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Mechanisms of Vasovagal Syncope in the Young: Reduced Systemic Vascular Resistance Versus Reduced Cardiac Output

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Background—Syncope is a sudden transient loss of consciousness and postural tone caused by cerebral hypoperfusion. The most common form is vasovagal syncope (VVS). Presyncopal progressive early hypotension in older VVS patients is caused by reduced cardiac output (CO); younger patients have reduced systemic vascular resistance (SVR). Using a priori criteria for reduced CO ($\downarrow$CO) and SVR ($\downarrow$SVR), we studied 48 recurrent young fainters comparing subgroups of VVS with VVS-$\downarrow$CO, VVS-$\downarrow$SVR, and both VVS-$\downarrow$CO&$\downarrow$SVR.

Methods and Results—Subjects were studied supine and during 70-degrere upright tilt with a Finometer to continuously measure blood pressure, CO, and SVR and impedance plethysmography to estimate thoracic, splanchnic, pelvic, and calf blood volumes, blood flows, and vascular resistances and electrocardiogram to measure heart rate and rhythm. Central blood volume was decreased in all VVS compared to control. VVS-$\downarrow$CO was associated with decreased splanchnic blood flow and increased splanchnic blood pooling compared to control. Seventy-five percent of VVS patients had reduced SVR, including 23% who also had reduced CO. Many VVS-$\downarrow$SVR increased CO during tilt, with no difference in splanchnic pooling, caused by significant increases in splanchnic blood flow and reduced splanchnic resistance. VVS-$\downarrow$CO&$\downarrow$SVR patients had splanchnic pooling comparable to VVS-$\downarrow$CO patients, but SVR comparable to VVS-$\downarrow$SVR. Splanchnic vasodilation was reduced, compared to VVS-$\downarrow$SVR, and venomotor properties were similar to control. Combined splanchnic pooling and reduced SVR produced the earliest faints among the VVS groups.

Conclusions—Both $\downarrow$CO and $\downarrow$SVR occur in young VVS patients. $\downarrow$SVR is predominant in VVS and is caused by impaired splanchnic vasoconstriction. (*J Am Heart Assoc*. 2017;6:e004417. DOI: 10.1161/JAHA.116.004417.)

Key Words: cardiac output • syncope • tilt-table testing • vasoconstriction • vasovagal syncope • young

Syncope is defined by rapid onset of transient loss of consciousness and postural tone attributed to cerebral hypoperfusion with spontaneous recovery.[1] The majority of syncope is attributed to simple faint, denoted vasovagal syncope (VVS),[2] and often triggered by upright posture.

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Upright posture causes subdiaphragmatic gravitational blood pooling, primarily within the venous system, that reduces central blood volume.[3] In the absence of skeletal muscle pump activity, this reduces venous return and cardiac output (CO). Blood pressure is maintained by baroreceptor-mediated increases in systemic vascular resistance (SVR), passive elastic recoil of venous blood, active splanchnic venoconstriction,[4] and an increase in heart rate (HR). Splanchnic vaso- and venoconstriction are integral to maintaining upright blood pressure (BP).[5] A representative time course of changes in BP and HR for a young VVS patient during 70-degree upright tilt testing is shown in Figure 1.

Typically, we discern 4 phases of cardiovascular response.[6–8] Following initial orthostatic hypotension,[9] BP stabilizes (phase 1) for a variable number of minutes. Thereafter, gradually progressive early hypotension occurs (phase 2) associated with reflexively increased HR. Because mean arterial pressure (MAP)=CO×SVR, decreasing BP during phase 2 could be attributed to decreasing CO, decreasing SVR, or a combination of both. During phase 3, there is a rapid decrease in BP and HR with circulatory collapse caused
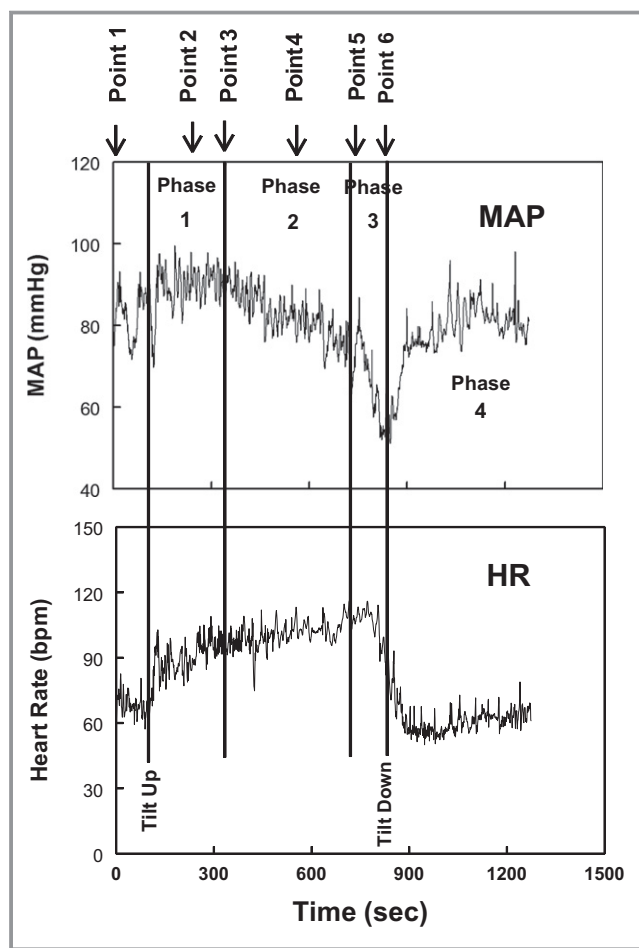
Figure 1. Head-up tilt table test for a vasovagal syncope patient. Mean arterial pressure (MAP) is shown in the top panel and heart rate (HR) in the bottom panel. Fiducial points are marked at the top. MAP and HR follow a characteristic time course comprising 4 stages: early blood pressure (BP) stabilization (phase 1, fiducial point 2); "progressive early hypotension" with BP slowly declining as HR increases (fiducial points 3–5); syncope with hypotension and bradycardia (phase 3, fiducial point 6). Phase 4 recovery of BP occurs within 30 seconds once supine.

by vasodilation related to withdrawal of sympathetic nerve activity and loss of adrenergic vasoconstriction.[10] Phase 4 recovery of BP occurs rapidly once supine.

