Local vascular responses affecting blood flow in postural tachycardia syndrome

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Stewart, Julian M., Marvin S. Medow, and Leslie D. Montgomery. Local vascular responses affecting blood flow in postural tachycardia syndrome. Am J Physiol Heart Circ Physiol 285: H2749–H2756, 2003.-Postural tachycardia syndrome (POTS) is defined by orthostatic intolerance associated with abnormal upright tachycardia. Some patients have defective vascular vasconstriction and increased calf blood flow. Others have increased peripheral arterial resistance and decreased blood flow. In 14 POTS patients (13–19 yr) evenly subdivided among low-flow POTS (LFP) and high-flow POTS (HFP) we tested the hypothesis that myogenic, venoarteriolar, and reactive hyperemic responses are abnormal. We used venous occlusion plethysmography to measure calf venous pressure and blood flow in the supine position and when the calf was lowered by 40 cm to evoke myogenic and venoarteriolar responses and during venous hypertension by 40-mmHg occlusion to evoke the venoarteriolar response. We measured calf reactive hyperemia with plethysmography and cutaneous laser-Doppler flowmetry. Baseline blood flow in LFP was reduced compared with HFP and control subjects (0.8 ± 0.2 vs. 4.4 ± 0.5 and 2.7 ± 0.4 ml/min·100 ml−1) but increased during leg lowering (1.2 ± 0.5 ml/min·100 ml−1) while decreasing in the others. Baseline peripheral arterial resistance was increased in LFP and decreased in HFP compared with control subjects (39 ± 13 vs. 15 ± 3 and 22 ± 5 mmHg·ml−1·100 ml·min−1) but decreased to 29 ± 13 mmHg·ml−1·100 ml·min−1 in LFP during venous hypertension. Resistance increased in the other groups. Maximum calf hyperemic flow and cutaneous flow were similar in all subjects. The duration of hyperemic blood flow was curtailed in LFP compared with either control or HFP subjects (plethysmographic time constant = 20 ± 2 vs. 29 ± 4 and 28 ± 4 s; cutaneous time constant = 60 ± 25 vs. 149 ± 53 s in controls). Local blood flow regulation in low-flow POTS is impaired.

myogenic vasconstriction; venoarteriolar vasconstriction; autonomic vasconstriction

POSTURAL TACHYCARDIA SYNDROME (POTS) (34) is characterized by symptoms of chronic orthostatic intolerance, such as lightheadedness, fatigue, headache, neurocognitive deficits, palpitations, nausea, and blurred vision, associated with an abnormal increase in heart rate, exceeding 30 beats/min, when upright (10). POTS is related to abnormal arterial vasoconstriction in the lower extremities (37). In some patients this takes the form of vasodilation and increased peripheral blood flow, which we have denoted “high-flow POTS,” present in both supine and upright positions and resulting in an increase in microvascular filtration and enhanced extravasation during orthostasis (39). Evidence suggests reduced norepinephrine release from the lower extremities; this may be considered a neurogenic defect in which baroreflex activation fails to result in appropriate vasoconstriction during orthostasis (19). In other POTS patients (designated “low-flow POTS”) we previously observed low peripheral blood flow, increased peripheral venous pressure, and increased peripheral arterial and venous resistances associated with dependent mottling, acrocyanosis, and sometimes edema (37).

Prior work has failed to demonstrate evidence for increased venous capacitance or distensibility in these patients (9), nor have abnormalities in orthostatic venous pressure or plasma albumin concentrations been demonstrable (37). On the contrary, data from Freeman’s laboratory (9) and our own work (37) suggest that patients have reduced peripheral capacitance. Although such patients may correspond to patients reported to have borderline low blood volume contributing to orthostasis (8, 20), decreased blood volume cannot explain prior observations showing an increase in leg blood flow during orthostasis when both local and reflex-mediated vasoconstriction should further diminish blood flow (40). We hypothesized that defective local regulation of blood flow may be important in low-flow POTS patients and may relate to the integrity of three classic mechanisms that affect local blood flow: the myogenic response, the venoarteriolar reflex, and the ischemic response in POTS.

