Regional blood volume and peripheral blood flow in postural tachycardia syndrome

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Stewart, Julian M., and Leslie D. Montgomery. Regional blood volume and peripheral blood flow in postural tachycardia syndrome. Am J Physiol Heart Circ Physiol 287: H1319–H1327, 2004—Variants of postural tachycardia syndrome (POTS) are associated with increased [“high-flow” POTS (HFP)], decreased [“low-flow” POTS (LFP)], and normal [“normal-flow” POTS (NFP)] blood flow measured in the lower extremities while subjects were in the supine position. We propose that postural tachycardia is related to thoracic hypovolemia during orthostasis but that the patterns of peripheral blood flow relate to different mechanisms for thoracic hypovolemia. We studied 37 POTS patients aged 14–21 yr: 14 LFP, 15 NFP, and 8 HFP patients and 12 healthy control subjects. Peripheral blood flow was measured in the supine position by venous occlusion strain-gauge plethysmography of the forearm and calf to subgroup patients. Using indocyanine green techniques, we showed decreased cardiac index (CI) and increased total peripheral resistance (TPR) in LFP, increased CI and decreased TPR in HFP, and unchanged CI and TPR in NFP while subjects were supine compared with control subjects. Blood volume tended to be decreased in LFP compared with control subjects. We used impedance plethysmography to assess regional blood volume redistribution during upright tilt. Thoracic blood volume decreased, whereas splanchnic, pelvic, and leg blood volumes increased, for all subjects during orthostasis but were markedly lower than control for all POTS groups. Splanchnic volume was increased in NFP and LFP. Pelvic blood volume was increased in HFP only. Calf volume was increased in HFP only. Splanchnic volume was increased in NFP and LFP. We therefore expect and observe pathophysiological heterogeneity in POTS. Our initial studies of POTS focused on peripheral venous pressure (Pv) and found that there were (at least) two separate populations of patients present, which at that time we distinguished on the basis of supine leg Pv: a group of POTS patients with high Pv, (exceeding control limits of 20 mmHg) and a group with normal Pv. However, later, when we examined supine peripheral blood flow in POTS patients prospectively grouped by calf Pv, as shown in Fig. 1 (a synthesis of data from previous papers), we found that the high Pv data were unimodal with decreased calf peripheral blood flow and increased peripheral resistance, but the normal Pv data were bimodal with increased supine calf blood flow and decreased supine arterial resistance in some patients and normal supine calf blood flow and normal supine arterial resistance in others. This suggests that there are (at least) two subgroups within the normal Pv group: a group of patients with increased blood flow and a group of patients with unchanged blood flow compared with control.

We currently think that peripheral blood flow and arterial resistance furnish useful and physiologically important markers to classify POTS. We therefore subscribe to three groups of POTS patients distinguished by peripheral blood flow and peripheral arterial resistance. They are as follows: 1) a high-blood flow, low-arterial resistance group with normal to decreased Pvp, now denoted “high-flow” POTS; 2) a low-blood flow, high-arterial resistance, high-Pvp group, now denoted “low-flow” POTS; and 3) a normal-blood flow, normal-arterial resistance group with normal Pvp, currently denoted “normal-flow” POTS.

We hypothesized that subsets of POTS have distinctive forms of thoracic hypovolemia accounting for postural tachycardia made apparent by orthostatic stress. On the basis of prior work, we proposed that isolated lower extremity flow abnormalities would prevail in high-flow POTS, widespread flow abnormalities or hypovolemia would prevail in low-flow POTS, and splanchnic regional redistribution would prevail in normal-flow POTS during orthostatic challenge. The purpose of the present investigation was to study blood volume and the regional redistribution of blood volume in POTS during orthostatic stress.

MATERIALS AND METHODS

Subjects and Experimental Outline

To test these hypotheses, we studied 37 consecutive POTS patients aged 14–21 yr (median = 17.2 yr, 11 men and 26 women) and 12 healthy control subjects. Peripheral blood flow was measured in the supine position by venous occlusion strain-gauge plethysmography of the forearm and calf to subgroup patients. Using indocyanine green techniques, we showed decreased cardiac index (CI) and increased total peripheral resistance (TPR) in LFP, increased CI and decreased TPR in HFP, and unchanged CI and TPR in NFP while subjects were supine compared with control subjects. Blood volume tended to be decreased in LFP compared with control subjects. We used impedance plethysmography to assess regional blood volume redistribution during upright tilt. Thoracic blood volume decreased, whereas splanchnic, pelvic, and leg blood volumes increased, for all subjects during orthostasis but were markedly lower than control for all POTS groups. Splanchnic volume was increased in NFP and LFP. Pelvic blood volume was increased in HFP only. Calf volume was increased above control in HFP and LFP. The results support the hypothesis of (at least) three pathophysiologic variants of POTS distinguished by peripheral blood flow related to characteristic changes in regional circulations. The data demonstrate enhanced thoracic hypovolemia during upright tilt and confirm that POTS is related to inadequate cardiac venous return during orthostasis.