Previous studies of adult VVS using pulse contour analysis of finger photoplethysmographic waveforms (ModelFlow method) showed that phase 2 hypotension was attributed to decreasing CO attributed, for the most part, to excessive blood pooling in the splanchnic circulation[5] whereas SVR was maintained or increased.[11] Previous studies of children and adolescents with VVS using ModelFlow methods showed that phase 2 hypotension was attributed to decreasing SVR whereas CO was maintained.[12] In contrast, other experiments using electrical impedance plethysmography methods to measure changes in regional blood flow and blood volume in young VVS patients showed reduced CO and increased SVR.[13,14]

To resolve these apparently contradictory results, we applied both finger photoplethysmographic and impedance plethysmographic techniques to a single group of young VVS patients and set a priori criteria for "reduced CO" and "reduced SVR."

We hypothesized that phase 2 hypotension occurs in young VVS patients either by decreased SVR ($\downarrow$SVR), decreased CO ($\downarrow$CO), or a combination of decreased SVR and decreased CO ($\downarrow$SVR+$\downarrow$CO). We further hypothesized that VVS patients with $\downarrow$CO have excessive splanchnic pooling compared to healthy volunteers, which is absent if $\downarrow$CO does not occur.

Methods

Subjects

To test these hypotheses, we recruited 48 patients with a history of recurrent fainting (30 female, 16.1±1.0 years) ranging in age from 12 to 19 years. Fainters were referred to our center for investigation after experiencing at least 2 episodes of fainting within the last 12 months. Data were analyzed for patients who experienced VVS during our upright tilt procedure, and who identified the presyncopal prodrome, and the postsyncopal postdrome as similar to their outpatient experiences. We also recruited 10 healthy nonfainting control subjects (6 female, 16.3±1.1 years). There were no differences in the ages, weight, and body mass index (BMI) between the groups.

Syncope patients gave a medical history and underwent a physical examination, electrocardiography, echocardiography, and prolonged monitoring, if needed, to exclude cardiac causes for syncope. Control subjects reported no clinical illnesses and had never fainted.

The diagnosis of VVS was primarily based on clinical history. Key diagnostic features encompassed predisposing situations, prodromal symptoms, physical signs, and postdrome recovery and symptoms.[2] In all patients, past fainting had been induced by prolonged standing and in 6 patients it was also triggered by noxious stimuli. Prodromal features included pallor, lightheadedness, nausea with abdominal discomfort, diaphoresis, a feeling of warmth, visual scotomata, or frank loss of vision. Following the faint, unconsciousness lasted less than 30 seconds when supine and most patients felt fatigued afterward. Exclusion criteria for participation in this study included any infectious or systemic disease (including other cardiovascular disease), other forms of orthostatic intolerance, competitive athletic training, recent long-term bed rest, use of nicotine-containing products, or pregnancy within the last year. Any medication for syncope was stopped for at least 2 weeks before participation in this study. No subjects were taking neurally active or vasoactive drugs at evaluation.

All subjects refrained from caffeine and xanthine-containing products for at least 72 hours before testing. All subjects were instructed to fast for at least 4 hours before testing. This study was approved by the Institutional Review Board of New York Medical College (Valhalla, NY). All subjects aged 18 or older signed an informed consent; those younger than 18 assented to participate and their parent or legal guardian signed an informed consent.

Protocol

Subjects arrived at our climate-controlled center at 9:30 AM after a 4-hour fast and were instructed about the tests and instrumentation. Subjects were then instrumented while supine. Beat-to-beat BP was measured by Finometer finger photoplethysmograph (FMS, Amsterdam, the Netherlands) on the right forefinger or middle finger. The Finometer uses the ModelFlow algorithm to estimate beat-to-beat CO by pulse-wave analysis. Before experiments began, ModelFlow CO was calibrated against an Innocor inert gas rebreathing CO measurement (Innovision, Glamsbjerg, Denmark) while supine. We continuously computed SVR by dividing the time average arterial pressure (MAP) by the ModelFlow CO averaged over each cardiac cycle. We also computed the pulse pressure (PP) for each cardiac cycle by subtracting the diastolic (DBP) from the systolic BP (SBP). We placed paired electrodes using anatomical landmarks to estimate thoracic, splanchnic, pelvic, and calf segmental blood volumes, blood flows, and vascular resistance by impedance plethysmography.[15] Respiratory plethysmography (Respitrace; NIMS Scientific, Miami Beach, FL) and capnography (Smith Medical PM, Waukesha, WI) measured changes in respiration and end tidal carbon dioxide ($ETCO_2$). An electrocardiograph measured HR from the beat-to-beat cardiac electrical interval. Signals were acquired at 200 samples/s, multiplexed, and analog-to-digital converted using custom software. These measurements are routine during our tilt-table studies.

Following instrumentation, subjects remained awake and supine for 30 minutes to acclimate. Baseline data comprised continuously measured HR, BP, $ETCO_2$, CO, SVR, and thoracic, splanchnic, pelvic, and calf segmental impedances and rate of change of impedances by impedance plethysmography. For purposes of comparison, we used averaged data for the 10 minutes immediately preceding tilt to determine baseline, supine values.

After supine data collections were complete, subjects were tilted upright to 70 degrees. Duration of upright tilt was 10 minutes in healthy volunteer controls whereas VVS patients remained upright until fainting was imminent. Tilt was performed without pharmacological provocation. Continuously measured HR, BP, $ETCO_2$, CO, SVR, and impedance data were recorded for off-line analysis. We limited the head-up tilt (HUT) testing in healthy volunteer subjects to 10 minutes. We have previously demonstrated that this is sufficient time for the comparison of orthostatic changes between control and VVS subjects.[11,14] Also, near fainting occurred, on average, between 10 and 11 minutes after starting upright tilt in VVS patients.

VVS patients had a clinical history of fainting, and each developed a classic vasovagal faint with hypotension followed by bradycardia during tilt-table testing. During this investigation, VVS patients were tilted back to supine when fainting was imminent, or when requested. Imminent postural vasovagal syncope was defined by a tilt-induced decrease in mean arterial pressure (MAP) to <60 mm Hg or a decrease in SBP <70 mm Hg associated with symptoms of impending loss of consciousness, severe lightheadedness, nausea, heat, and diaphoresis.

