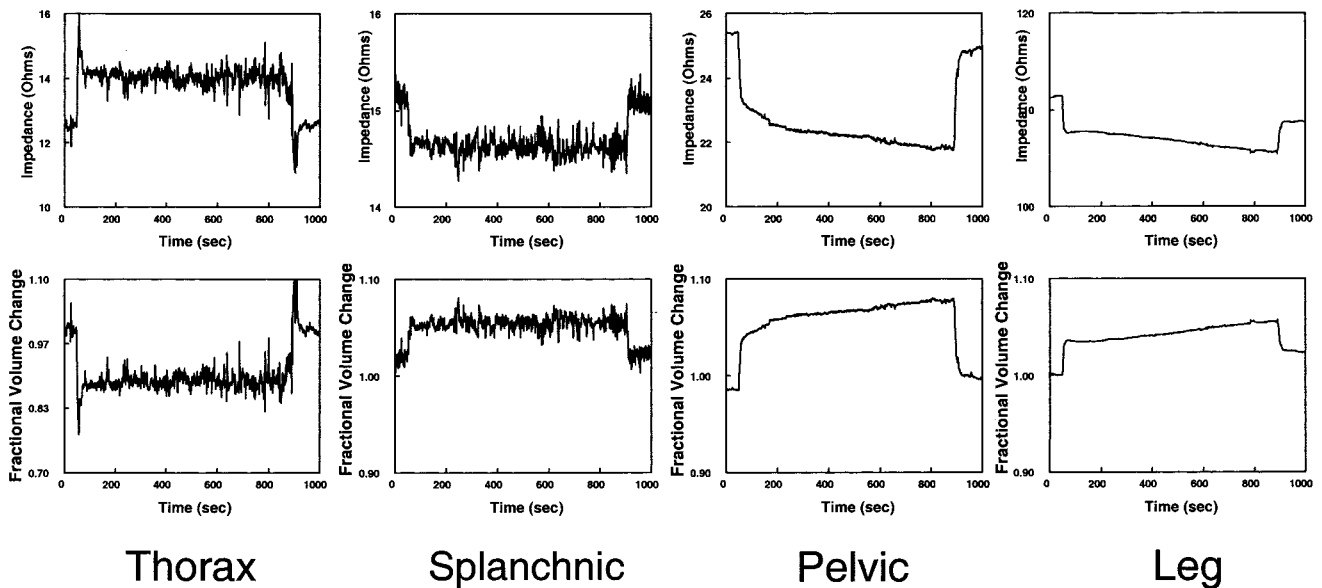
Figure 1. Time course of impedance (top) and segmental volume changes (bottom) are shown for individual segments in a representative control subject during upright tilt. In all subjects, thoracic impedance increases and splanchnic, pelvic, and leg impedance decreases during tilt, corresponding to a decrease in thoracic blood volume (ie, thoracic hypovolemia) and increased splanchnic, pelvic, and leg blood volume as expected through gravitational redistribution of blood volume.

by dividing the mean arterial BP in the right arm by the cardiac index.

IPG to Measure Changes in Segmental Blood Volume

IPG has been used to detect internal volume shifts,[20] including those produced during orthostatic stress.[21] We used a tetrapolar high-resolution impedance monitor (THRIM, UFI, Inc) to measure volume shifts in anatomic segments designated the thoracic segment, the splanchnic segment, the pelvic segment, and the leg segment.[20,22,23] Ag/AgCl ECG electrodes attached to the left foot and hand served as current injectors. Additional electrodes were placed in pairs representing the anatomic segments as follows: midline xiphoid process to supraclavicular area (the thoracic segment), iliac crest–midline xiphoid process (the splanchnic segment), knee–iliac crest (pelvic segment), and ankle–upper calf just below the knee (the leg segment). The IPG introduces a high-frequency (50-kHz), low-amperage (0.1-mA) constant-current signal between the foot and hand electrodes that is insensible to subjects. Electrical resistances were measured using segmental pairs as sampling electrodes. The distance between sampling electrodes (L) was measured. We estimated the change in segmental blood volume during tilt from the formula Δsegmental blood volume$=\rho \times (L/R_0)^{2 \times \Delta}R$,[24] where ρ is electrical conductivity of blood estimated as $53.2 \times \exp(Hct \times 0.022)$ (Hct=hematocrit, or packed cell volume, which we measured) given by Geddes and Sadler,[25] R_0 is the baseline resistance of a segment, and ΔR is change in resistance in a segment during postural change. Volume changes used for comparisons were calculated from maximum changes in ΔR during tilt using the average value of R_0 for the 60 seconds preceding tilt and then averaging over the entire change in resistance. We measured only changes in basal resistance during orthostatic challenge. We did not measure changes in impedance during each cardiac cycle used to estimate stroke volume. Such changes often cannot be reliably measured during upright tilt.

