Microvascular Filtration Is Increased in Postural Tachycardia Syndrome

Julian M. Stewart, MD, PhD

Background—Postural tachycardia syndrome (POTS) is related to defective peripheral vasoconstriction of dependent extremities with redistributive hypovolemia.

Methods and Results—To test whether enhanced microvascular filtration produces leg enlargement, we studied 12 patients 13 to 19 years of age with POTS and defective leg vasoconstriction and 13 age-matched healthy control subjects, with strain-gauge plethysmography used to measure venous pressure (Pv), forearm and calf blood flow, vascular capacitance, and the microvascular filtration coefficient (Kf). Measurements were made while the patient was supine and at steady state during upright tilt to 35°. Supine P was not different in POTS, but upright leg Pt tended to be increased above control. Arm and leg peripheral arterial resistance was decreased in the supine and upright positions in patients with POTS compared with control subjects (P=0.01, upright legs). Supine Kf was not significantly increased in the forearm in patients with POTS but was increased in the calf (9.3±2.2 versus 5.7±2.4 [10⁻³] mL/100 mL per minute per mm Hg, P=0.04), correlating with calf blood flow (r,=0.84, P=0.002). Kf was invariant with orthostasis. The hydraulic contribution to upright filtered flow at 35° tilt, the product of Kf and Pt, was approximately twice that of control (0.41±0.09 versus 0.19±0.04 mL/100 mL per minute, P=0.04).

Conclusions—Increased microvascular filtration accounts for enhanced leg swelling in patients with POTS with increased arterial blood flow. (Circulation. 2003;107:2816-2822.)

Key Words: vasodilation ■ blood flow ■ tachycardia

Chronic orthostatic intolerance is associated with postural tachycardia syndrome (POTS).1 POTS produces redistributive hypovolemia related to neurovascular deficiencies.2-3 Thus, Jacob et al4 demonstrated a low-renin form of hypovolemia in some patients, whereas a decrease in norepinephrine spillover consistent with lower limb adrenergic denervation has been shown5 and predicts blunted arterial vasoconstriction consistent with inappropriate vasodilation as demonstrated by Stewart.6 Enhanced blood flow in POTS occurs in the supine and upright positions, producing lower limb enlargement,7 often referred to as “dependent [venous] pooling,” assuming that excess blood is sequestered or “pooled” within the leg veins. Precisely how this occurs is unclear: Prior work has failed to demonstrate increased venous capacitance in POTS8 or increased venous pressure.9 Data have demonstrated contributions to limb enlargement from microvascular filtration.6,10,11 Thus, we hypothesized that orthostatic limb enlargement occurs through enhanced microvascular filtration in POTS.

Methods

Subjects: Patient and Control Subject Screening
We screened consecutive patients 13 to 19 years of age for chronic orthostatic intolerance lasting for >3 months, defined by the presence of lightheadedness, fatigue, headache, neurocognitive deficits, nausea, blurred vision, and abnormal sweating while upright with no other medical explanation. Patients with POTS on upright tilt to 70° and who had increased supine leg blood flow measured by venous occlusion plethysmography12 were included (see below). POTS was diagnosed by symptoms of orthostatic intolerance during tilt associated with an increase in sinus heart rate of >30 beats per minute or to a rate of >120 beats per minute during the first 10 minutes of tilt.13 The POTS population is segregated into two groups, based on venous pressure and blood flow: one group with normal venous pressure and high calf blood flow and a second with high venous pressure and low calf blood flow.6 Here, patients were retained only if they belonged to the high-flow group. Increased calf blood flow was defined as exceeding 3.6 mL/min per 100 mL of tissue, the largest calf blood flow measured in our control subjects. Twelve patients were recruited (10 girls, 2 boys; median age, 16.2 years).

Thirteen healthy control subjects, 13 to 19 years of age (10 girls, 3 boys; median, 16.0 years), with normal orthostatic response to 70° tilt, were also studied. These were recruited from adolescents referred for innocent heart murmur. Subjects with a history of orthostatic intolerance were specifically excluded.

Only children found to be free from heart disease on history taking, physical examination, and electrocardiographic and echocardiographic examinations were eligible. All subjects were free of systemic illnesses and were not taking medications. Informed consent was obtained. The Committee for the Protection of Human Subjects (institutional review board) of New York Medical College approved all protocols.

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Laboratory Evaluation

On a morning after the screening day, patients returned for measurements performed supine and during 35° upright tilt.