Detailed Methods

Fiducial event markers

In accord with our previous work,[14] we analyzed results at fiducial time markers rather than at specific time points. Fiducial markers identified times at which physiological events occurred. Although the actual time between physiological events varied, fiducial markers allowed for the study of events with corresponding responses specific for each fainter. Six defining events were determined from the BP trace of each VVS subject, represented by 1 subject (Figure 1).

The first fiducial point was baseline "supine." The second was chosen to be mid phase 1 ≈"1 minute" after HUT to avoid including the initial transient decrease in BP and increase in HR that follows orthostasis[16] with rapid recovery in both healthy volunteers and VVS patients. This has been denoted "initial orthostatic hypotension" and relates to a period of mechanical dysequilibrium caused by caudal central blood translocation and the normal lag in sympathetic vasoconstriction.[9] The third point was defined in fainters at the onset of the gradual decline in BP and is designated "early" this is the start of phase 2. BP falls off rapidly and abruptly at the transition between phase 2 and 3, which defined the "late" point (point 5), just before faint. We defined an additional "mid" point midway between "early" and "late" (point 4). The last fiducial point (point 6), designated "faint," was at the time of faint for VVS patients, or at 10 minutes for control subjects. Healthy control subjects did not have a significant fall in BP and did not faint. We defined equivalent fiducial time points for healthy volunteers by taking the actual time of occurrence of each fiducial marker event in VVS patients divided by the time from onset of tilt to determine the fractional time to marker, averaging that over all fainters, and multiplying by 10. Control subjects and VVS subjects were thus compared at equivalent times to allow for a uniform

evaluation of hemodynamic quantities across groups, and all subjects were represented at each fiducial point.

A priori VVS patient stratification based on ModelFlow criteria

CO decreases during tilt in healthy volunteers.[17] Past experiments using ModelFlow methods demonstrated an average maximum reduction of CO during upright tilt for 10 minutes of 11.2±5.1% (SD) in 58 comparable young control subjects. This CO reduction in control subjects is similar to values reported by de Jong-de Vos van Steenwijk et al.[12]

We defined 3 groups of VVS based on a priori criteria: (1) *decreased CO but not SVR* (designated "↓CO"), defined by CO decreased by at least 11.2% from baseline by "late" phase 2); (2) *decreased SVR but not CO* (designated "↓SVR") during tilt if ModelFlow estimated SVR decreased below baseline by "late" phase 2; and (3) *decreased CO+SVR* (designated ↓CO & ↓SVR) comprised the remainder of patients. All VVS patients fell within these group definitions. Subjects were therefore assigned to 1 of the groups based on post-hoc analyses of data recorded during tilt-table testing.

Measurement of changes in segmental blood volumes

Changes in segmental or regional blood volumes and segmental blood flows used impedance plethysmography (IPG) using a tetrapolar high-resolution 4-channel digital impedance plethysmograph (UFI, Morro Bay, CA) to measure impedances and the rate of change of impedances, as previously described.[18,19] These quantities were obtained within 4 anatomical segments defined by electrode placement on anatomical landmarks that delimit respective regional circulations. These were designated the thoracic segment (supraclavicular area to xyphoid process), the splanchnic segment (xyphoid process to iliac crest), the pelvic segment including lower pelvis to the knee (iliac crest to knee), and the

leg or calf segment (upper calf just below the knee to the ankle).

Measurement of changes in segmental blood flow

IPG was also used to estimate segmental or regional blood flows.[20] These methods have been validated in our laboratory against the reference standard indocyanine green dye technique and calf venous occlusion plethysmography and were used to measure leg, thoracic, and splanchnic blood flow, as previously described.[15,21]

Statistical Analysis

All data were digitized and stored and were analyzed offline with custom software. VVS patients were partitioned into 3 groups—VVS-↓CO, VVS-↓SVR, and VVS-↓CO & ↓SVR—as previously described. Including the healthy volunteer control group, there were 4 subject groups for comparison.

Baseline data for BP, HR, CI, SVR, and ETCO$_2$ are shown in absolute units in Table. We also analyzed time to faint for each of the 3 VVS groups. These were compared among the groups by 1-way ANOVA. A significant omnibus ANOVA test was followed by post-hoc pair-wise comparisons among groups. Scheffe's test was used to adjust the pair-wise comparisons for multiple comparisons. All tabular results are reported as mean±SEM.

Graphic data are shown as percent of baseline expressed as mean±SEM. Data were obtained from original time series averaged over 15-second intervals centered at the fiducial markers. Data were collected and analyzed by the same investigator throughout. We used repeated-measures ANOVA to compare group- and time-dependent differences at fiducial points. We assigned greatest importance to "group×time effects" representing the interaction of subject group with time-dependent changes during upright tilt. We assumed a covariance structure of compound symmetry. Reported P

Table. Baseline Hemodynamics

	Control	All Fainters	↓CO	↓CO &↓SVR	↓SVR
SBP, mm Hg	113±3	115±2	117±4	111±5	115±3
DBP, mm Hg	61±2	57±2	59±3	59±5	55±2*
MAP, mm Hg	78±2	76±1	79±3	76±5	75±2
HR, bpm	63±6	69±6	70±5	64±8	62±5
CI, L/min per m^2	4.7±0.5	4.8±0.2	5.1±0.5	4.4±0.4	4.7±0.3
SVR, mm Hg/L per minute	17.5±1.6	17.2±0.8	16.8±1.1	18.0±1.3	18.1±1.2
ETCO$_2$, Torr	41±1	43±1	41±1	42±1	44±1

CI indicates cardiac index in L/min per m^2 (liters per minute per square meter body surface area); DBP, diastolic blood pressure in mm Hg (millimeters of mercury pressure); ETCO$_2$, end tidal carbon dioxide in Torr; HR, heart rate in bpm (beats per minute); MAP, mean arterial pressure in mm Hg (millimeters of mercury pressure); SVR, systemic vascular resistance in mm Hg/L per minute (millimeters of mercury pressure per liter per minute); SBP, systolic blood pressure in mm Hg (millimeters of mercury pressure).
*P<0.05 compared to control.

values reflect the interaction term using the Greenhouse–Geisser correction. Statistical significance was set at $P \leq 0.05$. Results were calculated by using GraphPad Prism software (version 4.0; GraphPad Software Inc., La Jolla, CA).