MATERIALS AND METHODS

Subjects: Patient and Control Subject Screening

We collected data from patients aged 13–19 yr referred to our center for symptoms of orthostatic intolerance lasting for longer than 3 mo. Orthostatic intolerance was defined by the presence of lightheadedness, fatigue, headache, neurocogni-
tive deficits, palpitations, nausea, blurred vision, abnormal sweating, and a sensation of shortness of breath or heat while upright with no other medical explanation for the symptoms. An electrically driven tilt table (Cardiosystems 600, Dallas, TX) with a footboard for weight bearing was used for orthostatic stress testing. Patients who had POTS on a screening head-up tilt table testing at 70°C comprised the study group. POTS was diagnosed by symptoms of orthostatic intolerance during head-up tilt associated with an increase in sinus heart rate of >30 beats/min or to a rate of >120 beats/min during the first 10 min of tilt as defined in the adult literature (26, 33). Increases in heart rate of <30 beats/min or to heart rates <120 beats/min are generally regarded as normal. We used mercury in Silastic strain gauge plethysmography (SGP) to measure supine calf blood flow. Measurements were always made in the supine position at the beginning of experiments and followed a 30-min resting period. Occlusion cuffs were placed around the lower limb 10 cm above a strain gauge attached to a Whitney-type strain gauge plethysmograph (Hokanson). Blood flow was estimated in the supine position by standard venous occlusion methods (13) using rapid cuffs inflation to a pressure below diastolic pressure to prevent venous egress. Briefly infating a smaller secondary cuff to suprasystolic pressure prevented ankle blood flow. Arterial inflow in units of milliliters per 100 milliliters of tissue per minute was estimated as the rate of change of the rapid increase in limb cross-sectional area. We subdivided the POTS patients after the screening tilt test on the basis of calf blood flow. As mentioned above, prior work showed that the overall POTS population segregates into at least two groups on the basis of blood flow in the calf: one group with decreased calf blood flow and increased venous pressure compared with control subjects and a second group with normal to increased calf blood flow and normal venous pressure (40) compared with control subjects. For normative purposes we have collected calf blood flow data from 42 control subjects spanning a number of prior research periods. For purposes of this study, decreases calf blood flow was defined as <1.2 mL·min⁻¹·100 ml tissue⁻¹, which was the smallest calf blood flow we have measured in control subjects. Increased calf blood flow was defined as >3.6 mL·min⁻¹·100 ml tissue⁻¹, which was the largest calf blood flow we have measured in control subjects. Fourteen patients aged 14–19 yr were recruited for the current study (12 girls, 2 boys; mean age 16 ± 2 yr). There were seven girls who were low-flow POTS patients aged 14–18 yr and five girls and two boys who were high-flow POTS patients aged 14–19 yr.

Nine normal control subjects aged 15–19 yr (7 girls, 2 boys) were also studied after a screening upright tilt at 70° demonstrated a normal orthostatic response. Control subjects were recruited from among adolescents referred for innocent heart murmur. Subjects with a history of syncope or orthostatic intolerance were specifically excluded. Only children found on cardiac exam to be free from heart disease were eligible to participate.

All enrolled subjects were free of systemic illnesses and were not taking medications. There were no trained competitive athletes or bedridden subjects among the patients or the control subjects. 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.

**Laboratory Evaluation**

On a day other than the screening day, patients returned for further measurements of local vascular responses. All experiments were performed while the subject remained supine, i.e., there were no tilt components. Measurements were made in the leg only. Our methods were described previously (37, 38). Tests began between 9:00 and 10:30 AM after an overnight fast. The ambient room temperature varied from 25° to 27°C.

**Monitoring.** ECG strips were monitored continuously. Upper extremity blood pressure was continuously monitored with an arterial tonometer (Colin Instruments, San Antonio, TX) placed on the right radial artery recalibrated every 5 min against oscillographic blood pressure. Leg blood pressure was measured intermittently by oscillography 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). All data were multiplexed and synchronized.