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healthy volunteers aged 15–21 yr (median = 17.4 yr, 5 men and 7 women).

POTS patients were referred to our center for symptoms of orthostatic intolerance lasting for longer than 6 mo. Orthostatic intolerance was defined by the presence of lightheadedness, fatigue, headache, neurocognitive deficits, palpitations, nausea, blurred vision, abnormal sweating, and a sensation of shortness of breath or heat while upright with no other medical explanation for the symptoms. In all patients, POTS was confirmed on a screening upright-tilt table test at 70°. POTS was diagnosed by symptoms of orthostatic intolerance during the screening tilt test associated with an increase in sinus HR of ≥30 beats/min or to a HR of ≥120 beats/min during the first 10 min of tilt as defined in the adult literature (20, 29). We used mercury in-Silastic strain-gauge plethysmography to measure supine calf blood flow. Measurements were always made in the supine position at the beginning of experiments and followed a 30-min resting period. Occlusion cuffs were placed around the lower limb 10 cm above a strain gauge attached to a Whitney-type strain-gauge plethysmograph (Hokanson). Blood flow was estimated while subjects were in the supine position by standard venous occlusion methods (11) using rapid cuff inflation to a pressure below diastolic pressure to prevent venous egress.

Briefly inflating a smaller secondary cuff to suprasystolic blood pressure prevented wrist or ankle blood flow. Arterial inflow in units of milliters per 100 ml tissue per minute was estimated as the rate of change of the rapid increase in the limb cross-sectional area. We subdivided the POTS patients after the screening tilt test on the basis of calf blood flow. For normative purposes, we have collected calf blood flow data from 42 control subjects spanning a number of prior research protocols. For the purposes of this study, decreased calf blood flow was defined as ≤1.2 ml·min⁻¹·100 ml tissue⁻¹, which was the smallest calf blood flow that we have measured in control subjects. Increased calf blood flow was defined as ≥3.6 ml·min⁻¹·100 ml tissue⁻¹, which was the largest calf blood flow we have measured in control subjects. Therefore, we defined low-flow POTS as those POTS patients with calf blood flow <1.2 ml·min⁻¹·100 ml tissue⁻¹, high-flow POTS as those POTS patients with calf blood flow ≥3.6 ml·min⁻¹·100 ml tissue⁻¹, and normal-flow POTS as those POTS patients with calf blood flow ≥1.2 ml·min⁻¹·100 ml tissue⁻¹ and ≤3.6 ml·min⁻¹·100 ml tissue⁻¹. Fourteen patients aged 15–22 yr (median = 17.4 yr, all women) had low-flow POTS, 15 patients aged 13–19 yr (median = 16.5 yr, 7 men...
and 8 women) had normal-flow POTS, and 8 patients aged 14–20 yr (median = 15.8 yr, 2 men and 6 women) had high-flow POTS.

The healthy control subjects comprised friends of POTS patients who were age matched with patients. They were free from all systemic illness and had normal electrocardiograms, echocardiograms, and physical examinations. We excluded control subjects with a history of syncope or orthostatic intolerance.

There were no trained competitive athletes or bedridden subjects. No subjects were taking any medications for a minimum of 2 wk before the testing.

Informed consent was obtained, and all protocols were approved by the Committee for the Protection of Human Subjects (Institutional Review Board) of New York Medical College.

Protocol

Tests began in a temperature-controlled room (24–26°C) after an overnight fast on a day other than the screening day. After a 30-min supine acclimatization period, we measured blood volume by the indocyanine dye dilution technique. Supine hemodynamic measurements were then made. Subjects were upright tilted to 35° until a steady state was reached (∼15 min), and hemodynamic measurements were repeated. We and others have demonstrated that upright tilt to 35° produces autonomic changes due to orthostasis yet is tolerated by patients and control subjects (36).

We continuously measured blood pressure by arterial tonometry and HR by electrocardiogram and estimated thoracic, splanchnic, pelvic, and calf blood segmental volumes (defined below) by impedance plethysmography (IPG) throughout the entire experimental course.

We assessed peripheral blood flow, peripheral resistance, \( P_v \), and peripheral venous capacity while subjects were in the supine position and at steady state while subjects were upright by venous occlusion strain-gauge plethysmography.