Results

Baseline Supine Data

Supine data are displayed in Table, which shows data for controls, for all VVS patients combined, and for VVS patients stratified into the 3 subgroups on the basis of upright CO and SVR. There were no differences between the age, sex, and BMI of the 3 subgroups compared to controls. Stratified data are used for ANOVA. There were no baseline differences in SBP, HR, CI, SVR, or ETCO$_2$ between control and VVS groups. DBP was significantly reduced, compared to control ($P<0.025$), for VVS–↓SVR patients.

Upright Tilt Data

Time to faint

Healthy control subjects did not experience symptoms of orthostatic intolerance nor did they faint. There were 12 patients belonging to VVS–↓CO, 11 belonging to VVS–↓CO&↓SVR, and 25 belonging to the VVS–↓SVR group. VVS–↓CO&↓SVR resulted in the most precipitous decreases in BP during phase 2 and the shortest mean time from tilt up to syncope, averaging 350±50 seconds, compared to 902±118 seconds for VVS–↓CO and 674±102 seconds for VVS–↓SVR ($P=0.013$ for ANOVA; $P=0.010$ for VVS–↓CO vs

VVS–↓CO&↓SVR). Average time to faint inclusive of all groups was 640±70 seconds (10 minutes, 40 seconds).

Representative tracings during tilt, VVS groups

Figure 2 shows BP, HR, CO, and SVR for representative subjects belonging to each experimental group. There is an increase in HR in all during orthostatic stress. There is a gradual falloff in BP followed by rapid hypotension and bradycardia in all VVS patients, but not in controls. The initial step decrease in CO on tilt-up in the VVS–↓CO patients is attributed to the effects of gravity. CO thereafter progressively decreases throughout tilt whereas SVR increases. CO falls initially in the VVS–↓CO &↓SVR patient then rises slightly and decreases during the remainder of tilt. SVR initially increases on tilt-up, but then decreases during the remainder of tilt, whereas CO falls. CO increases above baseline in the VVS–↓SVR patient whereas SVR declines monotonically. At the time of imminent faint, all VVS patients experienced hypotension followed afterward by bradycardia whereas SVR and CO decreased. Averaged data showing percent changes in hemodynamic quantities from baseline values are shown in Figures 3 through 6.

HR, MAP, PP

Figure 3 shows that HR fell precipitously in all VVS patients at the time of faint. MAP and PP decreased significantly more throughout tilt in all VVS groups ($P<0.025$) compared to control subjects.

Regional blood flows

As shown in Figure 4, CO decreased progressively and more rapidly in VVS–↓CO and VVS–↓CO&↓SVR compared to control
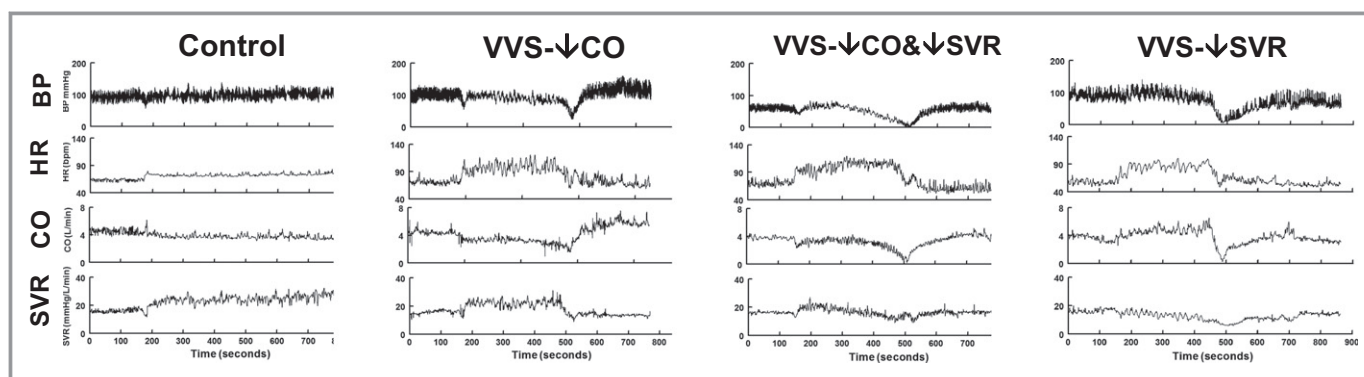

