Vascular perturbations in the chronic orthostatic intolerance of the postural orthostatic tachycardia syndrome

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Stewart, Julian M., and Amy Weldon. Vascular perturbations in the chronic orthostatic intolerance of the postural orthostatic tachycardia syndrome. J Appl Physiol 89: 1505–1512, 2000.—Chronic orthostatic intolerance is often related to the postural orthostatic tachycardia syndrome (POTS). POTS is characterized by upright tachycardia. Understanding of its pathophysiology remains incomplete, but edema and acrocyanosis of the lower extremities occur frequently. To determine how arterial and venous vascular properties account for these findings, we compared 13 patients aged 13–18 yr with 10 normal controls. Heart rate and blood pressure were continuously recorded, and strain-gauge plethysmography was used to measure forearm and calf blood flow, venous compliance, and microvascular filtration while the subject was supine and to measure calf blood flow and calf size change during head-up tilt. Resting venous pressure was higher in POTS compared with control (16 vs. 10 mmHg), which gave the appearance of decreased compliance in these patients. The threshold for edema formation decreased in POTS patients compared with controls (8.3 vs. 16.3 mmHg). With tilt, early calf blood flow increased in POTS patients (from 3.4 ± 0.9 to 12.6 ± 2.3 ml·100 ml⁻¹·min⁻¹) but did not increase in controls. Calf volume increased twice as much in POTS patients compared with controls over a shorter time of orthostasis. The data suggest that resting venous pressure is higher and the threshold for edema is lower in POTS patients compared with controls. Such findings make the POTS patients particularly vulnerable for edema fluid collection. This may signify a redistribution of blood to the lower extremities even while supine, accounting for tachycardia through vagal withdrawal.

ORTOSTATIC TACHYCARDIA SYNDROME has been described at least since 1940 (20) and is perhaps the most common reason for referral for chronic orthostatic intolerance (8, 10, 13, 19, 27, 35). Patients may be severely impaired and unable to work. Understanding of its pathophysiology remains incomplete. An operational definition of the syndrome (often denoted by the acronym POTS for postural orthostatic tachycardia syndrome) includes persistent symptoms of orthostatic intolerance such as lightheadedness, nausea, palpitations, weakness, retching, and fatigue in the upright position associated with an increase in heart rate of >30 beats/min from the supine to upright position or to a heart rate >120 beats/min within 10 min of head-up tilt (HUT). We reported the first pediatric cases of POTS. Data from our patients showed that POTS physiology underlies chronic orthostatic intolerance in the large majority of adolescents with the chronic fatigue syndrome (CFS) (33, 35). The data also showed loss of heart rate variability consistent with vagal withdrawal, increased blood pressure variability consistent with enhanced modulation of sympathetic tone while supine, and impaired baroreflex with a phase shift causing wide blood pressure swings uncompensated by compensatory heart rate changes. These changes were associated with edema and acrocyanosis of the lower extremities while upright, a phenomenon known as “pooling” that is often attributed to enhanced venous blood in dependent body parts during orthostasis and believed to be caused by autonomic dysfunction. Alternatively, we hypothesized that POTS results from a defect in arterial vasoconstriction or venous compliance. Such defects could redistribute blood toward dependent peripheral structures, causing reflex tachycardia through vagal withdrawal. Therefore, the aim of this study was to determine the arterial and venous vascular properties in POTS patients at rest and in response to orthostatic challenge.

METHODS

Patients and Controls

Thirteen consecutive patients aged 13–18 yr (11 girls, 2 boys), referred to our specialized center for chronic orthostatic intolerance, were studied. Patients for study were selected on the basis of orthostatic tachycardia syndrome on HUT. There is thus a conscious bias introduced to study the physiology of POTS. Patients with syncopal episodes were specifically excluded. Therefore, CFS patients who were recruited into the study were those with symptoms of orthostatic intolerance and POTS on testing. POTS is the most common orthostatic abnormality observed during HUT in adolescents with CFS (29, 35). Ten normal controls aged 12–17 yr (8 girls, 2 boys) were also studied. Orthostatic intolerance was characterized by lightheadedness, nausea

