Decreased skeletal muscle pump activity in patients with postural tachycardia syndrome and low peripheral blood flow

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STANDING UP TRANSLOCATES a large fraction of the thoracic blood volume into the dependent body parts and thereby reduces venous return. When upright systemic venous return is sufficiently impaired, orthostatic intolerance (OI) occurs and may be related to decreased blood volume, enhanced gravitational pooling of blood within the dependent veins in the lower body, or loss of vascular volume through microvascular filtration (28). A principal defense against OI in humans is the “skeletal muscle pump,” in which contractions of leg and gluteal muscles propel venous blood back to the heart (1, 38). Many investigations of OI deliberately subvert the muscle pump by use of tilt tables or lower-body negative pressure. However, recent work has reinforced the importance of muscle pump activity in relieving OI (20).

Skeletal muscle integrity is dependent on adequate blood flow whether an individual is supine or upright; muscle ischemia produces reduced muscle mass (3, 8). Impairment of blood flow may cause skeletal muscle wasting, which may further compromise muscle flow through its effects on the muscle pump (5).

We have previously identified a subset of patients with chronic OI that also have decreased supine and upright peripheral blood flow and high arterial resistance. We denoted this group as having low-flow postural tachycardia syndrome (low-flow POTS; Ref. 33, 35). POTS is identified with chronic OI (17, 23, 30, 37). In the present work, we investigated the hypothesis that low calf blood flow results in a decrease in muscle pump activity.

MATERIALS AND METHODS

Subjects and Experimental Outline

To test this hypothesis, we studied three groups of subjects: controls, patients with POTS and low calf blood flow, and patients with POTS and normal calf blood flow. In all subjects, POTS was confirmed on a screening, upright tilt-table test at 70°. POTS was diagnosed by the presence of symptoms of OI during the screening tilt test that were associated with an increase in sinus heart rate >30 beats/min or to a rate of >120 beats/min during the first 10 min of tilt as defined in the adult literature (23, 29).

The first group comprised 10 healthy female volunteers aged 15–22 yr (median, 18 yr) who were free from all symptoms of OI. Only female volunteers were chosen to best match our low-flow POTS subjects, who are exclusively female. Volunteers were recruited from among a population of young people referred for innocent heart murmur. Only those found to be free from heart disease on cardiac exam were eligible to participate. None of the control subjects had POTS during the screening tilt test.

The second group comprised 12 females aged 15–21 yr (median, 17 yr) who were referred to our center for symptoms of OI lasting for >6 mo. OI 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 the individual was upright with no other medical explanation for the symptoms. Patients were retained in this group for additional study if supine calf blood flow was decreased below our normal range (see below) and comprised the low-flow POTS subjects.

A third group of subjects comprised 7 females aged 16–20 yr (median, 17 yr) referred to our center for symptoms of OI who were retained for additional study in this group if their calf blood flow was within our normal range (see below); these individuals comprised the normal-flow POTS subjects.

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There were no bedridden subjects among the patients or controls. No subjects had any form of systemic or circulatory disease, and none were taking medications. Informed consent was obtained, and all protocols were approved by the Committee for the Protection of Human Subjects of New York Medical College.

Experiment Outline

While the patients were supine, we assessed heart rate, blood pressure (BP), and blood volume using indocyanine green dye-dilution methods and forearm and calf peripheral blood flow, venous pressure ($P_v$), and venous capacitance using strain-gauge occlusion plethysmography. Calf strain gauges were used to measure calf skeletal muscle pump function on standing patients.

Details of Methods

Tests began between 9:00 and 9:30 AM after patients fasted overnight. The room temperature ranged from 23 to 25°C. After a 30-min acclimatization period, tests were performed in the following order allowing time for recovery in between: supine blood flow and arterial resistance measurement, skeletal muscle pump function (tiptoe test), repeat supine blood flow and arterial resistance measurement, blood volume measurement by indicator dye dilution, and venous capacitance measurement.