Tilt-Table Testing

After supine vascular measurements were complete, the patients were tilted to 70° for a maximum duration of 30 minutes. An electrically driven tilt table (Colin Instruments) with a footboard was used. BP, heart rate, forearm and calf size by strain gauge plethysmography, and IPG measurements were obtained continuously.

Statistics

Tabular data concerning supine and upright heart rates and BPs were compared by 2-way ANOVA comparing data before and after upright tilt and between subject groups. When significant interactions were demonstrated, the ratio of F values was converted to a t distribution by use of a Scheffé test, and probabilities were determined thereafter. All tabular results are reported as mean±SD. Graphic data are shown as mean±SEM when appropriate. Significance was defined as a probability value of $P<0.05$. Unblinded data were collected and analyzed by the same investigator throughout.

Results

Results are shown in the Table and in Figures 1 to 5. Of the 34 patients referred for fainting, 24 fainted during upright tilt (S+) and 10 did not faint (S−). None of our control subjects fainted.

Supine Systemic Hemodynamics

These are shown in the Table. Heart rate, BP, normalized blood volume, cardiac index, and total peripheral resistance, measured supine, were not different for S+, S−, or control.

Peripheral Hemodynamics Supine and Upright (Forearm and Calf Blood Flow, Peripheral Resistance, Venous Pressure, and Capacitance)

These are shown in the Table.

Supine heart rate was not different for S+ or S− or control. Heart rate increased with tilt for all subjects but increased to a greater extent in S+ and S− patients ($P<0.025$). Data are shown at 3 minutes after onset of tilt and at maximum heart rate during the procedure.