Details of the Method

Strain-gauge measurements: peripheral blood flow, \( P_v \), peripheral arterial resistance, and venous capacitance. We used venous occlusion strain-gauge plethysmography to measure forearm and calf blood flow. Supine measurements were made while subjects were in the supine position using occlusion cuffs placed around the upper and lower limbs ∼10 cm above a strain gauge attached to a Whitney-type strain-gauge plethysmograph (Hokanson). Blood flow was estimated while subjects were in the supine position and while subjects were tilted to 35° using rapid cuff inflation to a pressure below diastolic pressure (e.g., 40 mmHg) to prevent venous egress (11). Briefly inflating a smaller secondary cuff to suprasystolic blood pressure prevented wrist and ankle blood flow. Systolic and diastolic blood pressures of the arm and leg were determined by oscillometry. Arterial inflow in units of milliliters per 100 ml of tissue per minute was estimated as the rate of change of the rapid increase in the limb cross-sectional area. Capacitance vessel pressure (\( P_v \)) was also assessed in the steady state: after the strain-gauge dimension returned to baseline after blood flow measurement, we measured \( P_v \) by gradually increasing the occlusion cuff pressure until an increase in limb volume occurred. \( P_v \) so measured closely approximates invasive catheter measurements in humans (2).

Peripheral resistance was calculated using the following formula: \((MAP - P_v)/resting flow\), where MAP is mean arterial pressure calculated as \((systolic blood pressure + 2\times diastolic blood pressure)/3\). Peripherical resistance was assessed in the supine and upright position in all subjects using forearm and calf flow, MAP in the arm and the calf, and forearm and calf \( P_v \), in both positions.

We measured venous capacitance using our previously documented techniques (32, 34). In brief, while subjects were in the supine position, the limb was gently raised above the heart level until no further decrease in volume was obtained. After recovery, we used 10-mmHg steps in pressure, starting at the first multiple of 10 larger than \( P_v \), to a maximum of 60 mmHg. This produced progressive limb enlargement. Pressure was maintained for 4 min until a steady state was achieved. At lower congestion pressures, the limb size reaches a plateau representing venous filling alone. At higher pressures, a plateau is not reached. Instead, there are two components superimposed: a linear component representing microvascular filtration (33), which can be extracted from the total curve by least-squares methods (27), and a residual curve that reaches a plateau, which represents filling of capacitance vessels. Once the volume response is partitioned, capacitance is calculated from the sum of residual portions, to which is added the estimate of supine venous volume obtained from raising the limb (32).

HR and blood pressure monitoring. The electrocardiogram was monitored continuously. Right upper extremity blood pressure was continuously monitored with an arterial tonometer (Colin Instruments; San Antonio, TX) placed on the right radial artery and recalibrated automatically every 5 min against oscillometric blood pressure. Leg blood pressure was measured intermittently by oscillometry on the calf contralateral to the strain gauge and used to calculate the calf MAP. Electrocardiogram and tonometric pressure data were interfaced to a personal computer through an analog-to-digital converter (DataQ Ind: Milwaukee, WI). These data were multiplexed with strain gauge, and impedance data were effectively synchronized.

Dye dilution measurement of blood volume, cardiac output, and total peripheral resistance. The indocyanine green dye dilution technique (1) employing a noninvasive spectrophotometric finger photosensor (DDG, Nihon-Kohden) was used to estimate blood volume, cardiac output, and total peripheral resistance. This technique has been verified during clinical studies (12, 15). First-pass kinetics were used to obtain cardiac output by Stewart’s classical area under the curve method (31). Cardiac index was obtained by dividing the cardiac output by the patient surface area computed from the following formula of Dubois and Dubois (5): body surface area \((m^2) = (weight^{0.425})\times(height^{0.725})\times0.00718\), with weight in kilograms and height in centimeters. The dye decay curve is a monoeponential representing clearance by the liver. Once the hematocrit was measured, we extrapolated the dye decay curve to the time of dye injection (time = 0), yielding estimated blood volume. Total peripheral resistance was estimated by dividing the MAP measured while subjects were in the supine position 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 (25), including those produced during orthostatic stress (3, 6). We used a tetrapolar high-resolution impedance monitor four-channel digital impedance plethysmograph (UFI) to measure volume shifts in four anatomic segments designated the thoracic segment, the splanchic segment, the pelvic segment incorporating the lower pelvis to upper leg, and the leg segment (23, 25, 39). Ag/AgCl electrocardiographic electrodes were attached to the left foot and left hand, which served as current injectors. Additional electrodes were placed in pairs representing anatomic segments as follows: the ankle-upper calf just below the knee (the leg segment), the knee-iliac crest (pelvic segment), the iliac crest-midline xiphoid process (the splanchic segment), and the midline xiphoid process to supraclavicular area (the thoracic segment). The IPG introduces a high-frequency (50 kHz), low-amperage (0.1 mA root mean square) constant-current signal between the foot and hand electrodes. This is completely insensible to the subjects. Electrical resistance values were measured using the segmental pairs as sampling electrodes. Anatomic features were selected as the most appropriate locations for comparing changes within and across patients. This combination of electrodes gives highly repeatable changes in computed volume shifts and has been tested in a wide range of experiments by our group (22–24). The distance between the sampling electrodes \( L \) was measured carefully with a tape measure. We estimated the change in blood volume in each segment during the upright tilt from the following formula:
\[ \Delta \text{Segmental blood volume} = \rho \cdot (L/R_c)^2 \cdot \Delta R(9) \]