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and vomiting, palpitations, fatigue, headache, blurred vision, abnormal sweating, and a sensation of heat while upright. POTS patients all complained of three or more symptoms of orthostatic intolerance for at least 3 mo. Technically adequate tracings were obtained from all patients with orthostatic tachycardia, five of whom fit criteria for CFS (10). Controls were recruited from adolescents referred for innocent heart murmur. Patients with a history of syncope or orthostatic intolerance were specifically excluded. Adequate tracings were obtained from all normal controls. Only children found on cardiac examination to be free from structural or arrhythmic heart disease were eligible to participate. Enrolled patients were free of all obvious systemic illnesses and were not taking neurally active or vasoactive medications. There were no trained competitive athletes among patients or controls. There were no completely bedridden patients. Thus deconditioning as occurs in microgravity should not have occurred here. 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.

Definitions

Significant hypotension during HUT was common and defined by a decrease in systolic blood pressure of 30 mmHg or more. POTS was diagnosed by symptoms of orthostatic intolerance during HUT associated with an increase in sinus heart rate of >50 beats/min or with a rate of >120 beats/min during the first 10 min of tilt. Hypotension was not requisite. Criteria were selected for consistency with those given for adults in the literature (13, 19), but they may not be entirely appropriate for adolescents, in whom a higher heart rate may be more appropriate.

Patient Assessment

A questionnaire concerning symptoms of orthostatic intolerance was used but will not be presented here. This incorporated items in the Centers for Disease Control definition of CFS, a review of systems, and scales to quantify the impact of symptoms on the subject's cognitive, physical, and social functioning. Pertinent laboratory tests included complete blood count with leukocyte differential; erythrocyte sedimentation rate; serum levels of alanine aminotransferase, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorus, glucose, blood urea nitrogen, electrolytes, and creatinine; determination of thyroid-stimulating hormone; and urinalysis, all of which were normal in every instance. Patients were also tested for Lyme disease with Lyme ELISA and Western blot because Lyme disease is endemic in the New York area. Patients with active Lyme disease were specifically excluded. A routine cardiovascular physical examination was performed and was supplemented by electrocardiographic and echocardiographic assessments to rule out heart disease.

Laboratory Evaluation

All testing was performed in the laboratory during a single day. Our methods have been previously described (31, 32). After overnight fast, tests began between 9 and 10 AM. The electrocardiogram was monitored continuously and recorded to assess cardiac rhythm. Blood pressure was continuously monitored with an arterial tonometer (Collin Instruments, San Antonio, TX) placed on the left radial artery and recalibrated every 5 min against oscillometric sphygmomanometer pressure. The oscillometric blood pressure unit is part of the Collin system, and the tonometer is automatically recalibrated against the cuff whenever oscillometric blood pressure is taken. The tonometer has been tested against peripheral arterial invasive blood pressure measurements in children and adolescents and is reliable (18, 41).

A respiratory impedance plethysmograph (model 200 non-invasive monitoring system, Respitrace) was used to monitor respiratory changes. Respiratory, electrocardiogram, and pressure data were interfaced to a personal computer through an analog-to-digital converter (DataQ Instruments, Milwaukee, WI), and custom-designed software was used to produce, display, and store R-R intervals, respiratory rate, and blood pressure (mean, systolic, diastolic, and phasic tracings) on a continuous basis. To demonstrate consistency with previous work, we also computed the low-frequency baroreceptor gain using the methods of Robbe et al. (26); time domain indexes of heart rate variability (1), including the mean R-R interval and the SD of the R-R interval (SDNN); and frequency domain indexes of heart rate variability (low- and high-frequency power) by using an autoregressive model to calculate the power spectrum (17, 22).

