Clinical and Physiological Effects of an Acute $\alpha$-$1$ Adrenergic Agonist and a $\beta$-$1$ Adrenergic Antagonist in Chronic Orthostatic Intolerance

Julian M. Stewart, MD, PhD; Jose Munoz, MD; Amy Weldon, RDCS

**Background**—Adrenergic agents are commonly used in the treatment of chronic orthostatic intolerance with postural tachycardia syndrome (POTS). POTS may be associated with increased limb blood flow (“high flow”) and defective orthostatic vasoconstriction or decreased limb blood flow (“low flow”) and potentially with small blood volume.

**Methods and Results**—We investigated the consequences of short-term intravenous administration of an $\alpha$-$1$ adrenergic agonist, phenylephrine, and a $\beta$-$1$ adrenergic antagonist, esmolol, in 14 patients with POTS aged 13 to 19 years. Indices of heart rate and blood pressure variability, peripheral blood flow, and arterial resistance were assessed, and the capacitance relation was computed for every subject using venous occlusion plethysmography. Patients were tilted to $35^\circ$ upright while medicated and while unmedicated, and measurements were repeated. Phenylephrine improved orthostatic tolerance and normalized hemodynamics and indices of heart rate/blood pressure variability while supine and while upright, producing significant peripheral vasoconstriction and venoconstriction (20% capacitance change). Esmolol did not improve orthostatic tolerance or hemodynamics. A subgroup of low-flow POTS patients had exaggerated venoconstriction to phenylephrine (50% capacitance change) but others had no response.

**Conclusions**—Phenylephrine, but not esmolol, improves orthostatic tolerance and hemodynamics in POTS. This lends support to the use of oral $\alpha$-$1$ agonists in the treatment of patients with chronic orthostatic intolerance. *(Circulation, 2002;106:2946-2954.)*

**Key Words:** blood flow ▪ vasoconstriction ▪ heart rate

Beta-adrenergic blockade has been a mainstay of treatment for orthostatic intolerance. Although most commonly used in acute orthostatic intolerance such as neurocardiogenic syncope, it is also often chosen as the first treatment for patients with chronic orthostatic intolerance with postural tachycardia syndrome (POTS). POTS is defined as the association of symptoms of orthostatic intolerance with an abnormal increase in heart rate early during orthostasis. Treatments such as $\beta$-blockade, which targets slowing of the heart rate, have been popular. Recent work indicates that chronic orthostatic intolerance often relates to decreased peripheral arterial vasoconstriction and increased supine peripheral blood flow (denoted here as “high-flow” POTS). Evidence suggests that the mechanism involves impaired norepinephrine secretion in the lower extremities. However, other POTS patients have increased peripheral vasoconstriction and decreased supine peripheral blood flow (denoted here as “low-flow” POTS), which may be associated with absolute hypovolemia.

Our goals in this study were to investigate the physiological and clinical consequences of short-term administration of a short-acting $\alpha$-$1$ adrenergic agonist, phenylephrine, and a short-acting $\beta$-$1$ adrenergic antagonist, esmolol, in high-flow and low-flow POTS patients. We hypothesized that phenylephrine would improve orthostatic tolerance, peripheral vasoconstriction would be restored toward normal, and that venoconstriction would occur in high-flow POTS. We hypothesized that orthostatic tolerance would be modestly improved through venoconstriction in low-flow POTS. As a second working hypothesis, we assumed that $\beta$-$1$ blockade would at least improve orthostatic tolerance.

**Methods**

**Subjects**

We studied consecutive patients referred for investigation of symptoms of chronic orthostatic intolerance for $>3$ successive months. Orthostatic intolerance was defined by the presence of lightheadedness, fatigue, headache, neurocognitive deficits, palpitations, nausea, blurred vision, and abnormal sweating while upright with no other medical explanation. Associated tachycardia was detected during a screening head-up tilt-table test at $70^\circ$. POTS was defined by symptoms of orthostatic intolerance during upright tilt associated with a sustained increase in sinus heart rate $>30$ bpm or to a rate $>120$ bpm during the first 10 minutes of tilt. There were no completely bedridden patients. No patient had cardiovascular disease.

Received June 19, 2002; revision received September 17, 2002; accepted September 19, 2002.

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*Circulation* is available at [http://www.circulationaha.org](http://www.circulationaha.org) DOI: 10.1161/01.CIR.0000040999.00692.F3
or any form of systemic illness. None were taking medications at the time of testing.