where \( \rho \) is the electrical conductivity of blood estimated as 53.2 \cdot \exp(\text{Hct-0.022}) \) (where Hct is hematocrit, or the packed cell volume that we measured) given by Geddes and Sadler (10); \( R_0 \) is the baseline resistance of a specific segment; and \( \Delta R \) is the change in resistance in a specific segment during the maneuver. Volume changes used for intergroup comparisons were calculated from maximum changes in \( \Delta R \) during the orthostatic maneuver using the average value of \( R_0 \) starting immediately before the initiation of tilt and averaging over the entire change in resistance. \( \rho \) was regarded as constant during the maneuver. IPG measurements allowed us to trace blood volume changes in the various segments during orthostasis.

Low-angle tilt table testing. An electrically driven tilt table (Cardiosystems 600; Dallas, TX) with a footboard was used. Data for arm and calf blood pressure, blood flow, \( P_v \), and venous capacity were obtained while subjects were in the supine position. After supine vascular measurements were complete, the subjects underwent tilt to +35°. The angle of +35° was chosen because we have observed orthostatic stress comparable to −30 mmHg lower body negative pressure (LBNP), at which low- and high-pressure baroreceptors are unloaded (32–34). Subjects had no overt orthostatic intolerance or fainting over a 15-min time period at these angles, although light-headedness was often reported by POTS patients. During these tilts, arm occlusion cuffs were rapidly inflated to 45 mmHg to measure blood flow. Leg occlusion cuffs were inflated to a pressure just below diastolic pressure verified by blood pressure measured on the contralateral calf. Upright tilt increases calf arterial blood pressure due to hydrostatic forces. Forearm and calf flow were measured every 30 s for at least three recordings, which were averaged. In practice, flow and limb size reached a new steady state within ~2 min, which could be verified by observing the time course of impedance changes. Steady state was defined by no further change in limb flow, and a linear change in calf size at positive angles signifying complete capacitance vessel filling. We repeated measurements of forearm and calf \( P_v \). We reapplied sequential 10-mmHg pressure steps to compute the volume-pressure relation. The venous pressure at the strain-gauge transducer was assumed to differ from the pressure at the cuff because of the hydrostatic column of blood between the cuff and the gauge. We corrected for the height of this column of blood at given angle of tilt by adding 0.776 \cdot D \cdot \sin(\text{angle}), where \( D \) is the distance between the edge of the cuff bladder and the strain gauge and 0.776 is a conversion factor from centimeters of blood to millimeters of mercury.

Statistics. Tabular data concerning supine and upright blood flow, \( P_v \), impedance blood volume shifts, capacitance, and peripheral resistance were compared by two-way ANOVA, with data compared before and after upright tilt. When significant interactions were demonstrated, the ratio of \( F \) values was converted to a \( t \)-distribution using Scheffé’s test, and probabilities were thereafter determined. Thereafter, unpaired \( t \)-tests corrected for multiple small samples were used for between-group comparisons, and paired \( t \)-tests corrected for multiple small samples were used for between-group comparisons during tilt. All results are reported as means ± SE. Significance was defined as a \( P \) value of <0.05. Unblinded data were collected and analyzed by the same investigator throughout.

RESULTS

Results are depicted in Figs. 2–4 and in Tables 1 and 2. All subjects were able to perform the 35° tilt.

Supine Systemic Hemodynamics

Supine systemic hemodynamics are shown in Table 1. Cardiac index measured while subjects were in the supine position was decreased in low-flow POTS compared with control (\( P < 0.01 \)) and increased in the high-flow patients compared with the low-flow patients (\( P < 0.025 \)). Total peripheral resistance was significantly increased above control in low-flow POTS (\( P < 0.05 \)), was not different from control in normal-flow POTS, and was significantly lower than control in high-flow POTS (\( P < 0.025 \)). Blood volume was decreased in low-flow POTS compared with high-flow POTS (\( P < 0.025 \)) and tended to be decreased compared with control subjects (\( P = 0.08 \)). Blood volume (see Table 1) was not different from control for normal-flow POTS or for high-flow POTS patients. Blood volumes of 58–74 ml/kg fall within the normal range, with 58 ml/kg being at the low end of normal (30).