Figure 2. Blood pressure (BP), heart rate (HR), cardiac output (CO), and systemic vascular resistance (SVR) for representative subjects during head-up tilt table testing. Shown from left to right are healthy control subjects (Control), VVS syncope patients who have a decrease in CO but no decrease in SVR designated (VVS–↓CO), VVS syncope patients who have a decrease in CO and SVR during tilt designated (VVS–↓CO &↓SVR), and VVS syncope patients who have a decrease in SVR during tilt but no decrease in CO designated (VVS–↓SVR). There is an increase in HR rate with orthostasis in all subjects. BP first gradually declines, followed by rapid hypotension and bradycardia in all VVS. VVS–↓CO &↓SVR patient has a decrease in CO and initial increase in SVR, which then decreases for the remainder of tilt. CO in the VVS–↓SVR patients trends above baseline whereas SVR declines monotonically. At the time of faint, all VVS patients experienced hypotension followed rapidly by bradycardia whereas SVR and CI decreased. CI indicates cardiac index; VVS, vasovagal syncope.
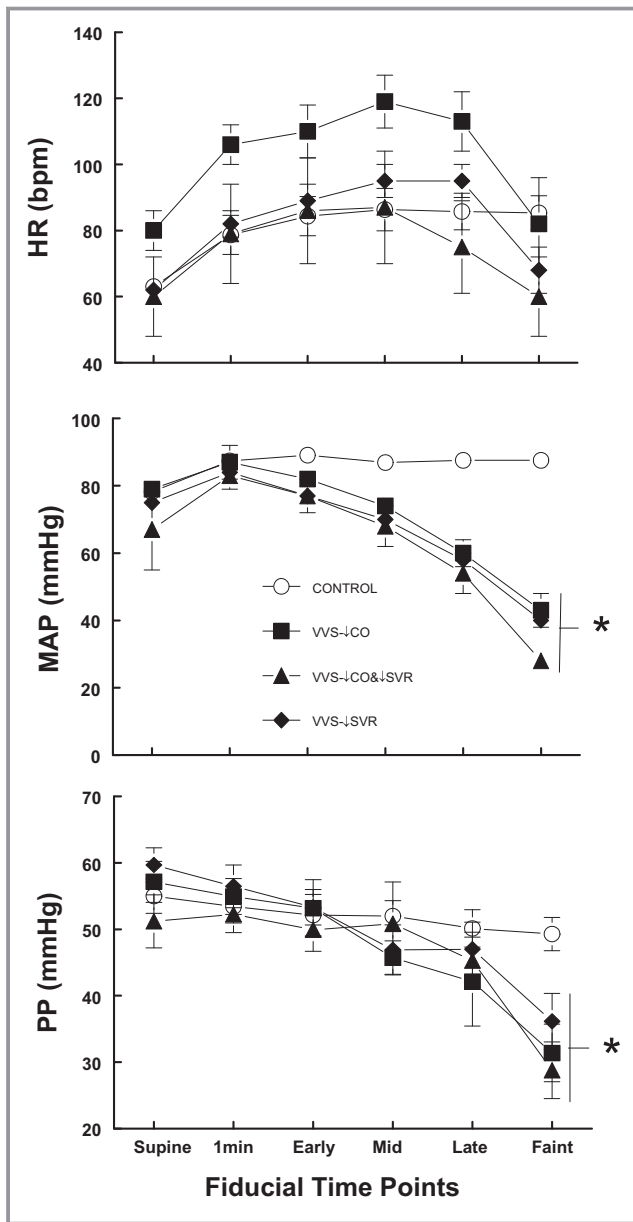
Figure 3. Averaged heart rate (HR), mean arterial pressure (MAP), and pulse pressure (PP) during upright tilt. HR appears in the upper panel, MAP in the middle panel, and PP in the lower panel at designated fiducial time points. Control data are shown as open circles (○), VVS–↓CO data are shown as black boxes (■), VVS–↓CO &↓SVR are shown as black triangles (▲), and VVS–↓SVR are shown as diamonds (♦). HR fell precipitously in all VVS patients at the time of faint. MAP and PP decreased significantly throughout tilt in all VVS ($P<0.025$) compared to control subjects, as shown by the asterisk ("*"). VVS indicates vasovagal syncope.

($P<0.01$). CO was significantly increased above control in VVS–↓SVR before faint ($P<0.001$). Control subjects had an initial decrease in CO by 1 minute, which was thereafter sustained. Splanchnic blood flow decreased from baseline ($P<0.001$) in control and in VVS–↓CO and VVS–↓CO&↓SVR. However, splanchnic blood flow increased progressively

during tilt in VVS–↓SVR ($P<0.0001$). Splanchnic blood flow trended lower in VVS–↓CO compared to control.

Pelvic blood flow decreased in all groups and was not different from control in VVS–↓SVR. Pelvic blood flow was reduced, compared to control, during tilt in VVS–↓CO and VVS–↓CO&↓SVR ($P<0.001$). Calf blood flow decreased similarly with tilt for all subjects.

Regional blood volumes

Figure 5 shows that the percent of central blood volume (% CBV) decreased in all subjects. %CBV decreased significantly more than control ($P<0.01$) in all VVS patients until just before faint. Splanchnic blood volume increased during tilt in all subjects, but was significantly greater than control for VVS–↓CO and VVS–↓CO&↓SVR ($P<0.001$). Splanchnic blood volume was not different from control in VVS–↓SVR. Pelvic blood volume increased similarly in all groups during tilt. Calf blood volume increased with tilt for all subjects. Calf blood volume increased more than control in VVS–↓CO and VVS–↓SVR ($P<0.025$).

Regional arterial resistances

Figure 6 shows that SVR increased by 1 minute above baseline for all subjects, but then decreased progressively in VVS–↓CO&↓SVR and VVS–↓SVR. SVR increased similarly to control in VVS–↓CO by definition. Splanchnic resistance increased similarly in control and VVS–↓CO up to the time of faint when R_{Spl} decreased in all VVS. Following an initial increase, splanchnic resistance decreased in VVS–↓SVR and VVS–↓CO&↓SVR compared to control ($P<0.025$). At no time did R_{Spl} significantly increase above supine in VVS–↓SVR.

Pelvic resistance increased in all groups and was larger than control in VVS–↓CO until the time of faint. R_{Pelv} decreased for all VVS at the time of faint. Calf resistance increased initially from baseline in all subjects, then decreased in all VVS compared to control.

Discussion

VVS occurs when arterial pressure decreases below that which provides adequate cerebral blood flow to maintain consciousness. We have previously shown that syncope is defined by a decrease in cerebral blood flow that is accompanied by a loss of cardiovagal baroreflex and effective cerebral autoregulation.[22,23]