On another day as part of the protocol, patients underwent upright tilt at 35° for 15 to 20 minutes. We retained only those patients able to tolerate this tilt without severe orthostatic symptoms, which resulted in 14 patients aged 13 to 19 years (median, 16.8 years; 11 girls and 3 boys) who participated in the study. Of the 14 patients, 11 fulfilled criteria for chronic fatigue syndrome. There were no healthy control subjects in medication protocols because that was deemed ethically unsuitable. However, supine normative data were available for control subjects in medication protocols because that was deemed ethically unsuitable. However, supine normative data were available and are included in Table 1 for comparison. The Committee for the Protection of Human Subjects of New York Medical College approved all protocols. The parents for subjects <18 years signed a consent form.

**Laboratory Evaluation**

The ECG was monitored and recorded continuously. Blood pressure was monitored continuously with an arterial tonometer (Collin Instruments) recalibrated every 5 minutes against an oscillometric sphygmomanometer pressure. ECG and pressure data, along with strain gauge information, were interfaced to a personal computer through an A/D converter (DataQ Ind) with sampling at 200 Hz in each channel and displayed continuously.

**Peripheral Vascular Evaluation**

Mercury in silastic strain gauge plethysmography was used to measure the resting venous pressure ($P_v$), forearm and calf blood flow, and the forearm and calf volume-pressure relation in the supine and 35° upright tilted position. Methods were adapted from the work of Gamble et al.14–16 (Figure 1).

**Measurement of Blood Flow**

Occlusion cuffs were inflated suddenly to a pressure just below diastolic pressure to prevent venous egress. Diastolic pressure was verified when supine and when tilted by oscillometry in the arm and calf contralateral to the strain gauges. We used a secondary cuff to prevent wrist and ankle flow. Arterial inflow in units of mL/(100 mL of tissue) per minute was estimated as the rate of change of the rapid increase in limb cross-sectional area.

**Supine, Unmedicated Baseline Data**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=14)</th>
<th>Low Flow (n=6)</th>
<th>High Flow (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>80±2</td>
<td>76±2</td>
<td>80±2</td>
</tr>
<tr>
<td>HR, min⁻¹</td>
<td>65±2</td>
<td>77±7</td>
<td>79±9</td>
</tr>
<tr>
<td>HRV, ms²/Hz</td>
<td>3055±313</td>
<td>1296±279</td>
<td>1748±502</td>
</tr>
<tr>
<td>LF HRV, ms²/Hz</td>
<td>804±98</td>
<td>407±112</td>
<td>473±133</td>
</tr>
<tr>
<td>HF HRV, ms²/Hz</td>
<td>1747±252</td>
<td>625±181</td>
<td>1067±257</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>0.52±0.10</td>
<td>0.92±0.11</td>
<td>0.54±0.09</td>
</tr>
<tr>
<td>Blood pressure variability, mm Hg²/Hz</td>
<td>5.8±1.7</td>
<td>3.6±0.5</td>
<td>8.9±2.0</td>
</tr>
<tr>
<td>Baroreflex gain</td>
<td>30±2</td>
<td>24±2</td>
<td>21±2*</td>
</tr>
<tr>
<td>$P_v$ (arm), mm Hg</td>
<td>8±1</td>
<td>9±1</td>
<td>11±1</td>
</tr>
<tr>
<td>Arm flow, mL·100 mL⁻¹·min⁻¹</td>
<td>3.2±0.3</td>
<td>2.3±0.3*</td>
<td>4.5±0.5*</td>
</tr>
<tr>
<td>Arm arterial resistance, mm Hg·100 mL⁻¹·100 mL⁻¹·min⁻¹</td>
<td>26±4</td>
<td>32±4</td>
<td>17±2*</td>
</tr>
<tr>
<td>Arm capacitance, mL/100 mL tissue</td>
<td>5.1±0.5</td>
<td>3.9±0.4</td>
<td>4.6±0.4</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>78±2</td>
<td>73±3</td>
<td>77±2</td>
</tr>
<tr>
<td>Leg flow, mL·100 mL⁻¹·min⁻¹</td>
<td>2.7±0.3</td>
<td>1.6±0.4*</td>
<td>3.9±0.4*</td>
</tr>
<tr>
<td>Leg arterial resistance, mm Hg·100 mL⁻¹·100 mL⁻¹·min⁻¹</td>
<td>30±4</td>
<td>40±5</td>
<td>21±4*</td>
</tr>
<tr>
<td>Leg capacitance, mL/100 mL tissue</td>
<td>4.0±0.4</td>
<td>3.7±0.4</td>
<td>4.6±0.4</td>
</tr>
</tbody>
</table>

Data are mean±SEM. MAP indicates mean arterial pressure; HR, heart rate; HRV, heart rate variability; LF, low frequency; and HF, high frequency.