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

Supine and upright peripheral hemodynamics are shown in Table 2.

Supine HR was increased in both high-flow POTS (\( P < 0.025 \)) and low-flow POTS (\( P < 0.001 \)) but was not different from control in normal-flow POTS. HR increased in all subjects during tilt and was significantly (\( P < 0.025 \)) greater than control in all POTS patients. The highest HRs tended to be recorded in low-flow POTS patients.

Resting arterial blood pressure was not different among the groups. There was no significant change in arm blood pressure with upright tilt. Leg blood pressure increased in all subjects by similar amounts during upright tilt, but there was no difference among subject groups. The increase in leg blood pressure was commensurate with the pressure predicted from gravitational considerations.

We measured venous pressure in forearms and calves while subjects were in the supine and upright positions. Forearm \( P_v \) was similar for all groups of subjects and was unchanged by tilt to 35°. Supine calf \( P_v \) was increased in low-flow POTS compared with control (\( P < 0.025 \)). The magnitude of measured upright \( P_v \) was not commensurate with the pressure predicted from gravitational considerations. Thus the change in \( P_v \) was significantly (\( P < 0.01 \)) less than the change in arterial pressure for all subject groups during tilt.

Forearm blood flow decreased significantly with tilt (\( P < 0.05 \)) for control subjects. Supine resting forearm blood flow in low-flow patients tended to be decreased compared with control, but this did not achieve significance. Upright forearm blood flow was significantly decreased (\( P < 0.05 \)) in low-flow patients compared with control. Supine forearm blood flow was significantly increased in high-flow patients (\( P < 0.025 \)) compared with control and remained increased when subjects were upright. Supine and upright data in normal-flow POTS were similar to control. By design, calf blood flow was significantly decreased in low-flow patients (\( P < 0.001 \)) when they were in the supine position but increased significantly (\( P < 0.01 \)) when they were upright to flow rates similar to control subjects. Supine calf blood flow was increased in high-flow patients (\( P < 0.0001 \)) compared with control subjects and remained increased when subjects were upright.

Supine calf arterial resistance was significantly increased in low-flow POTS (\( P < 0.025 \)) but was not different from control when subjects were upright. Supine calf arterial resistance was significantly decreased in high-flow POTS (\( P < 0.05 \)) com-
pared with control and did not change with tilt. There were no significant differences in calf arterial resistance between control and normal-flow POTS, although upright resistance tended to be somewhat higher in the normal-flow POTS group.

Venous capacitance was decreased only in low-flow POTS patients compared with control ($P < 0.025$).

Impedance and Segmental Blood Volume Changes during Upright Tilt

Representative impedance and volume changes during orthostasis. Figure 2 shows the changes in segmental impedance and the corresponding calculated changes in segmental blood volumes during upright tilt in a typical representative normal control subject. There is an increase in thoracic impedance corresponding to a decrease in thoracic blood volume during orthostasis. Impedance decreases in splanchnic, pelvic, and leg segments during tilt, corresponding to increased blood volume in these segments. After the initial orthostatic volume shift, there was a gradual and nearly linear increase in pelvic and leg segments volume over time not observed in the splanchnic segment. Thorax and splanchnic impedance changes have superimposed respiratory signals accounting for their rougher configuration.

Segmental volume changes in POTS and control. Figure 3 shows the calculated changes in segmental blood volumes during upright tilt in representative control, low-flow POTS, normal-flow POTS, and high-flow POTS subjects. There were larger decreases in fractional thoracic volume in all POTS
subjects compared with the control subject and thus relative thoracic hypovolemia in POTS patients. There was a marked enhancement in splanchnic volume during tilt in the normal-flow POTS patient who had pelvic and leg volume changes that were otherwise similar to control. This contrasts with both low-flow POTS and high-flow POTS patients in whom segmental volume changes are largest in the leg segments, i.e., in the most dependent parts of the body. The high-flow POTS patient shown also had marked increases in pelvic volume.

Data averaged over all subjects are shown in Fig. 4. Thoracic volume decreased significantly for all subject groups during orthostasis but was significantly decreased in all POTS groups compared with the control group. The control volume decreased $12 \pm 3\%$, low-flow POTS volume decreased $25 \pm 5\%$ ($P < 0.025$), normal-flow POTS volume decreased $32 \pm 4\%$ ($P < 0.001$), and high-flow POTS volume decreased $30 \pm 5\%$ ($P < 0.004$).