Peripheral Vascular Evaluation

We used mercury-in-Silastic strain-gauge plethysmography to measure forearm blood flow and later calf blood flow, the forearm and calf compliance (volume-pressure) relationship, and the microvascular filtration (flow-pressure) relationship in the supine steady state in all patients. We also measured calf size change and calf blood flow during HUT. Methods were adapted from the work of Gamble et al. (11, 12) and are summarized in Fig. 1. Occlusion cuffs were first placed around the upper limb ~10 cm above a strain gauge of appropriate size attached to a Whitney-type strain-gauge plethysmograph (Hokanson). The cuff was inflated to a pressure of just below diastolic pressure to prevent venous egress. Wrist flow was briefly prevented by inflating a smaller secondary cuff to above systolic blood pressure. Arterial inflow in units of milliliters per 100 ml tissue per minute was estimated as the rate of change of the rapid increase in limb cross-sectional area shown in Fig. 1, bottom left. This assumes an approximate cylindrical segment of length $l$ and of volume $Al$, where $A$ is cross-sectional area. Assuming no change in segment length, a small change in area gives a change in volume of $\Delta V = Al \Delta l$ or a fractional change in volume of $(\Delta V/V) = \Delta l/lA$ = fractional change in area, which is the quantity measured by the strain-gauge plethysmograph. Flow measurements were repeated in triplicate. After it returned to baseline, we increased occlusion pressure gradually until limb volume change was just detected. This represents ambient venous pressure ($P_v$) (11) as shown in Fig. 2. Next we used 10-mmHg steps in pressure to a maximum of 60 mmHg, resulting in progressive limb enlargement. Independent data indicate that the $P_v$ distal to the congestion cuff approximates the cuff pressure (4). By fixing pressure, with the congestion cuff, a volume-congestion cuff pressure relationship can be obtained. At lower congestion pressures the limb size reached a plateau. With higher occlusion pressures, a plateau was not reached; instead, as shown in Fig. 1, bottom right, after initial curvilinear changes representing venous filling, the limb continued to increase in size linearly with time. The linear increase represents either venous creep (believed unimportant in humans (28)) or microvascular filtration. With the use of custom-designed software and modified linear least squares analysis by singular value decomposition (25), venous filling was separated from filtration.
Once the volume response was partitioned into contributions from filling of capacitance vessels and contributions from microvascular filtration, the limb volume vs. pressure relationship for capacitance vessels and the filtration rate vs. pressure relationship were constructed. Percent volume is measured, and volume is therefore expressed in normalized units of milliliters of volume change per 100 ml tissue, and filtration is expressed in normalized units of milliliters filtered per 100 ml tissue per millimeters of mercury, which approximates a microvascular filtration coefficient. Because veins and venules contain 80% of the body's blood, capacitance and compliance primarily reside in venous vessels. Under resting conditions, veins are partially filled. Therefore, congestion cuff pressure only caused an increase in limb size once the resting pressure was exceeded. We examined the "complete" volume-pressure relationship in representative patients. With occlusion cuffs deflated, the limb was progressively elevated while the patient remained supine. The height of the strain gauge above resting height was used to estimate hydraulic pressure using a factor of 1.055 for the density of blood. For consistency with the literature (6), we also obtained a "venous compliance" for both the calf and the forearm by measuring the difference between percent volume at 30 mmHg and percent volume at zero congestion pressure and dividing by 30 mmHg to obtain units of milliliters per 100 ml per millimeters of mercury. The filtration-pressure relationship was generally linear with its slope approximating the microvascular filtration coefficient in units of milliliters per 100 ml per minute per millimeters of mercury. The microvascular filtration coefficient was estimated by the slope of a linear least squares fit by using the singular value decomposition algorithm. The intercept with the pressure axis of the filtered flow-pressure graph is denoted P_i (isovolumetric pressure) and is the pressure at which microvascular filtration begins (differs from zero). We calculated the difference, P_i − P_v, by using paired data. This quantity represents the threshold for edema formation while supine. The same procedure was repeated in the calf with the leg congestion cuff placed just above the knee, to obtain flows, P_v, P_i, and the compliance and filtration relations for the lower limb.

**HUT Table Testing**

After supine vascular measurements were complete, the patients were tilted to 70° for a maximum duration of 30 min or until syncope, presyncope, or intolerable symptoms with or without significant hypotension occurred. An electrically driven tilt table (model 600, Cardiosystems, Dallas, TX) with a footboard for weight bearing was used. Baseline recordings of BP and heart rate in the supine position were obtained near the end of a 30-min resting period. The calf strain gauge remained in place and was used to measure the change in calf size with time over the course of tilt and to measure calf blood pressure.

