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Persistent splanchnic hyperemia during upright tilt in postural tachycardia syndrome

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Abstract

Previous investigations have allowed for stratification of patients with postural tachycardia syndrome (POTS) on the basis of peripheral blood flow. One such subset, comprising “normal-flow POTS” patients, is characterized by normal peripheral resistance and blood volume in the supine position but thoracic hypovolemia and splanchnic blood pooling in the upright position. We studied 32 consecutive 14- to 22-yr-old POTS patients comprising 13 with low-flow POTS, 14 with normal-flow POTS, and 5 with high-flow POTS and 12 comparably aged healthy volunteers. We measured changes in impedance plethysmographic (IPG) indexes of blood volume and blood flow within thoracic, splanchnic, pelvic (upper leg), and lower leg regional circulations in the supine posture and during incremental tilt to 20°, 35°, and 70°. We validated IPG measures of thoracic and splanchnic blood flow against indocyanine green dye-dilution measurements. We validated IPG leg blood flow against venous occlusion plethysmography. Control subjects developed progressive vasoconstriction with incremental tilt. Splanchnic blood flow was increased in the supine position in normal-flow POTS, despite marked peripheral vasoconstriction, and did not change during incremental tilt, producing progressive splanchnic hypervolemia. Absolute hypovolemia was present in low-flow POTS, all supine flows and volumes were reduced, there was no vasoconstriction with tilt in all segments, and segmental volumes tended to increase uniformly throughout tilt. Lower body (pelvic and leg) flows were increased in high-flow POTS at all angles, with consequent lower body hypervolemia during tilt. Our main finding is selective and maintained orthostatic splanchnic vasodilation in normal-flow POTS, despite marked peripheral vasoconstriction in these same patients. Local splanchnic vasoregulatory factors may counteract vasoconstriction and venoconstriction in these patients. Lower body vasoconstriction in high-flow POTS was abnormal, and vasoconstriction in low-flow POTS was sustained at initially elevated supine levels.

Keywords

vasoconstriction; blood volume; autonomic; orthostatic intolerance

Postural tachycardia syndrome (POTS) is a common illness characterized by symptoms of orthostatic intolerance in association with excessive upright tachycardia. Its pathophysiology remains unclear but could be produced by various physiological circumstances or disease states, resulting in reduced central blood volume in the upright position. Indeed, POTS has been shown to be linked to disturbed neurohumoral (20) or local vascular regulation (30), as well as to bona fide autonomic vasoregulatory dysfunction (13), which may exert their main effects through interactions with the autonomic nervous system.

Classification schemes are needed to help order this diversity. Hyperadrenergic states (19, 34), as well as autoimmune autonomic neuropathy involving antiganglionic antibodies (38), have been demonstrated. A more integrated physiological approach is based on blood volume status. Thus a subset of POTS patients have absolute hypovolemia (14, 20), whereas the remainder experience a redistributive form of hypovolemia, such that central thoracic blood volume is reduced in the upright position, even though overall blood volume is normal (32). We have adopted a classification strategy based on peripheral blood flow in which patients are placed in low-, normal-, and high-flow subgroups according to measurements of peripheral blood flow in the lower extremity (28, 29, 32). Although this scheme may seem less mechanistically driven than others, it is relatively easy to implement and has produced results that are consistent with peripheral autonomic (13) and blood volume findings (20) and points in new directions related to mechanisms of blood flow abnormality (27, 30, 32). Thus we have shown that “low-flow POTS” patients are often absolutely hypovolemic (32) and have abnormal local vascular regulatory mechanisms (30). A second subset, designated “high-flow POTS” patients, have normal to increased blood volume but have inadequate peripheral vasoconstriction, particularly in the lower extremities, in supine and upright positions (27).

The remaining POTS patients comprise those with normal peripheral blood flow and peripheral resistance and are characterized by normovolemia and normal resting cardiac output in the supine position (32). They appear healthy while at rest. These patients are the main focus of the present work. Recent work from our laboratory identified the splanchnic vasculature as the site of redistribution of blood volume during orthostasis at 35° upright tilt (32). Enhanced splanchnic hypervolemia and thoracic hypovolemia during modest orthostatic challenge are features of normal-flow POTS. The purpose of the present work was to explore the hypothesis that splanchnic blood flow remains increased throughout orthostatic stress, despite intense peripheral vasoconstriction. This accounts for orthostatic splanchnic hypervolemia and thoracic hypovolemia while suggesting that sympathetic innervation is intact. Our findings indeed demonstrate increased splanchnic blood flow and splanchnic hypervolemia, despite excessively decreased lower body blood flow (i.e., peripheral vasoconstriction) during stepwise incremental tilt-table tests.