Supine peripheral blood flow, arterial resistance, and venous capacitance. We used mercury-in-Silastic strain-gauge plethysmography to measure supine forearm and calf blood flow. Measurements were always made with patients supine at the beginning of the experiments and followed a 30-min resting period. Measurements were repeated 20 min after the tiptoe test after a second supine resting period. Occlusion cuffs were placed around the upper and lower limbs ~10 cm above a strain gauge that was attached to a Whitney-type strain-gauge plethysmograph (Hokanson). Blood flow was estimated by standard venous occlusion methods (12) using rapid cuff inflation to a pressure $>$40 mmHg but less than diastolic pressure to prevent venous egress. Briefly inflating a smaller, secondary cuff on the ankle or wrist to suprasystolic BP prevented foot or hand blood flow. Arterial inflow values (in units of ml·100 ml tissue$^{-1}$·min$^{-1}$) were estimated as the rate of change of the rapid increase in limb cross-sectional area. Previously we collected peripheral blood flow data from 42 control subjects spanning a number of prior research protocols. For purposes of this study, we used those data to define decreased calf blood flow as $<$1.2 ml·100 ml tissue$^{-1}$·min$^{-1}$, which was the smallest calf blood flow we had measured in prior control subjects. Capacitance vessel pressure ($P_v$) was assessed with subjects in the supine steady state. After the strain-gauge dimension returned to baseline following blood flow measurement, we measured $P_v$ by gradually increasing the occlusion cuff pressure until an increase in limb volume was just detected (34). In separate experiments, $P_v$ was verified to closely approximate invasive catheter-based $P_v$ measurements with human subjects under supine and upright conditions (4). Peripheral resistance was calculated using the formula

$$\text{peripheral resistance} = \frac{(\text{MAP} - P_v)}{\text{resting blood flow}}$$

where MAP is the mean arterial pressure calculated as (systolic BP + 2 x diastolic BP)/3.

Capacitance measurement methods are summarized in Fig. 1. To determine overall limb capacitance, the limb was gently raised above 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, which resulted in progressive limb enlargement. Independent data indicate that the $P_v$ distal to the congestion cuff approximates the cuff pressure (4). Pressure was maintained for 4 min until a steady state was achieved. At lower congestion pressures, the limb size reached a plateau as shown in Fig. 1. With higher pressures, a plateau was not reached, but as shown in Fig. 1 (bottom, right), after initial curvilinear changes that represent venous filling were complete, the limb continued to increase in size linearly with time for a given pressure step. The linear increase represents microvascular filtration that we have discussed elsewhere (32). There is a critical pressure, typically greater than $P_v$, called the isovolumetric pressure of Gamble (11) that is denoted $P_i$. At values above $P_i$, the lymphatic system cannot compensate for increased filtration, and the limb enlarges at a rate proportional to the imposed pressure. Thus pressure steps between $P_i$ and $P_v$...
result in a plateau, whereas pressure steps above $P_c$ result in a curve that is asymptotic to a straight line with positive slope. We used a least-squares singular value decomposition technique (27) to fit a straight line to the many points that comprise the linear microvascular filtration contribution to filling at each occlusion pressure (Fig. 1, bottom, right). The linear portion was then electronically subtracted from the total curve to obtain a residual curve that reached a plateau. This residual portion represents filling of capacitance vessels.

Once volume response was partitioned, capacitance was calculated from the sum of residual portions that are shown as intravascular filling in Fig. 1. To this we added the estimate of supine venous volume ($V_v$) obtained from raising the limb (31).

**Skeletal muscle pump function: tiptoe test.** Skeletal muscle pump testing followed initial supine blood flow measurements. The method was adapted from the work of Nicolaides (25). A strain gauge was secured at the maximum circumference of the calf, which was measured to the nearest millimeter using a tape measure. The leg was lifted by the ankle to an angle of 15–35° to empty venous blood from the calf and obtain the estimated minimum calf volume. The patient then swiveled off the examining table to a standing position while taking care not to dislodge the strain gauge. Weight bearing was initially maintained on the leg contralateral to the strain gauge. Balance was maintained by use of a stand-up walker. A representative recording of volume changes is shown in Fig. 2. Single tiptoe maneuvers were performed by going up on the toes using both legs to bear weight for 1 s. This generally produced calf emptying.