Resting arterial BP was not different among the groups. There was no significant change in arm BP with upright tilt. Arm and leg venous pressures, supine blood flows, arterial resistance, and venous capacitance were similar for all subjects.
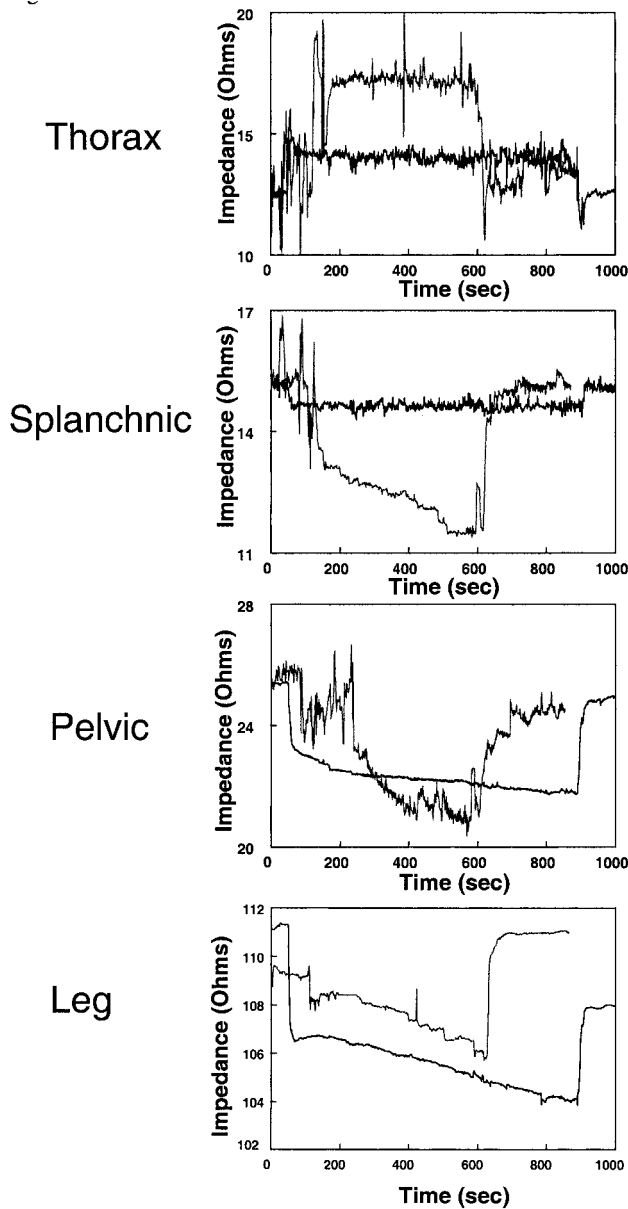
Figure 2. Comparable changes in impedance for representative control subject (black) and a representative syncopal subject (red). There is greater increase in thoracic impedance and greater decrease in splanchnic impedance in S+ compared with control, corresponding to enhanced thoracic hypovolemia and splanchnic hypervolemia in S+.

Impedance and Segmental Blood Volume Changes During Upright Tilt

Representative Control Subject Impedance and Volume Changes During Orthostasis

Figure 1 shows changes in segmental impedances and calculated blood volumes during upright tilt in a representative control subject. Thoracic impedance increased corresponding to decreased thoracic blood volume during tilt. Decreased splanchnic, pelvic, and leg-segment impedances during tilt corresponded to increased blood volumes in these segments. After the initial orthostatic volume shift, there is a gradual linear increase in pelvic and leg volume
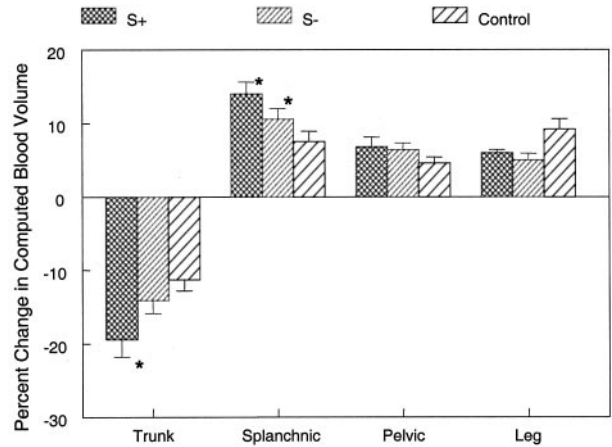

Figure 3. Changes in thoracic, splanchnic, pelvic, and leg blood volumes during upright tilt. S+ results are shown as blue bars; S− results are shown as red bars; control results are shown as black bars. There is decreased thoracic blood volume in S+ paired with increased splanchnic blood volume compared with control (*P*<0.01). Splanchnic blood volume was also increased (*P*<0.05) in S− patients. Pelvic and leg blood volume changes were not different from control.

related to microvascular filtration, which is not observed in the splanchnic segment. Thorax and splanchnic impedance changes have superimposed respiratory signals accounting for irregularities.