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**Fig. 1.** Measurements made during venous occlusion plethysmography (arterial flow and venous filling). *Top:* typical experiment in which blood flow is measured in triplicate by venous occlusion followed by incremental occlusions using 10-mmHg steps to determine compliance and microvascular filtration relationships. *Bottom left:* forearm blood flow. Derivation of limb blood flow by fitting a slope to the initial portion of the occlusion curve is depicted. *Bottom right:* venous filling and capillary filtration. Means by which volume changes during pressure steps can be partitioned into contributions from venous filling and microvascular filtration is depicted.

**Fig. 2.** Compliance relationship (*A*) and microvascular filtration relationship (*B*) for a single representative postural orthostatic tachycardia syndrome (POTS) patient. *x*-Axis intercept of the volume change-cuff pressure, resting venous pressure (P_v). *x*-Axis intercept of the flow-cuff pressure line, isovolumetric pressure at which microvascular filtration begins (P_i).
flow every minute by intermittent venous occlusion to 80 mmHg. Patients with a positive test were returned immediately to the supine position, and the test was terminated (33). No pharmacological potentiation was employed. For comparison purposes, we used calf blood flow at \( \text{late tilt} \)

Statistics

Data were compared by two-way analysis of variance for repeated measures. When significant interactions were demonstrated, the ratio of \( F \) values was converted to a \( t \) distribution by using Scheffe’s test, and probabilities were thereafter determined. A Bonferroni correction was used to correct for small samples. All results are reported as means \( \pm \) SE. Statistically significant differences are reported for \( P < 0.05 \).

RESULTS

Supine Data

Representative limb blood flow and sequential pressure steps to determine limb volume vs. pressure relationships are shown in Fig. 1. Figure 1, bottom right, also shows the methods used to separate contributions of capacitance vessel filling from contributions of microvascular filtration. Results were repeatable in the same patients. Below a critical pressure \( (P_v) \) equal to the resting venous pressure, there was no change in volume with increasing cuff congestion pressure. At somewhat higher cuff pressures, there was an initial nonlinear rise in volume that reached a plateau corresponding to capacitance vessel (venous) filling at the congestion pressure. At even higher cuff pressures, limb volume increased at first nonlinear with time and then continued to increase linearly. This pattern of volume change corresponds to a supposition of venous filling and microvascular filtration. Figure 1, bottom right, shows the means used to separate venous filling from microvascular filtration at high congestion pressure: using least squares methods [singular value decomposition (25)], we fit a straight line to the final linear portion of the curve, extended the line back to the time that a step increment in pressure is applied, and performed a “curve stripping” to separate the two contributions. Therefore, we could separate contributions from venous filling (the plateau) from contributions from microvascular filtration (the linear portion) as a function of congestion pressure, which appears as separate compliance curves and microvascular filtration curves in Fig. 2, A and B, respectively.

Figure 2 depicts representative volume vs. pressure relationship and filtration rate vs. pressure relationship. Curves generated may be extrapolated back to 0% change in volume to obtain \( P_v \) and \( P_i \), respectively. We also measured the pressure at which the diameter of the limb just began to increase to obtain a more accurate estimate of \( P_v \). The volume-pressure (compliance) relationship is in general curvilinear, with a plateau at high pressure corresponding to completely filled veins. In some cases, when \( P_v \) was high, the amount of venous filling was quite small, because at such resting \( P_v \) the veins are almost entirely filled at resting venous pressure.

“Complete” pressure volume relations are shown in Fig. 3 for representative patients. In Fig. 3, pressures lower than \( P_v \) were estimated from the hydrostatic column height at the strain gauge \( (h) \) and blood density \( (\rho) \) from the formula \( P = \rho gh \), where \( g \) is acceleration due to gravity. We will return to the importance of the complete volume-pressure relationship below.

Supine data are shown in Table 1.