In the current studies, we have partitioned the HR-BP response to an orthostatic challenge into 3 phases. During phase 1, there is BP stability. In phase 2, there is a slow fall in BP and an increase in HR. Phase 3 is characterized by a rapid fall in BP that is accompanied with bradycardia. The underlying mechanisms for these 3 patterns is not well
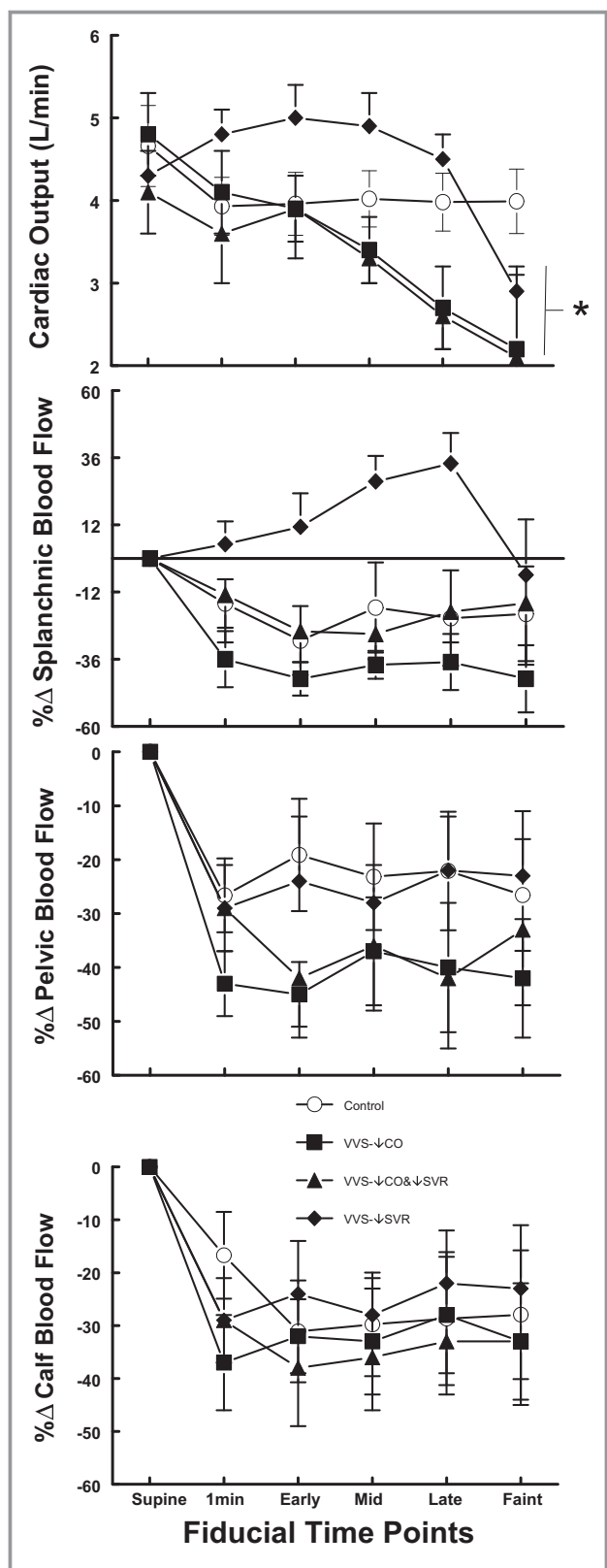
Figure 4. Regional blood flows during upright tilt. The top panel shows the cardiac output (CO) in L/min, the second shows percent change in splanchnic blood flow (%Δ Splanchnic Blood Flow), the third panel shows percent change in pelvic blood flow (%Δ Pelvic Blood Flow), and the bottom panel shows percent change in calf blood flow (%Δ Calf Blood Flow). Control data are shown as open circles (O), VVS-↓CO data are shown as black boxes (■), VVS-↓CO &↓SVR are shown as black triangles (▲), and VVS-↓SVR are shown as diamonds (♦). CO decreased progressively and more rapidly in VVS-↓CO, and VVS-↓CO&↓SVR compared to control ($P<0.01$), as shown by the asterisk ("*"). Calf Blood Flow decreased similarly with tilt ($P<0.001$) for all subjects, as shown by the asterisk ("*")*. SVR indicates systemic vascular resistance; VVS, vasovagal syncope.

sought to elucidate which of these mechanisms were responsible for syncope in this age group and provide data by measuring a wide variety of factors, including HR, CO, SVR, $ETCO_2$, and regional impedance data.

All the responses observed in this study were of the combined vasovagal variety, with a combination of hypotension and HR reduction. We chose to segregate them into 3 groups; ↓CO, ↓SVR, and ↓CO &↓SVR. The large preponderance (25 of 48) belonged to the ↓SVR group. Importantly, MAP reductions were similar in all 3 groups and distinctly different from the controls that had no significant change in MAP, but the mechanisms underlying the reduction varied between the groups. And, given that VVS by these constructs takes more than 1 hemodynamic form, our results will be discussed in relation to each form.

Decreased CO Without Decreased SVR Occurs in a Subset of Young VVS Patients and Is Related to Splanchnic Blood Pooling

A minority of young fainters in our cohort (those with VVS-↓CO; 11 of 48) had phase 2 hypotension determined by reduced venous return, similar to that reported in adults.[11] This contrasts with a previous study, showing reduction of SVR as the sole mechanism of VVS in children and adolescents.[12] Reduced venous return is consequent to excessive splanchnic blood pooling within the capacitance vessels of the liver and mesentery[13] and, to a lesser extent, within the calf, but not within the pelvic vasculature where pooling remains similar to control. Venous pooling accounts for the excessive central hypovolemia that characterizes VVS.[24] SVR is increased because of increased pelvic vascular resistance and splanchnic vasoconstriction. This also implies that splanchnic pooling in VVS-↓CO patients occurs in the absence of decreased splanchnic vasoconstriction. This could occur were there an increase in splanchnic capacitance (decreased venoconstriction). However, venoconstriction and arterial vasoconstriction usually progress in parallel.[25]