**Peripheral vascular evaluation.** We used SGP to measure calf blood flow and calf capacitance vessel pressure (venous pressure, Pᵥ) in the supine steady state. The strain gauge was placed on the calf at the point of maximum circumference, and the congestion cuff and secondary cuff were placed to measure calf blood flow data as described in Subjects: Patient and Control Subject Screening.

We measured blood flow and Pᵥ in the calf at rest. We measured calf blood flow during dependency (hanging) of the leg off the examination table, which activates in parallel the myogenic response by increasing leg arterial pressure and the venoarteriolar response by gravitational increasing leg venous pressure (4, 17, 30, 32). We measured calf blood flow during a sustained increase in supine venous pressure to 40 mmHg, which activates only the venoarteriolar response (16, 28, 35). We measured calf blood flow after ischemia for 4 min to evoke the reactive hyperemic response (5, 22). We measured calf cutaneous blood flow in the contralateral limb after 4 min of ischemia to evoke the skin hyperemic response. The protocol for venous occlusion plethysmography is shown schematically for a representative subject in Fig. 1.

**Venous occlusion plethysmography protocol.** After a 30-min resting period, flow measurements were performed at least in triplicate. After the protocol returned to baseline, we measured Pᵥ by gradually increasing the occlusion cuff pressure until an increase in limb volume was just detected. In separate experiments Pᵥ was verified to closely approximate invasive catheter-based measurements of venous pressure in supine and upright conditions in humans (2).

Taking care to avoid occlusion of conduit arteries, we lowered the leg off the side of the examining table such that the strain gauge was ~40 cm below the table surface. This increases static venous and arterial pressure by ~0.776 × 40 = 31 mmHg, where the factor 0.776 converts from centimeters of blood to millimeters of mercury. This pressure should activate myogenic and venoarteriolar responses in parallel (7, 17). After 3 to 4 min, when leg volume had stabilized, flows were remeasured. The leg was replaced on the table surface. We then used a double occlusion cuff arrangement (an outer cuff wrapped around an inner cuff), inflating the inner cuff to a steady 40 mmHg, producing venous hypertension and evoking the venoarteriolar reflex. Flow was remeasured after 4 min by intermittently inflating the surrounding cuff to 70 mmHg. This additional inflation was sufficient to provide additional transient venous occlusion to measure blood flow. A similar protocol was previously validated by Gamble et al. (11). Cuff pressures were similar in both cuffs when the outer cuff was inflated. Finally, we imposed an ischemic pressure (30 mmHg above the leg systolic pressure) for 4 min. We released the ischemic occlusion and measured reactive hyperemic flow with repeated 50-
mmHg venous occlusions as shown in Fig. 2. Separate preliminary data from impedance plethysmography used to monitor calf blood flow indicate that a pressure 30 mmHg above systolic blood pressure is sufficient to eliminate calf blood flow.

**Cutaneous reactive hyperemia.** We used a laser-Doppler flowmeter (Perimed) placed on the lateral aspect of the contralateral calf to measure cutaneous blood flow. Laser-Doppler flowmetry is a standard means for assessing skin microvascular perfusion (31). Baseline flow was measured in arbitrary perfusion units. Using a thigh occlusion cuff, we again applied an ischemic pressure (30 mmHg above the leg systolic pressure) and after 4 min released the cuff, measuring cutaneous blood flow until baseline flow was reestablished.

**Hemodynamic comparisons.** We compared baseline supine blood flow and baseline resting arterial resistance \( = \frac{\text{mean arterial pressure (MAP)} - P_e}{\text{resting flow}} \). We measured and compared blood flow alone during leg dependency. We measured and compared arterial resistance \( = \frac{\text{MAP} - 40 \text{ mmHg}}{\text{blood flow}} \) during 40-mmHg venous hypertension, because venous pressure was constrained to 40 mmHg. We measured overall reactive calf blood flow during the period of reactive hyperemia as shown in Fig. 2 from the initial slopes of venous occlusion curves.