Blood pressure was not different supine, although heart rate significantly increased in POTS patients. Baroreflex gain decreased. We have reported this previously (32) and have demonstrated baroreflex changes.

Fig. 3. Compliance relationships for representative control and POT patient plotted in 2 different ways. A: volume change measured from the unfilled state at zero pressure. A residual volume could exist. B: changes in volume measured by using the resting pressure and corresponding volume as the reference. Once plotted with reference to a common pressure-volume zero \( (A) \), the curves are similar.
and blunting of time domain (e.g., SDNN) and frequency domain (high- and low-frequency spectral components of heart rate variability), as recapitulated here, which are consistent with vagal withdrawal.

\( P_v \) was significantly greater and \( P_i \) was significantly smaller for POTS patients in the calf but not the forearm. This resulted in a much smaller value for \( P_i - P_v \), corresponding to a lower threshold for microvascular filtration and edema formation in these patients, even in the supine position at baseline vascular tonus. No difference in the microvascular filtration coefficient could be demonstrated, although variances were large.

Apparent calf compliance was lower for POTS patients when calculated by conventional means. However, as shown in Fig. 4, this apparent compliance difference represents a shift in apparent compliance curves due to the higher \( P_v \) in POTS and disappears once volume change is measured relative to zero filling (Fig. 3). Therefore, there is no apparent difference in the volume-pressure compliance relationship between POTS patients and controls. There was no consistent difference in arm or leg blood flow supine.

### Upright Data

The HUT data appear in Table 2 and Fig. 5. As depicted by the representative tracings in Fig. 5, POTS patients had very marked and rapid increases in calf size immediately after HUT. POTS patients character-
A chronic change in blood flow can alter tissue hydrostatic and oniotic pressure, which results in the maladaptive change in $P_t$. Similar fluid shifts and altered pooling appear in the work of Brown and Hainsworth (3), who showed excessive pooling in individuals with chronic orthostatic intolerance. Pooling is enhanced with orthostasis with resultant reflex vagal withdrawal and tachycardia. Data suggest that chronically increased upright blood flow results from inadequate arterial vasoconstriction in the lower extremities. Further experiments documenting changes in lower extremity and simultaneous blood flow and volume, extremity blood pressures, venous efflux, and alterations in blood compartmentalization will be necessary to confirm this conjecture.

Our results are consistent with findings in chronic orthostatic intolerance studied by Jacob et al. (16) and Furlan et al. (10). Thus Jacob et al. (16) noted decreased blood volume in some patients with this syndrome that was associated with increased plasma catecholamines, and Furlan et al. (10) demonstrated increased muscle sympathetic nerve activity at rest, which was blunted during orthostasis, consistent with inadequate vasoconstriction. They found an increased ratio of low-frequency to high-frequency heart rate variability, consistent with vagal withdrawal, and increased low-frequency blood pressure spectral power in their patients with chronic orthostatic intolerance and orthostatic tachycardia. These data are similar to our heart rate and blood pressure results.

Our volume-pressure data are consistent with the work of Halliwell et al. (15), who developed methods to rapidly measure limb venous compliance in humans. Using a similar mercury-in-Silastic strain-gauge arrangement, these investigators first inflated cuffs to 60 mmHg and then deflated cuffs using a linear fall of 1 mmHg/min. They also used step changes in pressure. The data are comparable to ours, although small differences arising from their use of large initial pressure steps are apparent and may relate to activation of the venoarterial reflex.

Measuring compliance by computing the change in limb volume from resting state to 30 mmHg occlusion pressure as performed by Convertino et al. (5), however, yields different results, suggesting decreased compliance. However, single step changes in occlusion pressure do not account for the resting pressure $P_v$ which would result in an apparent shift in the compliance curve even while the “real” compliance relation measured from true zero pressure remains unaltered. On the contrary, when the compliance relation is computed, our data do not show a difference between POTS patients and normal controls, at least while supine. This observation implies that increased resting $P_v$ causes increased venous volume in the lower extremities. The data do not address whether the compliance relation is altered by orthostasis, which awaits further investigation. Thus the issue of active vasoconstriction cannot be addressed.
The cause of blunted vasoconstriction with orthostasis remains to be determined. POTS often occurs after an infectious or inflammatory condition. Although results are mixed, patients with POTS may have significant increases in vasoactive cytokine release, which could theoretically change vascular properties. Such associations are still largely anecdotal.