MATERIALS AND METHODS

Subjects and Experimental Outline

To test this hypothesis, we studied 32 POTS patients and 12 healthy volunteer control subjects. The POTS patient data were collected from consecutive subjects.

POTS patients were referred to our center for orthostatic intolerance for >6 mo. Orthostatic intolerance was defined by lightheadedness, exercise intolerance, headache, fatigue, neurocognitive deficits, palpitations, nausea, vomiting and abdominal pain, blurred or altered vision, and shortness of breath or a sensation of heat in the upright position, 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 heart rate of >30 beats/min or to >120 beats/min during the first 10 min of tilt as defined in adult subjects in the literature (16, 23). We used occlusion cuffs placed around the mid thigh above a mercury-in-Silastic strain gauge (Hokanson) placed at midcalf to measure supine calf blood flow by venous occlusion strain-gauge plethysmography (SGP). Measurements were made in the supine position at the beginning of experiments after 30 min of rest. Blood flow was measured in the supine position by standard venous occlusion methods (7). We used criteria gleaned from calf blood flow data previously collected from >60 healthy volunteer subjects spanning prior research protocols to subdivide the POTS patients after the tilt test on the basis of calf blood flow. For purposes of this study, “normal” calf blood flow was defined as $>1.2 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml tissue}^{-1}$, which is the smallest calf blood flow that we have measured in control subjects, and $<3.6 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml tissue}^{-1}$, which is the largest calf blood flow we have measured in control subjects. We defined normal-flow POTS patients as those with values between these limits, low-flow POTS patients as those with calf blood flow $<1.2 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml tissue}^{-1}$, and high-flow POTS patients as those with calf blood flow $>3.6 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml tissue}^{-1}$.

Fourteen normal-flow POTS patients (14–22 yr of age, median 17.2 yr, 3 males, 11 females), 13 low-flow POTS patients (15–22 yr of age, median 17.4 yr, 1 male, 12 females), and 5 high-flow POTS patients (14–19 yr of age, median 16.4 yr, 2 males, 3 females) were identified in this manner. POTS patients were not taking any medication at the time of testing.

Twelve healthy volunteers (14–21 yr of age, median 17.2 yr, 4 males, 8 females) were free from systemic illnesses and were not taking medications. All subjects had normal ECGs and echocardiograms and no evidence of cardiovascular or systemic illness. We excluded all subjects with a history of syncope or orthostatic intolerance. There were no trained competitive athletes or bedridden subjects. Informed consent was obtained from the subjects or from parents and subjects <18 yr old. All protocols were approved by the Committee for the Protection of Human Subjects of New York Medical College.

Laboratory Evaluation

We assessed blood pressure, heart rate, and estimated changes in thoracic, splanchnic, pelvic, and calf segmental blood volumes and blood flows by impedance plethysmography (IPG) in the supine position and throughout upright tilt (see below). Blood volume and cardiac output of all subjects were measured by indocyanine green (ICG) dye-dilution methods (see below).

Protocol

Tests began in a temperature-controlled room after an overnight fast. An intravenous catheter was placed in the right antecubital fossa. After 30 min of acclimatization and during continuous supine IPG to measure resistance (R_0) and beat-to-beat change in resistance (ΔR) of thoracic, splanchnic, pelvic, and leg segments, we estimated supine cardiac output, blood volume, and effective portal vein blood flow by the ICG dye-dilution technique. Next, calf blood flow was measured by SGP. We verified a correlation of impedance measurements of thoracic blood flow to dye-dilution cardiac outputs; we verified a correlation of impedance measurements of calf blood flow to SGP; and we verified a correlation of impedance measurements of splanchnic blood flow to the exponential decay coefficient of the concentration of ICG, which approximates portal blood flow divided by blood volume within a constant representing hepatic dye extraction (see below). On this basis, impedance flow estimates can be used to measure changes in segmental blood flows.