*P<0.05 compared with control; †P<0.05 compared with low-flow POTS.

**Measurement of $P_v$**

After returning to baseline, we increased occlusion pressure gradually until limb volume change was just detected. This represents ambient $P_v$.14,17

**Calculation of Arterial Resistance**

We used the mean arterial pressure, which was calculated as (mean systolic blood pressure)−(0.67×diastolic blood pressure), and $P_v$ to calculate the arterial resistance to blood flow in units of mm Hg · (mL/100 mL of tissue)⁻¹ · min⁻¹ from the following equation: (mean arterial pressure minus $P_v$) / blood flow.

**The Volume-Pressure Relation at Venous Pressure <P**

With cuffs deflated and the subject supine, we progressively elevated the limb, measured the elevation at the level of the strain gauge, and recorded the simultaneous decrease in limb volume with each elevation. $P_v$ at the strain gauge was estimated from the hydraulic formula $P_v = P - (0.776×h)$, where the constant 0.776 is the pressure conversion factor from centimeters of blood to mm Hg, and $h$ is the height of the strain gauge above the table. By fixing pressure with limb elevation, the portion of the capacitance vessel volume-pressure relation <$P_v$ was obtained.

**The Volume Pressure Relation at Venous Pressure >P**

After returning to baseline, we increased pressure in the occlusion cuff in 10 mm Hg steps to 60 mm Hg, starting at the first multiple of 10 exceeding $P_v$. By fixing pressure with the congestion cuff, the portion of the capacitance vessel volume-pressure relation >$P_v$ was obtained.

**Vascular Filling**

Increasing pressure steps are associated with plethysmographic changes in limb volume, which include contributions from both capacitance vessel filling and microvascular filtration.8 Curvilinear changes representing venous filling and the limb continue to increase linearly in size with time because of filtration. We used a modified least-squares analysis and curve stripping to separate venous filling from filtration. Details have been reported previously.8
Computation of the Volume-Pressure Relation (Compliance Relation)
The overall volume-pressure relation was constructed after curve stripping resolved the capacitance contribution to limb enlargement. Capacitance is assumed to primarily reside in veins and venules.

Normalization of the Volume-Pressure Relation for Comparison
Strain gauge plethysmography measures volume changes in normalized units of mL/100 mL of tissue. We designated the maximum increase in normalized volume as capacitance, in accord with the...
definitions of Rothe.18 Capacitance may vary from patient to patient and from condition to condition. To facilitate comparison, we further normalized the volume-pressure relation for each individual subject and at every condition (supine, upright, phenylephrine, and esmolol) by dividing the normalized plethysmographic volume by the supine baseline (unmedicated) capacitance for each patient. Once normalized, comparisons of the effects of medications or of upright tilt on the volume-pressure relation become simplified, and averaging over groups of patients becomes possible. Any consistent increase or decrease in capacity with upright tilt would be detected as an increase or decrease in the ordinate of the curve with respect to the normalized supine volume-pressure curve. Thus, for example, venoconstriction shows up as a decrease in the normalized relation.

Upright Tilt and Medication Protocol
Patients performed 2 laboratory sessions. During the first session, after a 30-minute period of quiet rest, measurements of peripheral vascular function were performed supine. The patient was then tilted to 35°, and peripheral vascular measurements were repeated when the heart rate, blood pressure, and peripheral blood flow had reached steady values. Patients returned 10 to 14 days after the first session for a second laboratory session (Figure 1). Supine resting peripheral vascular studies were repeated. Phenylephrine was started as an infusion at an initial dose of 0.5 μg · kg⁻¹ · min⁻¹ and titrated upward until either the heart rate decreased by 15% to 20% or the systolic blood pressure increased by 15% to 20% from baseline. When supine studies were complete, the patient was tilted upright to 35° while maintaining the phenylephrine infusion. Vascular studies were repeated at steady state. The patient was placed supine, phenylephrine was discontinued, and the patient was allowed to recover fully. Esmolol was started using a rapid initial infusion of 300 μg/kg over 3 minutes and then at 200 μg · kg⁻¹ · min⁻¹, titrating upward, to attain a 15% to 20% decrease in heart rate or a 10% to 12% decrease in systolic blood pressure or to a maximum of 400 μg · kg⁻¹ · min⁻¹ while supine. When supine esmolol studies were complete, the patient was tilted upright to 35°, and vascular studies were repeated. If there were signs (significant hypotension) or symptoms of orthostatic intolerance such that the patient asked to be placed down, medications were immediately discontinued, the patient was placed supine, and testing was discontinued. Pilot studies indicated that phenylephrine was well tolerated but that esmolol tilts were not always well tolerated. Therefore, we were unable to randomize the order of phenylephrine and esmolol and always administered phenylephrine first.