Splanchnic segmental blood volume increased significantly for all subjects during orthostasis but was further significantly increased above control in normal-flow ($P < 0.005$) and low-flow subjects ($P < 0.01$). Control volume increased $16 \pm 2\%$, low-flow POTS volume increased $29 \pm 3\%$, normal-flow

![Fig. 3: Representative changes in thoracic, splanchnic, pelvic, and leg fractional volume changes during upright tilt in high-flow POTS (in red), low-flow POTS (in green), normal-flow POTS (in blue), and control subjects (in black). Splanchnic blood accumulates to the largest extent in normal-flow POTS patients, leg and pelvic blood accumulates in high-flow POTS patients, and leg blood accumulates the most in low-flow patients.](image-url)

![Fig. 4: Changes in thoracic, splanchnic, pelvic, and leg percent volume changes during upright tilt averaged over subject groups. Splanchnic changes dominate normal (Nl)-flow POTS. Low-flow POTS patients have widespread blood collection. High-flow POTS patients have blood pooling in the dependent body parts.](image-url)

### Table 1. Patient dimensions and supine-only hemodynamic data

<table>
<thead>
<tr>
<th>POTS</th>
<th>Control</th>
<th>Low flow</th>
<th>Normal flow</th>
<th>High flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body surface area, m²</td>
<td>1.75±0.10</td>
<td>1.71±0.05</td>
<td>1.76±0.07</td>
<td>1.76±0.07</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>62±3</td>
<td>57±4</td>
<td>64±5</td>
<td>61±7</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167±3</td>
<td>173±8</td>
<td>171±3</td>
<td>169±7</td>
</tr>
<tr>
<td>Normalized blood volume, ml/kg</td>
<td>70±5</td>
<td>58±4</td>
<td>69±4</td>
<td>74±4†</td>
</tr>
<tr>
<td>Cardiac index, l·min⁻¹·m⁻²</td>
<td>4.3±0.4</td>
<td>3.1±0.3*</td>
<td>3.7±0.6</td>
<td>5.1±0.7†</td>
</tr>
<tr>
<td>Total peripheral resistance, mmHg·l⁻¹·min⁻¹·m⁻²</td>
<td>19±1</td>
<td>38±7*</td>
<td>25±5</td>
<td>15±2*</td>
</tr>
</tbody>
</table>

Values are means ± SE. *$P < 0.05$ compared with control; †$P < 0.05$ compared with low-flow postural tachycardia syndrome (POTS) patients.
Table 2. Flow, pressure, and heart rate data before and during tilt

<table>
<thead>
<tr>
<th>POTS</th>
<th>Control</th>
<th>Low flow</th>
<th>Normal flow</th>
<th>High flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>67±3</td>
<td>81±5*</td>
<td>62±3</td>
<td>76±6*</td>
</tr>
<tr>
<td>Upright</td>
<td>80±3</td>
<td>102±6*†</td>
<td>93±4*†</td>
<td>93±5*†</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>79±2</td>
<td>82±4</td>
<td>80±3</td>
<td>80±2</td>
</tr>
<tr>
<td>Upright</td>
<td>80±2</td>
<td>83±5</td>
<td>85±4</td>
<td>77±8</td>
</tr>
<tr>
<td>Right leg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>74±2</td>
<td>78±5</td>
<td>72±2</td>
<td>72±4</td>
</tr>
<tr>
<td>Upright</td>
<td>113±4†</td>
<td>112±5†</td>
<td>105±3†</td>
<td>106±3†</td>
</tr>
</tbody>
</table>

Values are means ± SE. HR, heart rate; MAP, mean arterial pressure; PV, venous pressure. *P < 0.05 compared with control; †P < 0.05 compared with supine.

POTS volume increased 36 ± 5%, and high-flow POTS volume increased 17 ± 8%.

Pelvic segmental blood volume increased significantly for all subjects during tilt. Pelvic volume was further significantly increased above control in high-flow POTS only (P < 0.05), although there was a trend toward such an increase in low-flow subjects (P = 0.09). Control volume increased 15 ± 2%, low-flow POTS volume increased 20 ± 3%, normal-flow POTS volume increased 15 ± 5%, and high-flow POTS volume increased 21 ± 1%.

Calf segmental blood volume increased significantly for all subjects during tilt. Calf volume was further significantly increased above control in high-flow POTS (P < 0.025) and low-flow POTS (P < 0.05). Control volume increased 12 ± 2%, low-flow POTS volume increased 18 ± 2%, normal-flow

DISCUSSION

General Discussion

The results support the hypothesis of (at least) three physiological variants of POTS distinguished on the basis of peripheral blood flow and peripheral arterial resistance. The results suggest that the peripheral effects are associated with characteristic changes in regional blood volumes. The data emphasize the central importance of exaggerated thoracic hypovolemia during upright tilt in all POTS variants compared with control subjects and confirm that POTS is related to inadequate cardiac venous return during orthostasis. POTS physiology is the physiology of thoracic hypovolemia, which may explain tachycardia in terms of a reflex response.