After all supine parameters returned to baseline levels, we obtained steady-state changes in splanchnic impedance by subjecting the patients to upright tilt at an angle of 20° with the horizontal for 10 min. Hematocrit was measured at each angle of upright tilt, including the supine position. The duration of each stage of tilt was determined by prior pilot studies. Impedance flows and volumes were determined from resistance measurements while the patient gently held his/her breath in half inspiration. Subjects were then tilted to 35° and 70° upright, with 10-min pauses at each angle of tilt and breath hold as described above for measurement of resistance. In some POTS patients, 10 min of 70° tilt could not be sustained; in this case, measurements were made at the longest time upright (see below).

Details of the Method

Heart rate, respirations, and blood pressure monitoring—The ECG and relative respiratory volume by respiratory inductance plethysmography (Respirace, NIMS Scientific) were measured. Upper extremity blood pressure was continuously monitored with a finger arterial plethysmograph (Finometer, FMS) placed on the right middle or index finger. ECG, respiratory, and Finometer pressure data were interfaced to a personal computer through an analog-to-digital converter (model DI-720 DataQ, Milwaukee, WI). Finometer data were calibrated to a brachial artery oscillographic pressure at each angle of upright tilt. The Finometer contains software permitting a successful correction between finger and cuff brachial artery pressure on the same arm. All data were multiplexed with strain-gauge and impedance data and, thereby, synchronized.

Dye-dilution measurement of blood volume and cardiac output (supine only)

—We used the ICG dye-dilution technique to measure blood volume and cardiac output (1) and to estimate splanchnic blood flow in terms of portal uptake of the dye (24). We used a spectrophotometric finger photosensor (model DDG2000, Nihon-Kohden) that was validated by prior clinical studies (9, 11). The dye-decay curve fits a monoexponential, $V_0 \cdot \exp -Kt$, where K represents clearance by the liver divided by blood volume and clearance = $(1 - \text{hematocrit})QE$ (24). We define effective portal blood flow as $QE = K \cdot BV / (1 - \text{hematocrit})$, where BV is blood volume, Q is portal blood flow, and E is hepatic dye extraction ratio.

We measured the hematocrit and extrapolated the dye-decay curve to the time of dye injection (*time 0*), yielding estimated blood volume. A log-linear curve fit to the exponential decay yields the parameter K , which was used to estimate portal blood flow and, thus, splanchnic blood flow within a constant. Echo-Doppler measurements of portal venous blood flow and ICG clearance methods compare favorably (2).

Calf blood flow by SGP—We used venous occlusion SGP in all subjects to measure calf blood flow (see above). Supine measurements were made at the beginning of experiments and compared with impedance estimates of blood flow. Measurements were made in a standard manner, with an ankle cuff used to remove the foot circulation. We previously employed these techniques (30, 32).

IPG measurement of changes in segmental blood volumes and blood flows—IPG has been used to detect internal volume shifts during orthostatic stress (3–5). IPG is routinely used to measure changes in cardiac output in the form of impedance cardiography (4). We used this technique previously (29, 31, 33). Our device employs a tetrapolar high-resolution impedance monitor four-channel digital impedance plethysmograph (UFI) applied to four anatomic segments defined in practice by electrode placement: the thoracic segment (supraclavicular area to xiphoid process), the splanchnic segment (xiphoid process to iliac crest), the pelvic segment [lower pelvis (iliac crest) to knee], and the leg or calf segment (upper calf just below the knee to the ankle) (3, 18, 33, 39). Ag-AgCl ECG electrodes were attached at these segmental boundaries and also to the left foot and left hand, where they served as current injectors. The IPG uses a 50-kHz, 0.1-mA root-mean-square constant-current signal between the foot and hand electrodes. Electrical resistance values were measured by using the segmental pairs as sampling electrodes. The midline distance between the sampling electrodes (L) was measured with a tape measure. We also measured the circumferences of calf, thigh, hips, waist, and chest to obtain approximate volumes of each anatomic segment. We estimated the stepwise change in blood volume in each segment during each stage of the upright tilt from the following formula: segmental blood volume (ml) = $\rho(L^2/R_0R_1) \cdot R$ (5), where ρ is electrical conductivity of blood estimated as $53.2 \cdot \exp(\text{hematocrit} \cdot 0.022)$, given by Geddes and Kidder (6). We measured hematocrit from a venous sample taken from the antecubital vein. R_0 is the resistance of a specific segment before change in tilt angle, R_1 is the resistance after change in the tilt angle, and R is the change in resistance ($R_1 - R_0$) in a specific segment during the each incremental tilt step; ρ was regarded as constant during the maneuver.