We did not measure resistance during hanging of the leg, for technical reasons, nor during reactive hyperemia because the flow is constantly changing and \( P_e \) could not be assessed. Instead, we used flow as a surrogate for more appropriate resistance computations. Blood flow during reactive hyperemia was graphed as a function of time for each subject. We computed two statistics from this graph: the peak flow and the exponential time constant of falloff of the hyperemic flow, which we designated \( \tau \). We determined \( \tau \) for plethysmographic and laser-Doppler measurements of hyperemic flow by taking the natural logarithm of flow starting at maximum flow and fitting a least-squares straight line to the transformed data for every patient; \( \tau \) was computed as the negative inverse of the slope of this line and is expressed in seconds.

**Statistics**

Tabular data concerning leg lowering and 40-mmHg venous hypertension were compared by two-way analysis of variance on control, low-flow POTS, and high-flow POTS before and after the maneuvers. When significant interactions were demonstrated, the ratio of \( F \)-values was converted to a \( t \)-distribution with Scheffé’s test, and probabilities were
RESULTS

Results are shown in Table 1 and in Figs. 3–6. All data were obtained in the supine position. There were no significant differences in subject heights or weights. Subject heights were 167 ± 10 cm in control subjects, 168 ± 12 cm in high-flow POTS subjects, and 174 ± 12 cm in low-flow POTS subjects. Subject weights were 64 ± 8 kg in control subjects, 62 ± 12 kg in high-flow POTS subjects, and 58 ± 10 kg in low-flow POTS subjects.

Leg lowering, venous hypertension, and ischemia/reactive hyperemia maneuvers produced no change in heart rate or blood pressure. Male POTS patients only appeared among the high-flow group. There were only two male POTS subjects and two male control subjects. Gender differences, although important, were not directly considered.

Calf Blood Flow in Dependent Calf

Baseline leg blood flow and arterial resistance data are shown in Table 1. Flow during leg lowering was decreased for control (P < 0.04) and high-flow POTS (P < 0.05) subjects but increased in low-flow POTS subjects (P < 0.025). Changes in flow during leg lowering are shown in Fig. 3, and mean values are shown in Table 1. Figure 3 demonstrates decreased flow during leg lowering in both control and high-flow POTS subjects but increased flow in low-flow POTS subjects.

Calf Blood Flow and Peripheral Arterial Resistance During Venous Hypertension

Baseline peripheral arterial resistance was significantly increased in low-flow POTS subjects (P < 0.001) and decreased in high-flow POTS subjects (P < 0.02) compared with control subjects as shown in Table 1. Figure 4 and Table 1 show that during venous hypertension calf arterial resistance increased in control subjects (P < 0.05) and in high-flow POTS subjects (P < 0.01) but decreased in low-flow POTS subjects (P < 0.05). Resistance of low-flow POTS subjects was similar to that in control subjects during venous hypertension. The wider range of arterial resistance in low-flow POTS subjects is evident from Fig. 4.

Reactive Hyperemia

Figures 5 and 6 and Table 1 show reactive hyperemia data. In Figs. 5 and 6 maximum hyperemic flow is similar in all subjects. However, τ, the rate of decrease in blood flow after release of ischemia, was decreased in low-flow POTS subjects (P < 0.01) compared with either control or high-flow POTS subjects.

DISCUSSION

To summarize, blood flow does not decrease normally with leg lowering in low-flow POTS patients, consistent with a defect in either the venoarteriolar reflex, the myogenic response, or both.

Sustained venous hypertension to 40 mmHg, which should produce vasoconstriction by activating the venoarteriolar reflex, provokes vasodilation in low-flow POTS patients. There is decreased duration of the reactive hyperemic response in low-flow POTS compared with control subjects. Peak hyperemia is relatively unaffected. Thus local blood flow regulation in a subgroup of POTS patients with resting low-blood flow is impaired.

The data are subject to varied interpretation because the evoked responses, myogenic, venoarteriolar, and hyperemic, although classic means to alter local flow, are the result of interactions of localized neurogenic and biochemical mechanisms including metabolic, autacoid, local neurogenic, and smooth muscle actions. These mechanisms remain incompletely understood.