understood, but may involve non–heart-rate–related reductions in BP that can result from inadequate cardiac preload, inadequate ventricular contraction, or reductions in SVR. We
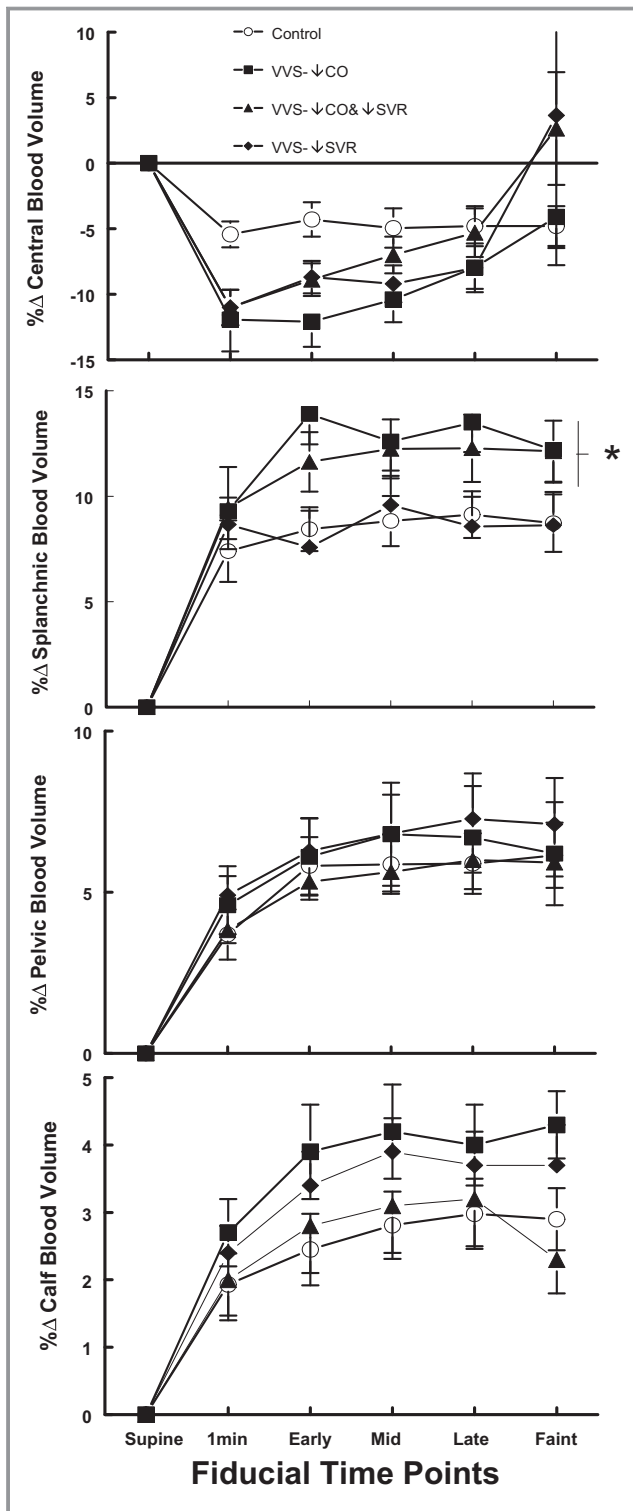
Figure 5. Percent change in regional blood volumes during upright tilt. The top panel shows the percent change in central blood volume (%Δ Central Blood Volume), the second shows percent change in splanchnic blood volume (%Δ Splanchnic Blood Volume), the third panel shows percent change in pelvic blood volume (%Δ Pelvic Blood Volume), and the bottom panel shows percent change in calf blood volume (%Δ Calf Blood Volume). Control data are shown as open circles (○), VVS-↓CO data are shown as black boxes (■), VVS-↓CO &↓SVR are shown as black triangles (▲), and VVS-↓SVR are shown as diamonds (◆). Splanchnic blood volume increased during tilt in all subjects, was greater than control for VVS-↓CO, and VVS-↓CO&↓SVR ($P<0.001$) as shown by the asterisk ("*"), and not different from control in VVS-↓SVR. CO indicates cardiac output; SVR, systemic vascular resistance; VVS, vasovagal syncope.

patients had the largest reduction in central volume and largest increase in splanchnic pooling of the 3 groups, contributing to reduced ventricular filling and reduced CO. This group of patients therefore may be most likely to benefit from hydration therapies, such as increased oral fluid intake and/or mineralocorticoid therapy to increase fluid retention.

Decreased SVR Occurs in a Majority of Young VVS Patients

The majority (75%) of our young VVS patients had reduced SVR during phase 2 presyncope, including 23% who also had reduced CO.

VVS-↓SVR Patients

VVS-↓SVR patients had no reduction in CO by definition. There was no excessive splanchnic pooling compared to healthy control subjects. Rather unexpected, however, was the finding of increased CO above baseline in many patients. There was a large increase in splanchnic blood flow above supine baseline consequent to marked reduction in splanchnic vascular resistance. Because there were no differences in pelvic or calf blood flows in VVS-↓SVR compared to control, elevated splanchnic blood flow sustains or increases venous return above baseline, whereas BP falls because of progressive reduction in cardiac afterload. Reduced splanchnic vasoconstriction should passively increase hepatic and mesenteric venous pressure and thus venous pooling.[26] The absence of increased splanchnic pooling during upright tilt suggests that the mesenteric and hepatic venous pressure is not increased, despite arterial vasodilation, that is, the physiological characteristics of an acute arteriovenous shunt resulting in maintained or even increased venous return.[27] If true, how can central hypovolemia occur in VVS-↓SVR to a similar degree as observed in VVS-↓CO patients? This can be rationalized as follows.

Despite the significantly larger increase in HR compared to the other 2 groups, these subjects had an observed reduction in CO. This suggests that the increased HR was unable to compensate for MAP reduction, or perhaps even contributed by reducing diastolic filling time below that appropriate for the relevant preload and ventricular state. In addition, these
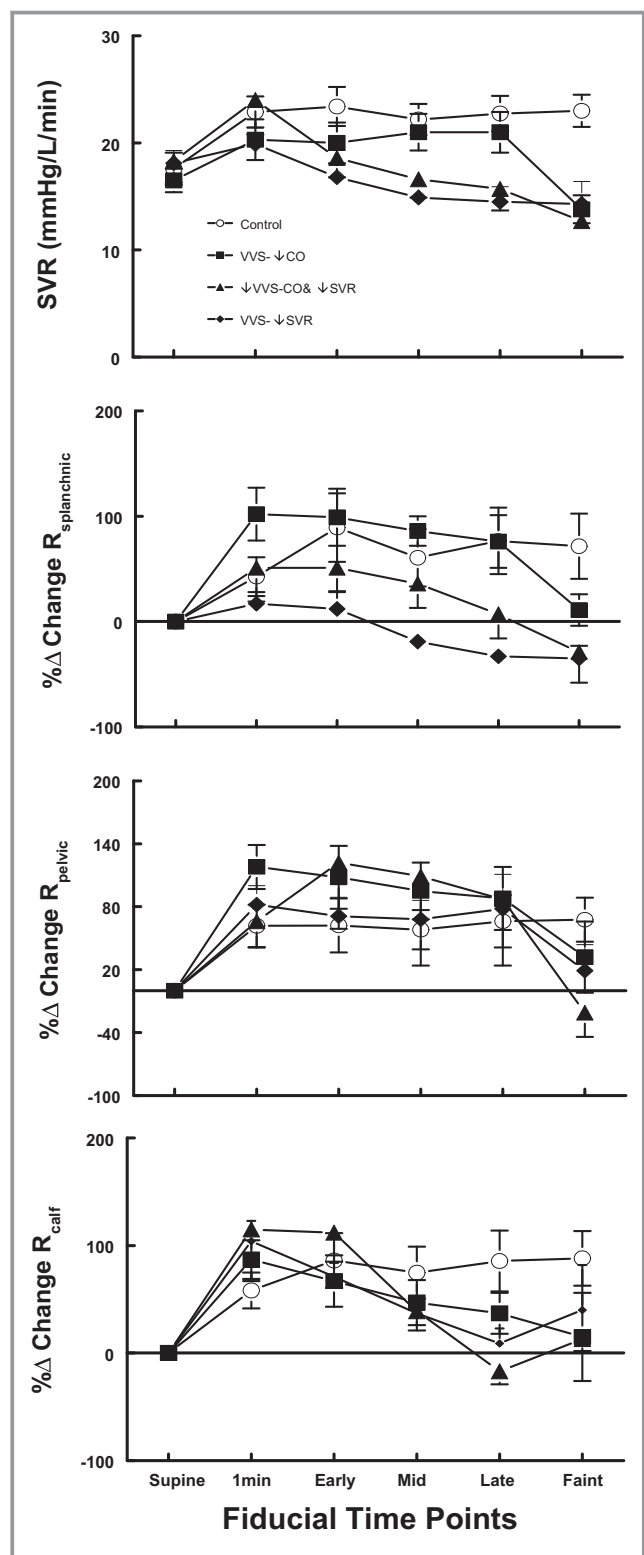
Figure 6. Percent change in regional arterial vascular resistance during upright tilt. The top panel shows the percent change in SVR, the second shows percent change in splanchnic resistance (%$\Delta R_{Splanchnic}$), the third panel shows percent change in pelvic resistance (%ΔR_{Pelvic}), and the bottom panel shows percent change in calf resistance (%ΔR_{calf}). Control data are shown as open circles (○), VVS-↓CO data are shown as black boxes (■), VVS-↓CO &↓SVR are shown as black triangles (▲), and VVS-↓SVR are shown as diamonds (♦). CO indicates cardiac output; SVR, systemic vascular resistance; VVS, vasovagal syncope.