IPG was also used to measure segmental blood flows (18). Transient blood flows have been quantitated during orthostasis (3, 18). Pulsatile changes in electrical resistance for each segment were employed to compute the time derivative R/t , which we used to obtain the blood flow responses of each body segment during each stepwise change in tilt angle.

Blood flow was estimated for an entire anatomic segment from the following formula: flow = $(HR \cdot \rho \cdot L^2 \cdot T \cdot R/t_{\max})/(R_0)^2$ (5), where HR is heart rate, T is ejection period, R is pulsatile resistance, and R_0 is baseline resistance at a given angle of tilt. Respiratory artifact was removed from the signal using a custom, Fourier-based frequency selection technique.

IPG flow is expressed in milliliters per minute for anatomic segment and can be normalized by dividing by estimated segmental volume.

Incremental tilt-table testing—An electrically driven tilt table (Colin Medical, San Antonio, TX) with a footboard was used. After supine measurements were complete, the subjects underwent tilt to +20°, 35°, and 70° at 10-min intervals (see above). Steady state was defined by a stable splanchnic blood volume, which could be determined in real time. In later experiments, we developed online extraction and estimation of segmental blood flow. Typically, splanchnic blood volume steady state was associated with stable splanchnic and thoracic blood flows.

Statistics

Values are means $\pm$ SE. Cardiac index, blood volume, calf blood flow by SGP, impedance estimates of blood flow, resting heart rate, and resting mean and systolic blood pressures were compared by one-way ANOVA, comparing control subjects and low-flow POTS, normal-flow POTS, and high-flow POTS patients. We used two-way ANOVA with repeated measures and simple contrasts for the blood flow and blood volume responses to incremental tilt. Results were calculated using Statistical Package for the Social Sciences software version 11.0.

RESULTS

Lightheadedness was often reported by POTS patients. POTS subjects tolerated 20° and 35° upright tilt without difficulty. Symptoms of orthostatic intolerance often developed during 35° tilt. For some POTS patients, 70° tilt was poorly tolerated and had to be discontinued. However, splanchnic steady state appeared to be complete in all subjects, and data were preserved for analysis. No POTS patient fainted. All volunteer control subjects tolerated 20° and 35° upright tilt without symptoms. General results are shown in Table 1 and Figs. 1–4.

Comparative Central and Peripheral Blood Flows: Validation of Impedance Flows in the Supine Position

Data for all control and POTS patient subgroups are shown in Fig. 1 and Table 1.

Cardiac index ICG vs. IPG—Figure 1 shows a correlation ($r = 0.67$) between cardiac index in the supine position measured by the ICG technique and cardiac index estimated by impedance. Comparison of cardiac index measured by ICG with cardiac index measured by IPG (impedance cardiac index) is not statistically different within individual groups (Table 1). In our hands, IPG systematically underestimated the dye-dilution standard ($P < 0.001$ by ANOVA for repeated measures).

Splanchnic blood flow ICG vs. IPG—Similarly, effective portal venous flow and IPG-estimated splanchnic flow in the supine position are reasonably well correlated ($r = 0.73$). Although there is no statistical difference between splanchnic flow measured by dye dilution (effective portal blood flow) or by IPG (normalized impedance blood flow) within

individual POTS groups, in our hands, IPG systematically overestimates the effective portal flow standard (Table 1; $P < 0.001$ by ANOVA for repeated measures).

Calf blood flow SGP vs. IPG—Supine resting calf blood flow measured by SGP is compared with blood flow measured by IPG for all control subjects and POTS patients in Fig. 1. Again, there is a correlation ($r = 0.72$) between venous occlusion and impedance methods. Table 1 shows no statistical difference between calf blood flow by SGP (venous occlusion calf blood flow) or by IPG (normalized impedance blood flow) within individual groups. However, in our hands, IPG systematically overestimates the strain-gauge venous occlusion standard ($P < 0.001$).

There is no statistical difference among linear regression fits throughout groups. This would suggest a rationale for using IPG to compare grouped data among patients.