Table 1. Hemodynamic properties

<table>
<thead>
<tr>
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<th>Control</th>
<th>High-Flow POTS</th>
<th>Low-Flow POTS</th>
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<tbody>
<tr>
<td>HR, beats/min</td>
<td>63 ± 2</td>
<td>77 ± 5*</td>
<td>80 ± 6*</td>
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<tr>
<td>Arm MAP, mmHg</td>
<td>78 ± 2</td>
<td>78 ± 2</td>
<td>85 ± 2</td>
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<tr>
<td>Leg MAP, mmHg</td>
<td>74 ± 3</td>
<td>76 ± 2</td>
<td>79 ± 5</td>
</tr>
<tr>
<td>Leg P&lt;sub&gt;c&lt;/sub&gt;, mmHg</td>
<td>12 ± 1</td>
<td>10 ± 1</td>
<td>21 ± 2*</td>
</tr>
<tr>
<td>Leg flow supine, ml·100ml·min&lt;sup&gt;-1&lt;/sup&gt;·min&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>2.7 ± 0.4</td>
<td>4.4 ± 0.5&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.8 ± 0.2&lt;sup&gt;*&lt;/sup&gt;</td>
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<td>Leg flow depended, ml·100ml·min&lt;sup&gt;-1&lt;/sup&gt;·min&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>1.8 ± 0.4†</td>
<td>2.9 ± 1.2&lt;sup&gt;‡&lt;/sup&gt;†</td>
<td>1.2 ± 0.5&lt;sup&gt;‡&lt;/sup&gt;†</td>
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<td>Leg arterial resistance before 40-mmHg occlusion, mmHg·ml·100ml·min&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>22 ± 5</td>
<td>15 ± 3&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>39 ± 13&lt;sup&gt;‡&lt;/sup&gt;</td>
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<td>Leg arterial resistance after 40-mmHg occlusion, mmHg·ml·100ml·min&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>28 ± 6†</td>
<td>23 ± 7&lt;sup&gt;‡&lt;/sup&gt;†</td>
<td>29 ± 13&lt;sup&gt;‡&lt;/sup&gt;</td>
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<td>Peak flow during reactive hyperemia, ml·100 ml·min&lt;sup&gt;-1&lt;/sup&gt;·min&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>17 ± 1</td>
<td>20 ± 2</td>
<td>14 ± 2</td>
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<tr>
<td></td>
<td>τ for plethysmography, s</td>
<td>28 ± 4</td>
<td>29 ± 4</td>
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<tr>
<td></td>
<td>τ for laser-Doppler cutaneous blood flow, s</td>
<td>149 ± 53</td>
<td>Not determined</td>
</tr>
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</table>

Values are means ± SD. POTS, postural tachycardia syndrome; HR, heart rate; MAP, mean arterial pressure; P<sub>c</sub>, venous pressure; τ, time constant of falloff of hyperemia. <sup>*</sup>P < 0.05 vs. control; †P < 0.05 vs. before hanging limb or imposing a 40 = mmHg pressure.
Calf Blood Flow in Dependent Calf

With the subject in the supine position, we lowered the leg by 40 cm, sufficient to produce an ~30-mmHg increase in both arterial blood pressure and venous pressure. The subject remained otherwise supine, thus avoiding changes in baroreflex activation. Since the work of Mellander et al. (29), leg dependency is known to activate the venoarteriolar reflex (see below). However, arterial pressure increases also and activates the myogenic response (7). Data in humans indicate that lowering the forearm or calf while resting in supine position produces potent changes in regional skin blood flow and vascular resistance that are indistinguishable from changes generated by upright posture (45). This standard maneuver (45) should produce a decrease in blood flow if local response is intact (14). Cutaneous arterial resistance is dependent on local positioning, and data indicate that cutaneous arterial resistance may contribute importantly to the change in peripheral arterial resistance during orthostasis (12, 17). Therefore, intact local/postural responses may be important for orthostatic tolerance.

Myogenic Response

Under room temperature conditions, flow in the skeletal muscle arterioles comprises the large majority of calf blood flow. Local skeletal muscle flow regulation is determined by the interplay of the effects of intravascular pressure (i.e., the myogenic response) and flow-mediated mechanisms dominated by passive distensibility. The myogenic response is triggered by increases in intravascular pressure and is characterized by a decrease in vascular resistance.