initially reduces central blood volume while maintaining or increasing CO; the cardiac silhouette shrinks on x-ray.[29] Similar changes occur during upright tilt of healthy volunteers subjected to whole-body heating: central blood volume is decreased whereas CO remains elevated[30]; SVR is greatly reduced and orthostatic stress is poorly tolerated.[31]

Splanchnic hemodynamic properties are distributed

Arterial vasoconstriction. The splanchnic vasculature has uniquely distributed arterial resistance, venous capacitance, and venous resistance properties. Arterial vasoconstriction can occur at the inflow of each splanchnic organ (stomach, small intestine, large intestine, liver, spleen, and pancreas) and is primarily mediated by sympathetic nerves releasing norepinephrine, which binds to α1-, α2-adrenergic receptors of the vascular smooth muscle. Splanchnic arterial vasodilation through β2 adrenergic receptors can also occur.[32]

Venous capacitance. In humans, splanchnic venous capacitance resides within the mesenteric venous system and the liver[25,33] which are aligned in series by the portal vein. Portal vascular resistance is ordinarily low and hepatic and mesenteric pressures are similar.[34] The hepatic and mesenteric capacitances have both α1- and α2-adrenergic receptors contributing to active venoconstriction, but lack β2 receptors.[35]

Venous resistance. Splanchnic venous resistance is localized at the hepatic veins, which serves a sphincter-like function.[36] Hepatic venoconstriction maintains hepatic and mesenteric capacitances at pressures a little higher than inferior vena cava pressure. There are few hepatic venous α-adrenergic receptors, but abundant β2 receptors that produce nitric-oxide–dependent venodilation.[33] Splanchnic pooling can be prevented if sufficient hepatic vein dilation equalizes hepatic and mesenteric venous pressures with inferior vena cava (IVC) pressure.[37]

Vasovagal syncope is associated with progressive increase in epinephrine in young patients

During orthostatic stress, circulating epinephrine increases in young VVS patients.[38,39] Epinephrine in physiological

Hemodynamics properties of an arteriovenous shunt

The chronic compensated physiological state of AV shunt includes reduced cardiac afterload, increased blood volume, and increased cardiac size with eccentric left ventricular hypertrophy.[28] Acutely, by unloading the heart, an AV shunt

concentrations further enhances splanchnic arterial vasodilation through β2-receptors[40] whereas hepatic venodilation equalizes hepatic with IVC venous pressure preventing splanchnic pooling.[41] Instead, a short-lived arteriovenous shunt would be created, supporting CO at the expense of SVR and BP, explaining our findings.

VVS–↓CO&↓SVR Patients

Patients with VVS–↓CO&↓SVR had splanchnic and calf blood pooling comparable to pooling observed in VVS–↓CO patients, combined with the afterload reduction of VVS–↓SVR. In VVS–↓CO&↓SVR patients, splanchnic arterial vasodilation occurred to a lesser extent than in VVS–↓SVR and estimated venous properties appear to be similar to control. The combined effects of splanchnic pooling and reduced SVR resulted in the earliest faints among the VVS groups.

Limitations

Fiducial time markers facilitate comparison of subjects undergoing similar physiological phenomena at different times (eg, the onset of rapid hypotension-bradycardia just before faint). However, it removes the absolute time dependence of the observed phenomena.

Although there were no differences between the age, sex, and BMI of the 3 subgroups compared to controls, the number of subjects in each group was relatively small. It is therefore possible that differences in these factors could be potential confounding variables.

We did not measure absolute blood volume or central blood volume while supine. This can affect the hemodynamics during vasovagal syncope.[42]

Impedance plethysmography of the splanchnic vasculature cannot distinguish blood pooling among the splanchnic organs (eg, liver vs mesenteric). Also, the technique measures fractional change in regional blood volumes and blood flows, which have been validated against reference standards in previous studies.[15,21]

We studied the healthy volunteers during 10 minutes of tilt, which was considered appropriate based on previous studies.[43] Increasing the time of HUT could potentially yield different information. However, the mean time to VVS was 10 to 11 minutes, and our results inform primarily on phase 2 hypotension, which started before 10 minutes in all VVS patients.

The Finometer yields relative measures of CO. Whereas we standardized supine CO against inert gas rebreathing CO, standardization was not performed during the tilt because the technique requires deep breathing, which would alter hemodynamics.

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Disclosures

None.

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