Resting Hemodynamics and Size Measurements

Age, weight, height, and body surface area were similar for all groups, although body weight tended to be greater for normal-flow POTS patients than for control subjects (Table 1; $P = 0.08$).

Supine heart rate and blood pressures—Heart rate was significantly increased above control subjects only in low-flow POTS patients in the supine position ($P = 0.014$). No differences were noted among systolic blood pressures. There was a significant increase ($P = 0.048$) in mean arterial pressure for the low-flow group, which may have contributed to increased total peripheral resistance. This was a consequence of increased diastolic pressure in this group not shown in Table 1 (diastolic pressure = 71 ± 3 mmHg in low-flow POTS patients compared with 58 ± 3 in control subjects, $P = 0.006$).

Supine blood volume and cardiac index

BLOOD VOLUME: Blood volume normalized to body weight was similar for control subjects and normal- and high-flow POTS patients but was decreased for low-flow POTS patients ($P = 0.011$). There was a trend toward increased blood flow in high-flow POTS patients that did not reach significance ($P = 0.2$) because of small numbers of patients.

CARDIAC INDEX: There was a decrease in overall cardiac index measured by ICG dye-dilution in low-flow POTS patients ($P = 0.01$), an increase in cardiac index in high-flow POTS patients ($P = 0.028$), and no difference in normal-flow POTS patients compared with control subjects. Impedance cardiac index measurements showed decreased values for low-flow POTS patients. High- as well as normal-flow POTS patients did not differ significantly from control subjects. Total peripheral resistance, calculated from ICG dye-dilution data as mean arterial pressure $\div$ cardiac index, was essentially related to the reciprocal of cardiac index, showing a significant increase ($P = 0.013$) in low-flow POTS patients and a significant decrease ($P = 0.007$) in high-flow POTS patients.

Segmental blood flow data

CALF: Calf venous occlusion plethysmography data in Table 1 are similar to those previously published (32) and are significantly different (by definition) among the POTS subgroups. Similar differences were found by using IPG methods. Thus flow was reduced in low-flow POTS patients ($P = 0.0001$), increased in high-flow POTS patients ($P = 0.0001$), and similar to control in high-flow POTS patients, regardless of the means of measurement.

SPLANCHNIC: Supine effective portal blood flow was not different between low-flow POTS patients and control subjects ($P = 0.1$) or high-flow POTS patients but was significantly increased in normal-flow POTS patients ($P = 0.002$). These data were paralleled by supine impedance data that demonstrated a significant increase ($P = 0.034$) in absolute and normalized blood flows in normal-flow POTS patients.

PELVIC: Pelvic blood flow was decreased in low-flow POTS patients ($P < 0.05$), with a trend toward increased blood flow in high-flow POTS patients ($P = 0.12$) that did not reach significance because of small numbers of subjects.

Changes During Incremental Upright Tilt

Heart rate and blood pressures

HEART RATE: Heart rate increased in all subjects at 35° and 70° upright tilt but was increased significantly in all POTS patients compared with control subjects ($P = 0.001$; Fig. 2). Heart rate was also significantly increased compared with control at 20° tilt in low-flow POTS patients ($P = 0.022$).

BLOOD PRESSURE: Mean arterial pressure was similar to control during tilt in the high-flow POTS patients. Mean arterial pressure was greater than in control subjects for low-flow POTS patients at 20° and 35° tilt ($P = 0.0015$) and was also significantly increased for normal-flow POTS patients at 35° tilt ($P = 0.048$).

Segmental blood volume changes during incremental tilt—Figure 3 shows the percent changes in segmental blood volumes during tilt.

THORACIC: Thoracic blood volume decreased progressively in all subjects as the tilt angle increased. Thoracic blood volume was significantly smaller ($P < 0.001$) for all POTS patients at 35° and 70° tilt than for control subjects.

SPLANCHNIC: Splanchnic blood volume increased progressively in all subjects as the tilt angle increased. Splanchnic blood volume was significantly ($P = 0.003$) larger at 35° and 70° tilt in low-flow POTS patients and, especially, normal-flow POTS patients than in control subjects. A small but significant ($P = 0.003$) increase in splanchnic blood volume was noted at 20° upright tilt in normal-flow POTS patients.

PELVIC: Pelvic blood volume increased progressively in all subjects as the tilt angle increased. Pelvic blood flow was significantly ($P = 0.05$) larger than in control subjects only in high-flow POTS patients at 70° tilt.