Segmental Impedance and Volume Changes in Syncope and Control

Figure 2 shows the changes in segmental impedance during upright tilt in the control subject and in an S+ patient. Thoracic impedance in S+ is increased more than control, indicating a greater decrease in thoracic blood volume.
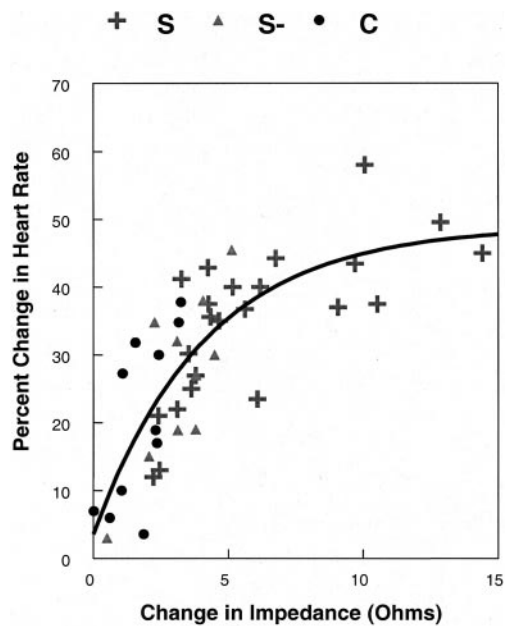

Figure 4. Relation between thoracic impedance and heart rate. Control subjects are shown in black, S+ in blue, and S− in red. Volume increases monotonically with change in blood volume for all groups.
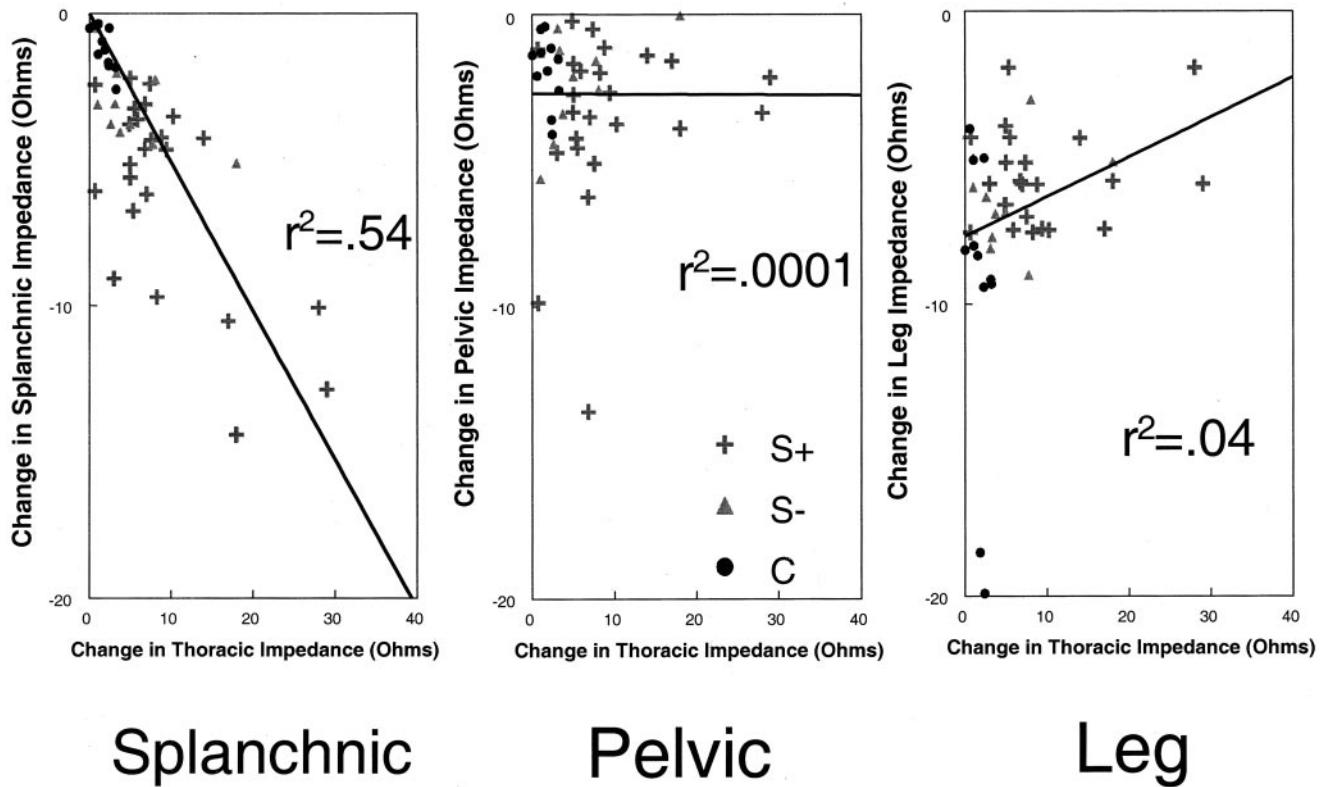
Figure 5. Correlations between thoracic impedance and splanchnic (left), pelvic (middle), and lower limb (right) impedances. Control subjects are shown in black, S+ in blue, and S− in red. Splanchnic and thoracic impedance are significantly correlated and vary similarly over all subjects. Changes in pelvic and leg impedances are unrelated to changes in thoracic impedance.