Monitoring

The arm blood pressure (BP) was continuously monitored by arterial tonometry (Colin Instruments) on the right radial artery recalibrated against oscillometric BP. Calf BP was measured intermittently by oscillometry. Data were interfaced to a personal computer sampling at 200 Hz.

Peripheral Vascular Evaluation

We used mercury-in-silastic, strain-gauge plethysmography (SGP) to measure forearm and calf blood flows, the forearm and calf venous pressure, $P_v$, overall venous capacitance, and the microvascular filtration (flow-pressure) relation while supine and during steady-state upright 35° tilt. Methods are summarized in Figure 1.

After a 30-minute resting period, flow measurements were performed in triplicate. We increased occlusion pressure gradually until limb volume change was just detected at $P_v$. Pressures less than $P_v$ do not increase limb size. We used the mean arterial pressure (MAP), calculated as $0.33 \times \text{systolic BP} + 0.67 \times \text{diastolic BP}$, and $P_v$ to calculate the arterial resistance to blood flow in units of mm Hg/(mL/100 mL tissue) per minute from $\frac{\text{MAP} - P_v}{\text{flow}}$.

To determine limb capacitance, the limb was raised above heart level until no further decrease in volume occurred. Then, we used 10–mm Hg pressure steps, starting at the first multiple of 10 exceeding $P_v$, to a maximum of 60 mm Hg. The venous pressure distal to congestion approximates the cuff pressure. Pressure was maintained for 4 minutes to reach a steady state. At lower pressures, limb size reached a plateau shown in Figure 1. At higher pressure steps, a plateau was not reached, but after initial curvilinear venous filling, the limb increased linearly in size with time. The linear increase represents microvascular filtration. Above a critical pressure typically greater than $P_v$, denoted $P_i$, the lymphatic system cannot compensate for filtration and the interstitium enlarges at a rate proportionate to imposed pressure. Pressure steps between $P_v$ and $P_i$ result in a plateau, whereas pressure steps above $P_i$ result in a curve asymptotic to a straight line with positive slope. We used least-squares techniques to fit a straight line to the many points comprising the linear microvascular filtration contribution to filling. The linear portion was then electronically subtracted from the total curve to obtain a residual curve that reaches a plateau representing filling of capacitance vessels.

Capacitance was calculated from the sum of residual portions shown as “intravascular filling” in Figure 1, to which was added the estimate of supine venous volume obtained from limb raising. The microvascular filtration relation (filtration rate versus pressure) was constructed (Figure 2) for each subject. Normalized volume is

Figure 1. Representative supine limb plethysmographic tracing. Blood flow is assessed by sudden venous occlusion shown on the left of the top panel and in expanded detail in the left lower panel. Least-squares fit is superimposed to obtain estimates of flow. After measurement of $P_v$, the limb is pressurized by using 10–mm Hg pressure increments beginning at 20 mm Hg. Change in limb volume for a pressure step from 20 to 30 mm Hg is shown in the right lower panel. This has been partitioned into contributions from intravascular capacitance vessel filling and from microvascular filtration.
expression occurs only above a critical occlusion pressure, \( P_i \). The slope is \( K_f \), the microvascular filtration coefficient. By extrapolation the \( y \)-intercept or the normalized filtered flow at zero hydraulic pressure may be obtained, which is related to interstitial pressures, oncotic pressure, and lymphatic drainage (see text for details).

expressed in units of (mL volume change/100 mL tissue), normalized filtration rate is expressed in units of (mL/100 mL tissue per minute), and normalized filtration coefficient, \( K_f \), the slope in the linear relation shown in Figure 2, is expressed in units of (mL/100 mL tissue per minute per mm Hg). The intercept with the pressure axis of the flow-pressure graph is \( P_i \), which approximates the net oncotic pressure gradient for microvascular filtration or \( \sigma (P_{oc} - P_i) \), where \( \sigma \) is the reflection coefficient, \( P_{oc} \) is vascular oncotic pressure, and \( P_i \) is tissue oncotic pressure. Pappenheimer and Soto-Rivera\(^{17} \) established that filtration does not occur at pressures less than \( P_i \). The extension of linear fit to negative flow is a “virtual flow,” which estimates the \( y \)-intercept with the filtration axis, the normalized filtered flow at zero hydraulic pressure, comprising contributions from lymphatic flow and osmotically driven filtration.