Once the single tiptoe was complete, the contralateral leg again carried the subject’s weight while the calf volume recovered. Repeat single tiptoe maneuvers were performed. Later, the subject performed 10 tiptoes in a row taking ~1 s per tiptoe. The sequence of multiple tiptoes was repeated. Sequential tiptoe exercises gave the most consistent emptying of calf veins. The complete venous volume is designated $V_V$. The ejection volume of a tiptoe is designated $V_e$, and the residual volume is $V_r$. The ratio of $V_e/V_v$, which is the ejection fraction, is used as a normalized index of skeletal muscle pump adequacy. A decrease in ejection fraction therefore corresponds to a decrease in pump function independent of muscle mass. The ratio of $V_r$ to $V_v$ was also calculated. This was included despite redundancy with the ejection fraction, because it is a conventionally used index.

We used data from multiple tiptoe sequences for these indices.

The time to 90% recovery of calf volume ($V_{90}$) from a singleton tiptoe was used as an index of the venous filling. Multiple sequential tiptoes are less useful for this purpose because of time-dependent effects. The velocity of recovery to 90% volume ($0.9 \times V_v/V_{90}$) represents an index of the average venous filling rate. The force necessary for the maneuver varies from patient to patient according to weight. However, this form of muscular stress is thought to most physiologically represent the ability of the skeletal muscle pump to enhance venous return when an individual is upright (25).

**Monitoring.** Each subject was continuously monitored by electrocardiogram (ECG) and an arterial tonometer (Colin Instruments; San Antonio, TX) placed on the right radial artery to measure upper-extremity BP. The tonometer was maintained at heart level and recalibrated every 5 min against oscilometric BP as is standard for this device. While patients were supine, calf BP was measured intermittently by oscillometry on the calf contralateral to the experimental leg. ECG and pressure data were interfaced to a personal computer through an analog-to-digital converter (DATAQ; Milwaukee, WI) along with strain-gauge outputs. All data were multiplexed with strain-gauge information and were temporally synchronized.

**Dye-dilution blood volume measurement.** We used an indocyanine green dye-dilution technique (2). In the past, green dye methods were technically difficult because they required continuous withdrawal of blood from an arterial site for indicator assay. Indicator detection has been simplified by noninvasive spectrophotometric methods that use a finger photosensor (DDG, Nihon Kohden); these methods have been repeatedly verified during clinical studies (13, 14). Extrapolation of the dye decay curve, which is a monoexponential, repeatedly yields estimated blood volume with accuracy.

**Statistics and data analysis.** Tabular data concerning blood flow, $P_c$, and peripheral resistance were compared by one-way ANOVA comparing volunteers and OI patients. When significant interactions were demonstrated, the ratio of $F$-values was converted to a $t$-distribution using Scheffé’s test, and probabilities were determined thereafter. Tabular data are presented as means ± SE. Pearson correlation coefficients were computed when appropriate. 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. 3–5 and in Tables 1 and 2.

**Size and Hemodynamic Data**

Body surface area and weight values were similar in control and POTS subjects (Table 1). Blood volume was not significantly decreased in POTS patients compared with control patients, although there was a nonsignificant trend ($P = 0.17$) among low-flow POTS patients for decreased blood volume. On the other hand, calf circumference was significantly decreased in low-flow POTS patients ($P < 0.025$) compared with controls.

Supine heart rate values were higher ($P < 0.03$) in low-flow POTS compared with control patients, but mean arterial BP and $P_c$ measurements were not significantly different among the three groups. Calf arterial blood flow was lower by study design, whereas calf arterial resistance was increased ($P < 0.003$) in low-flow POTS compared with control subjects. Calf venous capacity was significantly ($P = 0.002$) reduced in low-flow POTS individuals. We found no differences among groups in forearm blood flow, forearm arterial resistance, or forearm venous capacity, although resistance tended to be increased in normal flow POTS patients ($P = 0.08$).
Calf muscle contraction relates to calf muscle mass.