Fig. 3. Changes in calf blood flow caused by lowering the leg. High-flow POTS data (left), control data (middle), and low-flow POTS data (right) are shown. The 2 male high-flow POTS subjects and 2 male control subjects are indicated by the darkened lines. Although arterial resistance is the most appropriate measure of effect, it cannot be calculated accurately during leg dependence because venous pressure cannot be accurately measured. Calf blood flow decreases in high-flow POTS and control subjects but increases in low-flow POTS subjects. This suggests a defect in myogenic and/or venoarteriolar responses in low-flow POTS.

Fig. 4. Changes in arterial resistance caused by imposing an increase in venous pressure to 40 mmHg on the leg. High-flow POTS data (left), control data (middle), and low-flow POTS data (right) are shown. Resistance increases in high-flow POTS and control subjects but decreases in low-flow POTS subjects. This suggests a defect in venoarteriolar responses in low-flow POTS.
by the actions of NO (41). Although it is often common to differentiate myogenic mechanisms as intrinsic to the smooth muscle on the one hand from flow-mediated endothelial mechanisms as NO dependent on the other, it now seems clear that arteriolar myogenic tone can be affected by mechanisms that modify Ca²⁺-dependent smooth muscle contraction, including NO. Thus recently Ungvari and Koller (44) demonstrated that NO released in response to flow or added by a NO donor results in decreases in myogenic tone by decreasing smooth muscle Ca²⁺ sensitivity. Moreover, the same group showed that there is an intimate relationship among myogenic response, reactive hyperemia, and NO-dependent vasodilation confirmed in vitro (24). In our subjects, pressure-mediated vasoconstriction occurs in control subjects and high-flow POTS subjects but not in low-flow POTS subjects. This suggests an abnormality of the myogenic response (or the venoarteriolar reflex) and could relate to changes in endothelium-dependent vasodilation at least for skeletal muscle.

Calf Blood Flow and Peripheral Arterial Resistance During Venous Hypertension

Arterial vasoconstriction occurs when venous pressure is elevated above 25 mmHg (29). In recent experiments, lowering of the limb has been used to accomplish this, but in their original efforts Henriksen and coworkers (16, 35) used venous hypertension in the calf produced by an occlusion cuff placed just proximal to the knee. The reflex is present in both skeletal muscle and skin (15, 16). It is dependent on local nerve integrity but independent of brain innervation because it is present during regional anesthesia and after spinal cord transection but eliminated by the application of local anesthesia. Originally this was attributed to an α-adrenergic mechanism, but recent carefully conducted experiments by Crandall et al. (4) demonstrated that adrenergic mechanisms are not involved. Rather, the reflex may relate to a neurally mediated, nonadrenergic local process. Interpreting our patient data within this context, vasoconstriction related to venous hypertension (the venoarteriolar reflex) occurs in control subjects and high-flow POTS subjects but not in low-flow POTS subjects; rather, vasodilation occurs. Similar vasodilation occurs during orthostasis in low-flow POTS (40). This may also suggest an abnormality of the myogenic response (as above) or could relate to other locally mediated responses.

Reactive Hyperemia

Reactive hyperemia occurs in most tissue systems as marked vasodilation and increase in blood flow in response to an ischemic stimulus (36). Bayliss (1) published the first observations of the phenomenon and attributed the response to a purely myogenic mechanism. Current thinking supports a role for the myogenic response and prostaglandins in producing peak flow of the hyperemic response (21), but other tissue-related factors are likely mediators for the “excess cumulative blood flow,” i.e., the total amount of blood delivered in excess of that absent during ischemia (25). It is this excess blood flow that seems deficient in low-flow POTS subjects compared with control subjects and high-flow POTS subjects. Local vasoactive substances including adenosine (3) and NO have been proposed and received support, although nitric oxide synthase (NOS) inhibition affects only excess flow and not peak flow in humans (5, 42), at least in skeletal muscle. The recent work by Koller and Bagi (24) used an in vitro rat skeletal muscle arteriole preparation exposed to combinations of pressure (myogenic) and flow (endothelium mediated) stimuli during experimental ischemia and subsequent dilation (hyperemia). They found that the peak amplitude of dilation was
critically affected by pressure but not flow. They found that the duration of the falloff in flow was only affected when flow itself was also changed and that this could be inhibited by endothelial NOS inhibition. Thus the duration of the hyperemic response in skeletal muscle arterioles was at least partly modified by NO. Interpreting our data within Koller’s framework leads us to propose that NO-dependent mechanisms for local regulation could be deficient in our subjects, resulting in shortened duration of reactive dilatation.