LEG (CALF): Leg blood volume increased progressively in all subjects as the tilt angle increased. Leg blood volume was significantly larger at 35° and 70° tilt in low- and, especially, high-flow POTS patients than in control subjects. Leg volume tended to decrease compared with control subjects in normal-flow POTS patients, but this did not reach statistical significance.

Segmental blood flow changes during incremental tilt—Figure 4 shows the percent changes in segmental blood flows during tilt.

THORACIC: Thoracic blood flow decreased progressively in all subjects as the angle of tilt increased. Thoracic volume was significantly smaller than in control subjects ($P = 0.023$) for all POTS patients at 35° and 70° tilt.

SPLANCHNIC: Splanchnic blood flow decreased progressively for control subjects and high-flow POTS patients but not for normal- or low-flow POTS patients. Splanchnic blood flow was actually significantly ($P = 0.034$) increased at 70° tilt in normal-flow POTS patients compared with patients in baseline supine conditions. Overall, there was no significant change in low- and normal-flow POTS splanchnic blood flows compared with those of patients in resting conditions at 35° and 70° tilt, although splanchnic blood flow decreased at 20° tilt in low-flow POTS patients.

PELVIC: Pelvic blood flow decreased progressively for control subjects and normal-flow POTS patients but not for low- or high-flow POTS patients, in whom it remained unchanged compared with baseline supine conditions. Pelvic blood flow was significantly ($P = 0.032$) decreased compared with control in normal-flow POTS patients at 70° upright tilt.

LEG (CALF): Leg blood flow changes closely followed pelvic blood flow changes (or vice versa) and, therefore, decreased progressively for control subjects and normal-flow POTS patients but not low- or high-flow POTS patients in whom leg flow remained unchanged. Leg blood flow was significantly ($P = 0.035$) decreased in normal-flow POTS patients at 70° upright tilt compared with that in control subjects.

DISCUSSION

Main Findings in POTS Patients

Normal-flow POTS pool in splanchnic circulation due to increased splanchnic blood flow—Our most significant findings are that splanchnic blood flow is increased in the supine posture in normal-flow POTS patients and that it remains increased during incremental tilt (Fig. 4). Therefore, splanchnic blood volume progressively increases in normal-flow POTS patients (Fig. 3) over a range of tilt angles from 20° to 70°. At the same time, these patients have intense peripheral (leg and pelvic) vasoconstriction. This suggests that there is no generalized failure of sympathetic vasoconstriction but, rather, intact graded reflex-mediated peripheral vasoconstriction in normal-flow POTS. Such vasoconstriction may be compensatory for marked splanchnic pooling and could account for the severe degree of dependent acrocyanosis often found in these patients by means of stagnant hypoxia: gravitationally increased volume of lower extremity venous blood becomes

excessively desaturated because of increased oxygen extraction consequent to low blood flow.

If peripheral sympathetically mediated vasoconstriction is intact in normal-flow POTS, then there is either selective splanchnic denervation or intact autonomic splanchnic activity confounded by local vasoregulatory factors. Selective elimination of splanchnic sympathetic vasoconstriction appears unlikely, and there is ample precedent for vasodilation produced by local factors. Thus, for example, locally mediated vasodilation occurs normally after a meal (17, 26). Locally mediated vasodilation may be a feature of POTS, even in the absence of feeding, involving vasoactive substances such as vasoactive intestinal polypeptide, substance P, calcitonin gene-related peptide, and nitric oxide. Such vasoactive agents antagonize sympathetic vasoconstrictive effects (8, 12, 15, 35).

Uniform hypovolemia and reduced blood flow in multiple regional circulations in low-flow POTS patients—We found that splanchnic blood flow also does not change during tilt in low-flow POTS patients. However, blood flow is relatively uniformly reduced in these patients in the supine posture (Table 1) and during orthostatic stress (Fig. 4). This is associated with an increase in percent change in segmental blood volumes in the leg and pelvic segments. However, because overall blood volume is reduced in these subjects, it cannot be assumed that regional circulations contain increased blood volumes. This is in part the consequence of low blood volume but is also the result of an overall decrease in response to postural change previously shown in this subset of POTS patients (30).