Muscle pump activity

Table 2. Muscle pump measures

<table>
<thead>
<tr>
<th>Muscle Pump Measures</th>
<th>Postural Tachycardia</th>
<th>Normal flow</th>
<th>Low flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body surface area, m²</td>
<td>1.75±0.10</td>
<td>1.76±0.07</td>
<td>1.71±0.05</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>62±3</td>
<td>64±5</td>
<td>57±4</td>
</tr>
<tr>
<td>Calf circumference, cm</td>
<td>39±3</td>
<td>43±3</td>
<td>32±1*</td>
</tr>
<tr>
<td>Normalized blood volume, l/m²</td>
<td>2.6±0.5</td>
<td>2.4±0.7</td>
<td>2.2±0.3</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>67±3</td>
<td>62±3</td>
<td>79±5*</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>78±2</td>
<td>80±3</td>
<td>84±4</td>
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<tr>
<td>Venous pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm</td>
<td>9±1</td>
<td>11±1</td>
<td>10±1</td>
</tr>
<tr>
<td>Calf</td>
<td>14±1</td>
<td>14±2</td>
<td>17±1</td>
</tr>
<tr>
<td>Blood flow, ml-100 ml⁻¹·min⁻¹</td>
<td>2.6±0.3</td>
<td>2.7±0.3</td>
<td>2.0±0.3</td>
</tr>
<tr>
<td>Arterial resistance, ml-100 ml⁻¹·mmHg⁻¹</td>
<td>2.8±0.4</td>
<td>2.6±0.2</td>
<td>1.0±0.1*</td>
</tr>
<tr>
<td>Venous capacity, ml/100 ml</td>
<td>4.5±0.4</td>
<td>5.2±0.5</td>
<td>4.5±0.3</td>
</tr>
<tr>
<td>Calf</td>
<td>5.0±0.4</td>
<td>4.8±0.2</td>
<td>3.3±0.3</td>
</tr>
</tbody>
</table>

Values are means ± SE; *P < 0.05 compared with controls.

Muscle Pump Measures

In low-flow POTS subjects, Ve and ejection fraction were significantly decreased (P = 0.004), whereas fractional Vr was increased (P = 0.03; Table 2). The time to recovery and velocity of recovery were both decreased as expected with the decrease in arterial blood flow.

Ve and calf circumference. We used calf circumference as a surrogate for muscle mass. The relationship between Ve and calf circumference is shown in Fig. 3. A linear correlation (r = 0.72) was found; thus the amount of blood ejected during calf muscle contraction relates to calf muscle mass.

Calf size and blood flow. Conversely, we reasoned that if muscle mass is dependent on adequate blood flow, then we should be able to demonstrate a relationship between calf circumference and blood flow. This is shown in Fig. 4, which indicates a linear relation (r = 0.74).

Ejection fraction and calf blood flow. Extending this reasoning somewhat further, we proposed that the ability of the skeletal muscle to pump is best represented by the ejection fraction of the muscle pump (the ratio of Ve/Vv). The linear relation (r = 0.69) of ejection fraction with calf blood flow is shown in Fig. 5.

DISCUSSION

The data indicate that the amount of blood that can be ejected by the skeletal muscle pump relates to the calf circumference, which is used here as an indirect measure of calf muscle mass. The data also indicate that the ability of the calf skeletal muscle pump to eject blood while upright (the ejection fraction) is related to calf blood flow while supine. This suggests that diminished resting blood flow in some patients with POTS can worsen OI through impairment of the skeletal muscle pump.
Skeletal Muscle Pump Deficiency in POTS

We have also shown that calf circumference is decreased, calf ejection fraction is reduced, and calf venous capacity is reduced in relation to reduced calf blood flow in patients with low-flow POTS but not in those with normal-flow POTS. This suggests that decreased blood flow but not specifically POTS itself is associated with decreased muscle mass. Also, although skeletal muscle pump deficiency in low-flow POTS may take its origin in a vascular (flow) defect, it could become self-perpetuating through a progressive positive-feedback mechanism whereby decreased blood flow results in decreased muscle mass, decreased muscle mass results in decreased skeletal muscle pump function, and decreased muscle pump activity further decreases blood flow while upright. This suggests the potential benefit for these patients of interventions that enhance muscle mass or blood flow. However, it must be cautioned that a causal relationship between muscle blood flow and muscle mass cannot be inferred as only a relationship between these quantities exists. The data also suggest that the decreases in muscle mass, skeletal muscle pump ejection capability, and calf venous capacity may belong to a continuum of muscle function that extends from normal mass and pump activity to low mass and pump activity.

Low-Flow POTS and Hypovolemia

In our earlier work, we identified similarities between low-flow POTS patients and patients described by Fouad et al. (10) and Jacob et al. (15, 16) who had relatively decreased blood volumes. In the present study, blood volume tended to be decreased in POTS patients compared with control subjects, but this did not reach statistical significance \( (P = 0.17) \). Based on prior work and ongoing studies, we believe that arterial vasoconstriction in low-flow POTS is not accounted for by reflex response to hypovolemia. Thus although hypovolemia may be one factor in this illness, it is not likely to be the only factor that produces the disease. The results of Jacob et al. (16), therefore, may be consistent with chronic systemic vasoconstriction.