Splanchnic impedance is markedly decreased during tilt in S+ compared with control, indicating a greater increase in splanchnic blood volume. Tilt-related decreases in pelvic and leg impedance are similar.

Figure 3 depicts averaged changes in segmental blood volumes during tilt. There is a larger decrease in thoracic blood volume in S+ compared with control ($-19.4 \pm 2.4\%$ versus $-11.3 \pm 1.8\%$, $P < 0.01$) but no significant difference for S− ($-14.1 \pm 1.8\%$). There is a larger increase in splanchnic blood volume in S+ and S− compared with control ($14.4 \pm 1.8\%$, $P < 0.01$, for S+, $10.8 \pm 1.4\%$, $P < 0.05$, for S− versus $7.4 \pm 1.4\%$ for control subjects).

Origins of Presyncopal Tachycardia
We hypothesized that thoracic hypovolemia causes excessive presyncopal tachycardia in postural syncope. Therefore, we graphically analyzed the maximum heart rate during upright tilt as a function of change in thoracic impedance for all subjects. The results shown in Figure 4 demonstrate a monotonic relation in which heart rate increases as impedance increases (and volume decreases).

Relation Among Segmental Impedance Changes
To further explore the relation between the change in thoracic blood volume and changes in segmental blood volumes, we graphically compared changes in splanchnic, pelvic, and leg blood volumes with changes in thoracic blood volume during tilt. Figure 5 demonstrates that only thoracic and splanchnic segmental volume changes are significantly correlated.

Discussion

General Comments
Our principal findings are that patients with postural faint have, on average, a greater increase in thoracic impedance and decrease in splanchnic impedance corresponding to a greater decrease in thoracic blood volume and increase in splanchnic blood volume during orthostatic stress compared with control subjects. This correlates with an increase in heart rate during upright tilt but not with the degree of pelvic or leg hypervolemia during tilt. Thus, although leg and pelvic pooling indeed occur in all subjects during upright tilt, there are no differences in orthostatic leg and pelvic pooling between control and syncopal subjects.

Although significant splanchnic hypervolemia during upright tilt characterizes all patients (S+ and S−) with a history of postural fainting, increased tachycardia and thoracic hypovolemia during tilt occur in S+ patients compared with S− patients. As shown in Figure 3, these differences seem to be quantitatively but not qualitatively different.

The finding that splanchnic blood pooling is central to postural fainting is not surprising. The splanchnic circulation is the single most important venous reservoir. In humans, much of this blood storage occurs in the gastrointestinal tract, which has active venoconstrictive and arterial vasoconstrictive capabilities.[26] At rest, the splanchnic venous reservoir is large and highly compliant.[27] There is rich splanchnic innervation and good evidence that intact innervation of arterial and venous vasculature is required for BP maintenance

during postural changes.[28] Studies of sympathectomized animals support the vital role played by splanchnic blood mobilization through vasoconstriction and venoconstriction.[10] Although we did not measure neural parameters, the rapidity of change in splanchnic blood volume suggests rapid changes in splanchnic blood flow and venoconstriction, previously demonstrated by use of dye-infusion techniques.[29]

Our data show that splanchnic filling occurs during orthostasis in all subjects. Filling is limited by vasoconstriction, with elastic recoil emptying of veins, and by active venoconstriction. These mechanisms are, however, unable to prevent gravitational sequestration of blood within the splanchnic circulation even in normal subjects.