Lower body vasodilation in high-flow POTS patients—Data from high-flow POTS patients are similar to those previously reported by our group and showed increased cardiac index and peripheral blood flow, decreased peripheral resistance in the lower extremities and pelvic segment, and unchanged peripheral blood flow during orthostatic stress (30).

Gravitational Effects

Splanchnic, pelvic, and leg blood volumes progressively increased with angle of tilt in control subjects, despite progressively decreased blood flow in these segments. This finding demonstrates that gravitational filling of segmental venous structures is highly influenced by the hemostatic column of blood. Indeed, although Fig. 4 demonstrates a similar reduction in blood flow across segments in control subjects, Fig. 3 also shows a progressive increase, or gradient, in blood volume from splanchnic to pelvic to leg segment. One might then propose that increased blood volume in the splanchnic segment of normal-flow POTS best reflects deficient splanchnic vasoconstriction. However, because the splanchnic vasculature is known to respond to orthostatic stress with venoconstriction as well as arterial vasoconstriction (21, 22), this cannot be stated with certainty. Moreover, splanchnic venous and arterial tone typically covary (22, 25). Thus it may be reasonable to speculate that similar reductions in splanchnic arterial and venous constriction occur in POTS.

Comparison With Previous Work

Tani et al. (37) showed that splanchnic blood flow is increased during supine resting conditions in POTS patients. However, they reported that orthostatic splanchnic

vasoconstriction was similar in POTS patients and control subjects. Data were obtained by using duplex Doppler ultrasound of the superior mesenteric artery. Some of the differences between our results may be explained by our stratification scheme, in which POTS patients were partitioned among groups with different patterns of splanchnic blood flow response to orthostatic stress. Thus, if the subjects of Tani et al. comprised mostly high-flow POTS patients, differences could be rationalized. Differences in results could also relate to methods used to measure flow. Although superior mesenteric artery imaging is arguably a reference standard for measuring splanchnic blood flow, the celiac and inferior mesenteric arteries are not studied; therefore, their contribution to splanchnic blood flow is not included. Finally, different tilt protocols may have introduced differences in results, although we have regularly noted similar changes in normal-flow POTS patients tilted from the supine position to 70° tilt without intervening steps.

Limitations

Issues remain concerning the accuracy and validity of indirect measurement of blood flow using IPG. We have tried to resolve these issues by comparing impedance measurements with standard reference methods such as ICG dye dilution (for cardiac output and portal venous blood flow) and venous occlusion plethysmography (for calf blood flow). All comparisons show reasonable correlations between reference standard and impedance measurements. In each instance, we have used two techniques, which, although quantitatively somewhat different, gave similar directional results. Thus, within limits, more invasive testing can be replaced by noninvasive testing. However, although the ICG method can yield accurate cardiac outputs, neither this reference standard method (as implemented in the present study) nor impedance methods are capable of giving true absolute splanchnic flow data: the ICG method because we calculate dye clearance, rather than portal or hepatic blood flow, and the impedance method because it is suited only for detecting relative or percent changes in blood volume. Invasive measures to obtain hepatic extraction ratios in each subject are beyond the scope of the present studies and would require reassessments throughout incremental tilt. Also, it is clear from Fig. 1 and from our results that impedance methods yield systematically biased results in our hands and in this specific application using spot electrodes. However, by using IPG, we are working with a technique with superior temporal resolution but imperfect accuracy, which, however, seems sufficient and satisfactory to compare directional changes and relative magnitudes of changes in regional blood flow and blood volume among patients and volunteer control subjects undergoing similar testing.

ICG estimates of portal blood flow were hampered by the lack of computation of the hepatic dye extraction ratio. As explained in MATERIALS AND METHODS, there is an implicit assumption of equal extraction in all patients, with an extraction ratio of 1.0. We have not demonstrated whether the extraction ratio is different in POTS patients.

Direct measurement of sympathetic activity, such as muscle sympathetic nerve activity, better justifies our claim that peripheral sympathetic vasoconstriction is intact in normal-flow POTS patients. Such instrumentation is difficult in young subjects and, therefore, was not pursued. In addition, measurements of intact peripheral sympathetic activity could not be

used to imply intact (or damaged) splanchnic innervation. Directional changes in peripheral blood flow suggest intact sympathetically mediated peripheral vasoconstriction in normal-flow POTS patients.