An NO deficiency hypothesis unifies many of our past and present observations: thus low-flow patients are vasoconstricted and venuconstricted as expected. Vascular capacity is decreased in part because of the constricted venous circulation. Major defects in local flow regulation permit a postural increase in blood flow in these patients, which we reported previously (40). However, present data are indirect and circumstantial, and therefore an NO hypothesis remains speculative.

Moreover, the addition of our cutaneous hyperemia results further confounds the NO hypothesis. Recent data by Minson and colleagues (46) indicate that the duration of the falloff in flow in the cutaneous circulation is independent of inhibition of NO synthase with nitro-\(\text{L}\)-arginine methyl ester. Thus, if POTS physiology similarly affects cutaneous and skeletal muscle reactive hyperemia, the NO hypothesis becomes at best incomplete and other local factors, possibly interacting with NO, must exert effects.

Limitations

We only studied extremities. It is almost certain that more than the peripheral circulation is affected in POTS. Specifically, we do not know how the splanchnic or pelvic regional circulations are affected. Prior work indicates that splanchnic arterial inflow is abnormal in POTS (43). However, the lower extremities and buttocks are important pooling reservoirs during orthostasis (27), and thus the study addresses effects on a regional circulation, which is important to the abnormal orthostatic response.

We studied only legs. In pilot data we investigated forearm responses as well. These were similar to leg responses but less marked. Part of the impetus for studying legs was that local cutaneous changes were frequently demonstrable in the lower extremities but less frequently in the upper extremities. It may be that dependency and gravitational exposure are important to observed changes.

We did not elevate the legs to achieve venous emptying. Elevation to \(\sim 15^\circ\) is often used in standard Whitney-type strain gauge measurements to achieve maximum filling during venous occlusion. However, any raising or lowering of a limb affects arterial and venous resistance through venoarteriolar, venovenous, and myogenic mechanisms. If the purpose of a study is to measure limb flow in the supine position, then venous occlusion must be applied in the supine position. If the purpose is to measure limb flow with the limb raised, then venous occlusion must be applied with the limb raised. Although it is true that supine limbs may not completely empty after flow measurement, we truly seek to measure blood flow when venous return is indeed incomplete. Limb elevation to \(15^\circ\) often may be standard, but it only measures flow under limb-raised conditions and fails as a measurement technique during supine or dependent conditions.

Venous occlusion plethysmography is an intermittent technique and may not be appropriate for detecting early changes in reactive hyperemic blood flow. This is true. However, others have validated the technique (5, 23). Also, the central difference between hyperemia in low-flow POTS subjects and hyperemia in control subjects is the rate of recovery to baseline, which occurs more rapidly in low-flow POTS subjects. This is also true for cutaneous flow measurements, which also demonstrate similar peak flows.

Age limitations to generalizability may exist. We are therefore justified in our conclusions only across a maturational age range. Adolescents may not perfectly represent findings for mature adults. However, cardiovascular structure and function are essentially mature by puberty, and therefore, results can be regarded as at least qualitatively similar to older age groups. Moreover, adolescents generally have the advantage of absence of confounding illness such as heart disease, renal disease, hypertension, and diabetes. Also, the threshold for abnormal tachycardia in adolescents may be higher. Our own normative data suggest that extension to 35 beats/min may be appropriate. However, all of our POTS patients had heart rate increases exceeding 35 beats/min. In addition, the diagnosis of POTS requires symptoms of orthostatic intolerance during orthostatic challenge. We retained the 30 beats/min definition of POTS for consistency with the adult literature.

DISCLOSURES

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REFERENCES


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10. Gamble J, Christ F, and Gartside IB.