**Alternative Hypotheses**

**Lower extremity pooling in POTS but not autonomic failure.** On the one hand, patients with autonomic failure have little peripheral pooling; the general understanding is that control of the splanchnic bed and not the legs is crucial for orthostatic intolerance (31). On the other hand, we hypothesize that adolescents with POTS do not have circulatory autonomic failure at all. Other preliminary data (32) indicate that the Valsalva maneuver and timed respiratory variation are generally intact. Vagal withdrawal seems the rule. Most recent preliminary findings using brief HUT and intravenous phenylephrine indicate that the ability to slow the heart rate remains unimpaired. Also, Furlan et al. (10) have demonstrated sympathetic overactivity in their patients with POTS. The splanchnic venous bed is the largest venous pool in the body, with skin and muscle in the lower extremities the next largest. With orthostasis, the normal response is sympathetically mediated splanchnic emptying even while the lower limb veins are passively filling. Given an intact sympathetic response, pooling occurs largely in the dependent lower extremities. If circulatory sympathetic response is intact in POTS, then the splanchnic circulation should empty with orthostasis, even while exaggerated pooling occurs in the lower extremities. These speculations will need to be subjected to rigorous scientific verification.

**Pooling and a deconditioned muscle pump.** With regard to the muscle pump, resting muscle tone is probably normal in our patients because we did not find venous compliance abnormalities once volumes were corrected for $P_v$. This is not true of astronauts with prolonged microgravitational deconditioning (5, 6), in whom muscle mass and strength decreased and venous compliance increased. We infer that the muscle pump is intact in POTS. However, this is speculative and should be verified by experiment.

**Importance**

Upright posture is a defining characteristic of hominids. Rapid and effective circulatory and neurological compensations are needed to maintain blood pressure and consciousness. POTS is emerging as the most common reason for referral for chronic orthostatic intolerance (8, 10, 19, 27, 35). Patients are often unable to hold a job or attend school. POTS prevails in the large majority of adolescents with CFS syndrome (29, 33, 35) and has been reported in a series of adult CFS patients (2, 7, 37). CFS may represent the most severe form of POTS. A review of patients with delayed orthostatic hypotension (delayed POTS) demonstrated a high degree of association with chronic fatigue (7, 38).

POTS is common, affecting patients mostly in the age range of 12–50 yr, mostly women (~80%), often with onset after a viral infection or other inflammatory condition. There is an increasing prevalence in children and adolescents (35). Inflammation and POTS may be related. Among the mechanisms for this link are the chronic elaboration of cytokines with potent vasoactive consequences such as interleukin-1, interleukin-6, and tumor necrosis factor-α. Such a link seems established in the CFS in which POTS and neurally mediated syncope occur with high frequency (14, 24).

**Limitations**

**Patient selection.** The patients enrolled in the study were carefully selected to have POTS and are not necessarily representative of other illness classifications, such as typical CFS patients. Referral bias was present in this regard and also by excluding those patients and controls with prior syncope or other illnesses.

**Menstrual cycle.** The exact relation to the menstrual cycle should have been recorded in female patients and was not. This is a clear limitation of the study because of strong suspicions linking menses and the hormonal changes of the luteal cycle with changes in autonomic activity, vascular responsiveness, and therefore orthostatic tolerance (21). Often, particularly in younger teenagers, menses are irregular, and connections to plasma estrogen may be a preferred means to address this subject.

**Heart rate.** Adult criteria for POTS (heart rate increase of >30 beats/min) may not be entirely suitable for adolescents. However, all of our patients had at least a 35 beats/min rise with tilt and most had a 40 beats/min or greater rise. Although only small numbers were used, no control subject had a similar rise in heart rate. Therefore, we believe that the heart rate is significantly and abnormally increased in our patients.

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