35° Upright Tilt-Table Testing
After supine vascular measurements, the patients were tilted to 35° for 15 minutes to obtain steady-state measurements. Earlier work indicated that 35° tilt activates thoracic mechanoreceptors, producing an adequate orthostatic response.\(^{18} \) P, and limb blood flows were measured at steady state by SGP. SGP was used to assess microfiltration by increasing occlusion pressure from \( P_i \) in 10–mm Hg increments to a pressure less than the diastolic pressure confirmed by oscillometric BP of the contralateral calf. The filtration relation for upright posture was recalculated, and \( K_f \) was obtained by least-squares analysis. The height between the congestion cuff and the strain gauge was used to correct for hemostatic load differences by adding \( \rho \times g \times D \times \sin(35°) \) to the cuff pressure, where \( \rho \) is density of blood, \( g \) is gravitational acceleration constant, and \( D \) is the distance from cuff to strain gauge.

To estimate calf filtration driven by hydraulic forces during tilt, we calculated the product of \( K_f \) and calf \( P_i \).

Statistics
Ages were compared by the Mann-Whitney test. Tabular data were compared by 2-way ANOVA (control to POTS, supine, and upright). When significant interactions were demonstrated, ratios of coefficients, the Spearman rank-order correlation statistic was used.

Results
Ages were not different for patients with POTS and control subjects \( (P=0.14) \). Results are shown in Figures 3 to 5 and the Table.

Supine Measurements
Heart Rate, Blood Pressure, and Venous Pressure
Supine heart rate was increased \( (P=0.05) \) in POTS. Mean arterial BPs were not different from control subjects \( (P=0.17 \) arm, \( P=0.73 \) leg). Venous pressures were not different from control subjects \( (P=0.49 \) arm, \( P=0.50 \) leg).

Blood Flow and Peripheral Arterial Resistance
Data are shown in the Table. Supine calf blood flow was increased by selection. Supine forearm blood flow was increased in patients with POTS above that in control subjects \( (P=0.03) \). Peripheral arterial resistance was lower in POTS \( (P=0.05 \) arm, \( P=0.05 \) leg).

Capacitance
Arm and leg capacitance in POTS was not different from control capacitance \( (P=0.45 \) arm, \( P=0.41 \) leg).

Microvascular Filtration
Figure 3 shows the supine microvascular filtration relation group averaged over every subject. Averaged individual
microvascular filtration coefficients are listed in the Table. Averaged linear regressions were constructed with the use of all data points for a given group (patients with POTS or control subjects). Filtration was increased \( (P=0.04) \) in the calves of patients with POTS compared with control subjects. \( P_i \) was not different \( (P=0.19) \) compared with that in control subjects \( (P=0.025) \) of patients with POTS.

Figure 4 depicts the correlation between supine blood flow and the \( K_f \) in the forearm and calf. Arm filtration tended to be increased in POTS but was uncorrelated with blood flow \( (P=0.76) \). Leg filtration was significantly correlated \( (r=0.84, P=0.002) \) to calf blood flow.

### Upright Measurements

Heart rate increased \( (P=0.002) \) more in patients with POTS (\( \Delta \text{HR}=24 \pm 6 \) beats/min) than in control subjects (\( \Delta \text{HR}=15 \pm 7 \)). Blood flow remained higher \( (P=0.05 \text{ arm}, P=0.0001 \text{ leg}) \) and peripheral arterial resistance remained significantly lower in the leg than in control subjects \( (P=0.13 \text{ arm}, P=0.05 \text{ leg}) \). Arm BP remained unchanged, whereas leg BP increased similarly in patients with POTS and control subjects \( (P=0.0001) \) as the result of gravity. Leg venous pressure \( (P_v) \) increased in both groups \( (P=0.001) \) but tended to be higher in POTS \( (P=0.2) \). \( P_i \) was not different \( (P=0.45) \). Upright filtration coefficients were unchanged from supine (POTS: \( P=0.8 \text{ arm}, P=0.07 \text{ leg}; \) control: \( P=0.47 \text{ arm}, P=0.19 \text{ leg} \)).

To estimate filtration driven by hydraulic forces within the legs during tilt, we formed the product of \( K_f \) and calf \( P_v \). This was \( 0.41 \pm 0.09 \text{ mL/100 mL per minute} \) in patients with POTS and was increased \( (P=0.04) \) compared with that in control subjects \( (0.19 \pm 0.04) \).