Is Low-Flow POTS a Form of Deconditioning?

The answer depends on what is meant by deconditioning. Patients with low-flow POTS have reductions in blood flow and muscle pump activity that are disproportionate to and nearly independent of reported activity levels. Also, patients with normal-flow POTS have no defects in blood flow or muscle pump activity despite a clinically similar illness. Thus OI per se does not produce the blood flow and muscle pump findings.

In addition, low supine calf flow measurements and muscle pump defects do not occur in sedentary control subjects; nor do sedentary controls have OI. Comparison with cardiovascular deconditioning during congestive heart failure (CHF) shows that CHF patients may have muscle atrophy, but these patients have increased peripheral arterial resistance (24) and do not have OI. Deconditioning in patients with low-flow POTS more closely resembles “gravitational deconditioning” in that these individuals resemble subjects exposed to microgravity or chronic bed rest. None of our patients was bedridden, had immobilized limbs, or engaged in space travel. However, measurements of low leg blood flow, decreased plasma volume, and decreased amount and function of lower limb postural muscle were all shared by subjects exposed to a hypogravity environment (6, 19, 21, 22, 39, 40) along with decreased action of the skeletal muscle pump on return to normal gravity (7). The axial skeletal muscles and upper extremities were spared as in our patients with low-flow POTS (9). The details concerning adaptive behavior or molecular events that produce skeletal muscular changes during microgravity are not completely clear. Patients with low-flow POTS may comprise a model system for such study.

Physiological Classification of POTS

We previously reported on patients with high \( P_v \)/low flow and normal \( P_v \)/high flow. Although there was some difference between calf \( P_v \) values in the present work (normal flow, 14 ± 2; low flow, 17 ± 1 mmHg), this difference did not reach statistical significance. As we learn more about the syndrome, we are changing our classification scheme to better reflect our understanding of the pathophysiology. Previously, calf \( P_v \) was employed as the group parameter; presently, we instead use calf blood flow. This is not arbitrary but rather reflects our growing appreciation of the central role of regional blood flow in decreasing venous return to the heart. Presently, we categorize POTS into three groups based on supine calf blood flow: low flow, normal flow, and high flow. Our understanding of the pathophysiological mechanisms of these groups remains incomplete, and a speculative discussion is beyond the limited scope of the present work.

Limitations

We used calf circumference as a surrogate for muscle mass. It is possible that the composition of the calf tissue (e.g., the ratio of fat to muscle mass) might be altered in patients with POTS. However, this is not inherent in POTS but rather only associated with patients who have low resting calf blood flow.
We are in the process of employing and standardizing vibro-myographic tools (26) to define and quantitate postural muscle changes.

We measured calf and forearm blood flow and not skeletal muscle flow. However, in the supine position at least, plethysmographic blood flow is a reasonably accurate estimator of skeletal muscle blood flow (18).

We used supine blood flow to estimate skeletal muscle nutritive blood flow. It would be more suitable to use some average of upright and supine blood flow. Unfortunately, strain-gauge occlusion plethysmographic measurements of upright blood flow are very error prone. However, preliminary data measured by impedance plethysmography indicate that there is little decrease in calf blood flow in POTS subjects (−12 ± 11%) with standing, whereas control subjects demonstrate a significant decrease (−42 ± 8%). Nevertheless, in all positions, blood flow in control subjects significantly exceeded blood flow in patients with POTS. Thus irrespective of posture, blood flow is decreased in subjects with POTS compared with controls, although the differences decrease when individuals are upright.

Decrease in leg muscle mass could be due to disuse secondary to OI. This may be regarded as part of the cardiovascular deconditioning hypothesis of OI. However, CHF in which deconditioning occurs produces no such OI; quite the contrary. Also, our control subjects were nonathletes, our normal-flow patients with POTS and similar orthostatic disability had no such leg-mass reduction, and many of our subjects who were determined to “push through” their disability never achieved changes in muscle pump function. Nevertheless, we employed no objective measures of activity, nor did we measure maximal oxygen consumption and forms of cardiovascular deconditioning that could contribute to muscle wasting.

DISCLOSURE

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REFERENCES