Low-flow POTS. There appears to be a general deficit in blood flow regulation in low-flow POTS that is most notable in the dependent parts of the body. Prior work suggests that there are defects in local blood flow regulation in these patients (35). Mild absolute hypovolemia is also probably present and further contributes to the orthostatic intolerant response. Decreased peripheral venous capacitance provides evidence for either venous remodeling or persistent peripheral leg venoconstriction, which should tend to allow for cephalad redistribution of blood under resting conditions.

Normal-flow POTS. Normal-flow POTS is characterized by normal peripheral resistance in the supine and upright positions and specific venous pooling within the splanchnic vascular bed. The specific mechanism or mechanisms for such pooling remain undetermined.

High-flow POTS. High-flow POTS is characterized by inadequate peripheral vasoconstriction in both the supine and upright positions. This enhances cardiac output as in other high-output conditions.

Specific Discussion

Systemic hemodynamics. Low-flow POTS. HR is increased, supine cardiac index is decreased, blood volume tends to be decreased, and total peripheral resistance is increased before orthostatic challenge. These data are consistent with hypovolemic circulatory insufficiency. Low-flow POTS patients may be similar to the hypovolemic orthostatic intolerance patients described by Fouad and by Jacob et al. (7, 16, 18).

High-flow POTS. HR is increased, supine cardiac index is increased, and total peripheral resistance is decreased before orthostatic challenge. These data are consistent with a high-output circulatory state.

Normal-flow POTS. Supine HR is normal, cardiac index is normal, and blood volume and total peripheral resistance are similar to control before orthostatic challenge. These data are consistent with normal global and regional circulations at rest in the supine position.

Peripheral hemodynamics (within the context of systemic hemodynamics). Low-flow POTS. Peripheral resistance is markedly increased and blood flow markedly decreased in the lower extremity. Blood flow decreases, whereas peripheral resistance increases, in the arm consistent with autonomically mediated vasoconstriction during tilt (the arms are maintained at the
Heart level during tilt). Blood flow increases, whereas peripheral resistance decreases, in the leg during tilt. This is inconsistent with simple hypovolemia but consistent with abnormal local flow regulatory mechanisms, which we previously demonstrated in these patients (35). Venous capacitance is decreased. Within the context of hypovolemia, this suggests remodeling of the venous vasculature to accommodate reduced blood volume. Reduced venous volume might produce the increase in measured $P_v$ that we regularly find in this group of patients: proportionately more blood would be contained within the arterial circulation (provided no important arterial vasodilation). This observation is consistent with decreased norepinephrine release (autonomic dysfunction) demonstrated by Jacob et al. (17) and consistent with intact local flow regulation (13, 14) in similar POTS patients. The prevailing pathophysiological theory in high-flow patients is that they are “neuropathic;” they fit criteria for a long axon neuropathy with deficient norepinephrine release in the lower extremities and therefore ineffective postural vasoconstriction. They can, however, respond to exogenous $\alpha_1$-adrenergic agonists with effective vasoconstriction (a 40–60% increase in resistance and decrease in flow), with vasoconstriction (a 20% decrease in capacity), and with restoration of orthostatic tolerance in response to phentolamine infusion (36). Recent data (33) demonstrate that increased microvascular filtration drives fluid collection in the lower extremities during orthostasis in high-flow POTS.

**HIGH-FLOW POTS.** Peripheral resistance is decreased and peripheral blood flow is increased compared with control while subjects are in the supine and upright positions. This is associated with increased resting cardiac output and suggests that the high-output state occurs due to inappropriate peripheral vasodilation. This observation is consistent with decreased norepinephrine release (autonomic dysfunction) demonstrated by Jacob et al. (17) and consistent with intact local flow regulation (13, 14) in similar POTS patients. The prevailing pathophysiological theory in high-flow patients is that they are “neuropathic;” they fit criteria for a long axon neuropathy with deficient norepinephrine release in the lower extremities and therefore ineffective postural vasoconstriction. They can, however, respond to exogenous $\alpha_1$-adrenergic agonists with effective vasoconstriction (a 40–60% increase in resistance and decrease in flow), with vasoconstriction (a 20% decrease in capacity), and with restoration of orthostatic tolerance in response to phentolamine infusion (36). Recent data (33) demonstrate that increased microvascular filtration drives fluid collection in the lower extremities during orthostasis in high-flow POTS.

**NORMAL-FLOW POTS.** There is no difference in supine systemic or peripheral hemodynamics in these patients compared with control subjects. Given postural tachycardia, the data predict that regional volume redistribution is paramount in the pathophysiology of this group of POTS patients.