Capacitance was unchanged in the upright position. The consequences of similar upright capacitance but increased filtration in patients with POTS are illustrated in Figure 5. The early portions of curves for both control subjects and patients with POTS were curvilinear, whereas the later portions were linear, consistent with constant filtration at increased upright venous pressure. Filtration and venous filling contributions to leg enlargement were separated by the curve-stripping routine explained previously. The residual curves, representing the contribution from capacitance vessel filling, are similar, whereas the linear fits representing filtration are different.

### Discussion

Our data demonstrate that the microvascular filtration coefficient, \( K_f \), is increased in the lower limbs of patients with POTS and is correlated to the rate of blood flow. Blood flow is increased and arterial resistance is decreased in forearms and calves of patients with POTS. \( K_f \) is independent of posture in all subjects. There is a trend toward increased upright calf venous pressure in patients with POTS. The hydraulically driven filtration flux is increased in POTS. Increased microvascular filtration accounts for the enhanced leg swelling observed in patients with POTS with increased peripheral blood flow.
Microvascular Filtration Coefficient Is Increased in POTS

Quiet standing produces physiologically important microvascular filtration in healthy subjects.19 The filtration coefficient can be chronically altered through exercise or electrical stimulation as well as disease.20–22 Our previous work intimated at increased $K_f$ in patients with POTS11,23,24 but stopped short of any definitive statement because of patient heterogeneity, lack of subject selection, and technical considerations. It is now clear that patients with POTS with defective arterial vasoconstriction6,9 have increased microvascular filtration.

Brown and Hainsworth10 earlier concluded that orthostatic stress causes venous pooling. They used impedance plethysmography in healthy volunteers and in patients with orthostatic intolerance to demonstrate rapid initial calf enlargement corresponding to capacitance vessel filling and later linear enlargement corresponding to filtration during quiet standing. They did not relate linear changes to capillary filtration per se but were able to demonstrate that at least some patients with orthostatic intolerance had increased calf microvascular filtration rates.

Explaining Increased Microvascular Filtration Coefficient in POTS

$K_f$ is the product of the specific vascular permeability per unit surface area and the vascular surface area available for filtration.17 Our finding that $K_f$ is increased in POTS with increased peripheral blood flow could be explained by decreased precapillary vasoconstriction increasing the numbers of perfused capillaries (ie, capillary recruitment).25,26 This would tend to outweigh mechanisms such as the myogenic effect.27 Given the increase in blood flow, recruitment best fits the data.

Alternatively, the number of vessels available for filtration may have increased that is functionally indistinguishable from the precapillary hypothesis. Increased vessels may account for increased upright filtration in endurance-trained athletes.21

Another possibility is increased permeability.28,29 However, increased permeability fails to explain the correlation between lower limb flow and filtration.

$K_f$ Is Independent of Posture in Patients With POTS and in Control Subjects

Evidence from animal experiments26 suggests that $K_f$ is independent of acute changes in pressure and flow. Acutely, local regulatory systems match filtration to tissue metabolism. By using occlusion plethysmography, Gamble et al and others30–32 have shown that small pressure steps or upright tilt leave $K_f$ unchanged. These data were from normal animals and healthy human subjects and need not apply to patients with abnormal POTS. Nevertheless, our data show no dependence of $K_f$ on posture in both control subjects and patients with POTS.
Linear Filtration Relation and Lymph Flow

Previous work by Zweifach and Intaglia\textsuperscript{33} indicate that under normal conditions, capillary flow is unidirectional—predominantly from vessel lumen to interstitium—with lymphatic drainage removing filtered fluid. The Starling concept of capillary recirculation has been shown to be incorrect under most conditions in most vascular beds. There is no sustained absorption of interstitial fluid at low capillary pressure.\textsuperscript{34} Changes in plasma oncotic pressure are small (on the order of 3%) while traversing the capillary bed at ordinary flow rates and smaller yet with increased flow. POTS filtration is not a flow-limited process.\textsuperscript{35}

From the Landis-Starling relation, we have

\[
\text{Filtration} = K_f \times [(P_{\text{vasc}} - P_t) - \sigma (\Pi_{\text{vasc}} - \Pi_t)],
\]

where \(P_{\text{vasc}}\) is the vascular pressure, \(P_t\) the tissue pressure, \(\Pi_{\text{vasc}}\) and \(\Pi_t\) are corresponding oncotic pressures, and \(\sigma\) is the [protein] reflection coefficient. The net increase in limb tissue volume (exclusive of capacitance vessel filling) is \(dV_{\text{ol}}/dt=\text{Filtration} - \text{Lymphatic drainage}\).