The majority of the subjects were menstruating women. Previous studies demonstrated that the hormonal fluctuations that occur during the normal menstrual cycle may alter autonomic regulation of arterial pressure during various environmental stimuli (36), although there is no apparent effect on orthostatic tolerance (10). We did not control for menstrual cycle, except that female subjects were not actively menstruating during testing.

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Fig. 1.

Cardiac index (A) estimated by using indocyanine green (ICG) dye-dilution technique vs. impedance plethysmography (IPG), splanchnic blood flow (B) estimated using ICG dye-dilution technique vs. IPG, and calf blood flow (C) measured by venous occlusion plethysmography and estimated by IPG (abscissa). Data from all subjects were used. Correlation coefficients (r) are shown. In general, data showed fixed and proportionate biases. NI, normal.

Fig. 2.

Changes in mean arterial pressure (MAP) and heart rate (HR) during incremental upright tilt. MAP was increased in low-flow postural tachycardia syndrome (POTS) patients at 20° and 35° upright tilt. HR was significantly increased at 35° and 70° upright tilt. bpm, beats/min. *Significantly different from control, $P < 0.05$.

Fig. 3.

Percent changes in thoracic, splanchnic, pelvic, and leg blood volumes during incremental upright tilt averaged over subject groups. Splanchnic changes dominate normal-flow postural tachycardia syndrome (POTS). Blood pooling is widespread in low-flow POTS patients. Blood pools in the lower body in high-flow POTS patients. *Significantly different from control, $P < 0.05$.

Fig. 4.

Percent changes in thoracic, splanchnic, pelvic, and leg (calf) blood flow. Blood flow decreases for control in all segments. Blood flow does not change in splanchnic segment for normal-flow POTS, while leg blood flow is markedly reduced. Blood flow does not change in peripheral circulation (pelvic and leg) in high-flow POTS patients. Changes in blood flow are uniformly blunted in low-flow POTS patients. *Significantly different from control, $P < 0.05$.

Table 1

Patient dimensions and supine hemodynamic data

	Control (n = 12)	POTS		
		Low flow (n = 13)	Normal flow (n = 14)	High flow (n = 5)
Age, yr	18±1	20±1	19±1	16±1
Weight, kg	61±2	58±2	68±5	61±7
Height, cm	163±3	177±8	172±8	168±5
Body surface area, m ²	1.75±0.10	1.71±0.05	1.76±0.07	1.76±0.07
Normalized blood volume, ml/kg	72±3	58±4	70±6	78±4
ICG CI, l·min ⁻¹ ·m ⁻²	4.2±0.3	3.0±0.3*	3.9±0.5	5.5±0.4*
Total peripheral resistance, mmHg·l ⁻¹ ·min·m ⁻²	22±2	45±8*	28±4	14±2*
HR, beats/min	67±4	82±4*	66±3	76±6
SBP, mmHg	112±4	117±4	119±3	115±2
MAP, mmHg	76±2	85±4*	78±2	74±2
Venous occlusion calf blood flow, ml·100 ml ⁻¹ ·min ⁻¹	2.4±0.4	1.0±0.1*	2.3±0.1	4.4±0.3*
Calf arterial resistance, ml·100 ml ⁻¹ ·min·mmHg ⁻¹	31±5	61±4*	26±2	12±1*
Effective portal blood flow, ml·100 ml ⁻¹ ·min ⁻¹	25±3	19±2	40±3*	23±2
Impedance blood flows, ml/min				
Thoracic	6,682±841	3,591±711*	5,976±738	6,923±1,220
Splanchnic	1,537±233	1,216±260	2,347±266*	1,847±352
Pelvic	799±95	538±98*	618±127	1,055±121*
Leg	124±16	78±10*	109±17	199±11*
Impedance CI, l/m ²	3.8±0.3	2.3±0.4*	3.3±0.4	4.1±0.6
Normalized impedance blood flows, ml·100 ml ⁻¹ ·min ⁻¹				
Splanchnic	30±4	29±3	43±6*	26±4
Pelvic	11±2	7±1*	11±3	16±3*
Leg	2.4±0.2	1.1±0.1*	2.8±0.4	5.5±7*

Values are means ± SE; n, number of subjects. POTS, postural tachycardia syndrome; CI, cardiac index; ICG, indocyanine green; HR, heart rate; SBP, systolic blood pressure; MAP, mean arterial pressure.

* $P < 0.05$ vs. control.