Peripheral Hemodynamics, Supine and Upright

Supine heart rate, cardiac index, blood volume, and total peripheral resistance are similar to control for S+ and S− before orthostatic challenge. These data are consistent with normal global and regional circulations during supine rest.

Origins of Presyncopal Tachycardia

Upright heart rate is increased above control values in S+ or S−. From Figure 4, we see that heart rate increased with thoracic hypovolemia, suggesting that tachycardia is the result of cardiac underfilling and withdrawal of baroreflex stimulation. These findings are similar to those of Julu et al,[30] who demonstrated tachycardia and unstable BP preceding faints. Julu et al attributed their findings to decreased cardiac vagal tone and cardiac sensitivity to the baroreflex. Decreased vagal tone occurs with thoracic hypovolemia. Decreased baroreflex sensitivity is a consequence of hypovolemia.[31] Initially, all subjects were compensated during tilt. In syncopal subjects, there followed a symptomatic prodrome synchronous with progressive tachycardia and a slow fall in BP. This progressed to BP instability, followed by the actual faint. The data suggest that regional volume redistribution is paramount in the pathophysiology of postural fainters.

Segmental Impedance and Blood Volume Redistribution During Upright Tilt

Regional blood maldistribution is supported by findings of excessive upright splanchnic pooling correlated to excessive thoracic hypovolemia (in S+), the only physiological measures distinguishing fainters and control subjects. Segmental data thus indicate localized splanchnic venous pooling rather than global vascular abnormalities in postural fainters. Increased splanchnic pooling may occur as the result of failure of normal venoconstriction and arterial vasoconstriction with or without an increase in venous resistance[32] or as the result of increased splanchnic vascular compliance. Data from subjects with postural tachycardia syndrome indicate that inadequate splanchnic vasoconstriction may be paramount.[33] However, the present data cannot distinguish between these possibilities.

Limitations

Shortcomings of IPG

Segmental changes are reported as fractional volume changes. They are not quantitative measures of absolute volume. They are, however, good qualitative and directional measures of segmental volume changes. Nevertheless, drawing rigorous quantitative conclusions is probably not warranted.

Regional Circulations

We did not study all regional circulations. Past data have not indicated an important role for upper extremity or cerebral circulations in pooling phenomena. However, skin may serve as an important blood reservoir during body heating. Given neutral environmental conditions, thermal cutaneous contributions were probably small.

Orthostatic Blood Flow

We do not report thoracic, splanchnic, pelvic, or leg measures of vasoconstriction during orthostasis, which are important steps in determining mechanism. Although blood flows using impedance methods have been reported, they fall beyond the scope of the present work. Other techniques, such as Doppler ultrasound, may help in this regard. However, we are the first to establish the preeminent importance of orthostatic splanchnic blood pooling in simple faint.

Autonomic Changes

A direct measure of sympathetic activity, such as muscle sympathetic nerve activity, could have enhanced our ability to attribute flow and arterial resistance findings to autonomic dysfunction. However, the technique is available only to assess limb autonomic function and would add little to our splanchnic observations. Also, such instrumentation is regarded as problematic in young subjects.

Patient Age

Young adults and adolescents may not perfectly represent findings for mature adults. However, cardiovascular structure and function are essentially mature by puberty, and therefore, results should be at least qualitatively similar to older age groups. Moreover, younger patients have the advantage of absence of confounding illness, such as heart disease, renal disease, hypertension, and diabetes.

In summary, our data suggest that postural simple faint depends on thoracic hypovolemia related to splanchnic hypervolemia. Future work will determine how splanchnic venous sequestration is related to altered venous or arterial properties.

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