Under conditions where there is no increase in tissue volume \(dV_{\text{ol}}/dt=0\).

Lymphatic flow and filtered flow must be equal: Lymphatic flow \(= K_f \times [(P_{\text{vasc}} - P_t) - \sigma (\Pi_{\text{vasc}} - \Pi_t)]\).

This prevails at pressures less than \(P_t\), the threshold for microvascular filtration. When fluid filtration is low, it is balanced by lymph flow. Once \(P_t\) is exceeded, edema forms.\textsuperscript{37}

Arterial vasoconstriction defends against edema by restricting the rise in microvascular pressure during increased venous pressure. However, vasoconstriction is defective in POTS.\textsuperscript{9}

Thus, filtered flow exceeds lymphatic flow and edema results. The mass balance relation becomes \(dV_{\text{ol}}/dt=K_f \times [(P_{\text{vasc}} - P_t) - \sigma (\Pi_{\text{vasc}} - \Pi_t)] - \text{Lymphatic drainage}\).

During small pressure steps, there is no change in blood flow and a small decrement in precapillary sphincter resistance.\textsuperscript{32} Assuming tissue pressure, reflection coefficient, and oncotic pressures are unchanged during cuff occlusion, the rate of change in limb volume, \(dV_{\text{ol}}/dt\), is a function of \(P_{\text{vasc}}\) and lymphatic drainage, where \(P_{\text{vasc}}\) is determined by venous occlusion pressure. Most generally, one expects lymphatic drainage to change as \(P_{\text{vasc}}\) changes. However, we found that \(dV_{\text{ol}}/dt\) is linear in \(P_{\text{vasc}}\) alone. This has two implications. First, lymphatic drainage is independent of time and either constant (zero order) or changes linearly (first order) in \(P_{\text{vasc}}\). Olszewski et al.\textsuperscript{38} and Michel and Moyser\textsuperscript{39} demonstrated constant lymphatic pumping capability with increased venous pressure, making a zero-order process likely.\textsuperscript{37}

Second, the \(y\)-intercept \((P_{\text{vasc}}=0\) in Figure 2\) relates to the lymphatic drainage by the formula

\[
Y_{\text{intercept}} = K_f \times [(P_{\text{vasc}} - P_t) - \sigma (\Pi_{\text{vasc}} - \Pi_t)] - \text{Lymphatic drainage}.
\]

We know that \(P_{\text{vasc}}=\sigma (\Pi_{\text{vasc}} - \Pi_t)\) is not different between POTS and control and that \(P_t\) is small. A more negative \(y\)-intercept therefore implies increased lymphatic drainage for patients with POTS.

Do Other POTS Variants Have Increased Microvascular Filtration?

Some patients with POTS have reduced leg blood flow associated with increased \(P_t\).\textsuperscript{9} Some may have low blood volumes.\textsuperscript{2} Figure 6 shows preliminary results from 8 comparably aged patients with POTS with reduced leg blood flow. They do not have increased \(K_f\) \((P=0.48)\). The microvascular filtration relation does not differ from control.

**Limitations**

Interstitial oncotic and tissue pressures are unknown but are unlikely to change significantly with time and do not invalidate the principal results. On the one hand, it is true that if \(K_f\) increases without a change in large-molecule permeability, then oncotic pressure should decrease, partially counteracting filtration. On the other hand, increased capillary blood flow limits the effects of filtration on intravascular plasma concentration.

We studied extremities. It is clear that other regional circulations are affected in POTS. For example, work indicates that splanchnic arterial inflow is abnormal in POTS.\textsuperscript{40} However, the lower extremities and buttocks are important pooling reservoirs during orthostasis\textsuperscript{41} and thus the study addresses effects that are important to the orthostatic response.

Steady states were studied. We required stable conditions during which filtration could be measured. Potentially useful information could be missed. Steady-state requirements limited the use of larger tilt angles, since patients with POTS are often unable to maintain these angles long enough to complete measurements. It is possible to have used more rapid measurement techniques such as those used by Halliwell et al.\textsuperscript{42} However, these introduce additional time-dependent changes avoided by the incremental step protocol.

Age limitations to generalizability may exist. Adolescents may not perfectly represent findings in mature adults. However, circulatory structure and function is essentially mature by puberty, and results can be regarded as qualitatively similar to older subjects. Moreover, adolescents generally have the advantage of absence of confounding vascular illness.
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