**Segmental blood volume changes during upright tilt.** During upright tilt, we observed that blood empties from the thoracic segment and fills all other segments. This answers a nontrivial question concerning splanchnic filling during orthostasis. The splanchnic bed is the only regional circulation with known active vasoconstrictive as well as arterial vasoconstrictive capabilities (4, 28). Does it fill or empty during orthostatic challenge? We found that the splanchnic circulation fills during our experimental orthostatic conditions in all subjects including normal control subjects. Normal active and passive vascular changes are unable to prevent sequestration of blood within the splanchnic circulation during orthostasis even in normal subjects. At rest, the splanchnic venous reservoir is large and highly compliant (26). Thus, in control subjects subjected to orthostasis, we believe that the increase in splanchnic pooling is limited but not eliminated by vasoconstriction and venoconstriction.

**LOW-FLOW POTS.** These data indicate that despite potential global hypovolemia, thoracic blood volume is decreased above control during orthostasis. Decreases persist even if normalized to a proportionately smaller overall blood volume. There appear to be increased blood volumes in all segments in low-flow POTS, which, however, reach significance in splanchnic and calf circulations during the present experimental conditions. These are unexpected circulatory responses from volume-contracted subjects in whom upright vasoconstriction would be expected to reduce dependent volume shifts. Prior work from our laboratory indicates markedly abnormal local blood flow regulation mechanisms producing paradoxical changes in venaarteriolar and perhaps myogenic responses to limb dependence (35), which may be of wider anatomic importance in low-flow patients. A partial dysautonomia could also play a role here. Hypovolemia cannot account for the sum of all findings in low-flow POTS.

**HIGH-FLOW POTS.** High-flow patients collect blood in the lower extremities. This is predicted by prior work (37) and by the work of others (17). Prior data indicate that there is enhanced microvascular filtration in these patients (33). Thus a fraction of the volumetric change is filtrate rather than blood, which would actually tend to underestimate the amount of limb sequestered fluid (blood + filtrate) in the dependent extremities.

**NORMAL-FLOW POTS.** Impedance data are most interesting for this group of POTS patients in whom only splanchnic pooling occurs. The segmental data suggest localized splanchnic vascular abnormality as opposed to the global vascular abnormalities of low-flow POTS and the lower body abnormalities of high-flow POTS. Increased splanchnic pooling may occur as the result of failure of venoconstriction and arterial vasoconstriction with or without an increase in venous resistance (21) or as the result of increased splanchnic vascular compliance. The present data cannot distinguish between these possibilities. However, prior work indicates that splanchnic arterial inflow is abnormal in POTS (38). Potential candidates for splanchnic dysfunction include partial (regional) dysautonomia or alternatively local regulatory dysfunction.

**Limitations. SHORTCOMINGS OF IPS.** Segmental changes are reported as fractional volume changes. They are not quantitative accurate measures of absolute volume. They are, however, relatively good qualitative and directional measures of segmental volume changes, which, in our hands, gave repeatable results. 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 circulation in POTS, whereas cerebral blood flow is decreased in upright POTS patients (19). However, we did investigate the regional circulations most likely to account for large blood volume shifts in POTS.

**ORTHOSTATIC BLOOD FLOW.** We do not report thoracic, splanchnic, or pelvic measures of vasoconstriction during orthostasis. Although segmental blood flow measurements using impedance methods have been reported, they have not been completely validated against standard methods and therefore fall beyond the scope of the present work. Other techniques such as Doppler ultrasound may help in this regard. Clearly, measurements of selective regional changes in blood flow and peripheral resistance are essential to determining mechanism.

**AUTONOMIC CHANGES.** A direct measure of sympathetic activity such as muscle sympathetic nerve activity (MSNA) could have enhanced our ability to attribute flow and arterial resistance findings to autonomic dysfunction in high-flow POTS patients. However, such instrumentation is often regarded as
problematic in subjects of the age range used in our studies and was therefore not pursued. However, measurements of catecholamine spillover and MSNA (but not peripheral blood flow) have been intensively investigated by the Vanderbilt group in similar patients (8, 17).

TILT ANGLE. We chose to examine patients in the supine position and when tilted to 35°. Prior work has illustrated that 35° of upright tilt evokes the orthostatic response, although to a lesser extent than standing. However, our patients are often unable to sustain standing developing rapidly unstable findings. Therefore, a tolerable orthostatic stressor was chosen.

PATIENT AGE. Age limitations to generalizability may exist. 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 can be regarded as 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 to date suggest that POTS depends on thoracic hypovolemia, which can occur by diverse mechanisms. Regional sequestration of blood occurs in normal-flow and high-flow variants, whereas a degree of absolute hypovolemia and abnormal local blood flow regulation occurs in the low-flow variant. Although molecular mechanisms remain forthcoming, we hope the data presented may help focus the effort.

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