Heart Rate and Blood Pressure Variability
Heart rate and blood pressure variability analyses and computed low frequency baroreflex gain were used as ancillary indices of autonomic state. Continuous 500-beat RR interval and blood pressure beat sequences were digitized at 200 Hz, and ectopy was corrected. Beat epochs were linear-detrended. Frequency domain indices are reported. RR and blood pressure data were acquired as a sequence of discrete point events and transformed into an equivalent impulse train with pulses arranged at equal intervals equal to the mean RR interval, with impulse heights equal to the RR intervals or blood pressure as appropriate. Autoregression was performed to calculate RR interval spectrum, blood pressure power spectrum, and cross spectrum.19 We focused on low frequency (LF; 0.04 to 0.15 Hz) and high frequency (HF; 0.15 to 0.40 Hz) power bands. The total power was also calculated; this included contributions from ultra LF (<0.01 Hz) and very LF (0.01 to 0.04 Hz). The normalized cross-spectrum between RR and systolic blood pressure was used to calculate the magnitude of the transfer function at LF between systolic blood pressure and RR interval as an index of baroreceptor gain when coherence exceeded 0.5.19,20

Statistics
Data were compared by 2-way ANOVA for repeated measures. Paired data were used whenever possible (eg, for capacity computations). When significant interactions were demonstrated and when appropriate, the ratio of F values was converted to a t distribution using Scheffe’s test, and probabilities were thereafter determined. A Bonferroni correction was also used to correct for small samples. Except for volume-pressure curves, results are reported as mean±SEM. Significant differences are reported for P<0.05. Volume-pressure curve data are presented in their entirety. Data for individual subject groups given different medications were fit to a sigmoid curve using the following formula:

\[ V = a_0 + \frac{a_1}{1 + e^{-(P-a_0)/a_2}} \]

using a nonlinear least-squares method. \(a_0\), \(a_1\), \(a_2\), and \(a_3\) are fit parameters. \(V\) indicates venous volume, and \(e\) indicates the natural exponent.

Results
There was no change in the supine volume-pressure relationship from session 1 to session 2. Of the 14 patients, 6 had high-flow POTS (calf flow >3 mL/100 mL per minute) and 8 patients had low-flow POTS (calf flow <2 mL/100 mL per minute). We were able to perform phenylephrine testing on all 14 patients without sequelae. We performed esmolol studies on 5 of the 6 high-flow patients and 5 of the 8 low-flow patients before abandoning this form of testing. Of the 5 high-flow patients receiving esmolol, 2 fainted during 35° tilt, and 3 of the 5 low-flow patients experienced severe symptoms of orthostatic intolerance during 35° tilt requiring test termination before volume-pressure data could be collected. We thus cannot report upright tilt volume-pressure data for esmolol treatment.

Supine Results

Unmedicated Heart Rate and Blood Pressure Data
Heart rate variability and baroreflex gain were different for the low-flow and high-flow groups and decreased compared with control subjects. The ratio of LF/HF power was increased in the low-flow group (Table 1).

Unmedicated Peripheral Vascular Results
Arm and leg blood flow were increased in the high-flow group by definition. Peripheral arterial resistance was lower in the arms and legs of high-flow POTS patients, whereas leg P, was higher in low-flow subjects. Leg capacitance tended to be decreased in high-flow patients but did not reach significance in this study.

Effects of Medical Therapy on Heart Rate, Blood Pressure, and Variability Indices
With phenylephrine, heart rate variability and transfer gain increased and heart rate and blood pressure variability decreased for high-flow patients (Figure 2). Similar changes were observed in low-flow POTS patients, except for blood pressure variability, which was unaffected. Heart rate variability but was generally unaffected by esmolol.

Effects of Medical Therapy on Peripheral Vascular Parameters
P, was unchanged in the arm or leg by phenylephrine or esmolol (Figure 3). Supine arm blood flow was significantly decreased by phenylephrine in low- and high-flow POTS,
whereas arterial resistance was increased. Supine leg blood flow was decreased in high-flow POTS, but leg arterial resistance increased. Esmolol decreased high-flow arm blood flow and increased arterial resistance only in the high-flow group. Arm and leg capacitance was decreased for both POTS groups given phenylephrine and was unaffected by esmolol.

**Effects of Medical Therapy on Volume-Pressure Relations and Capacitance**

Phenylephrine produced a downward shift in the volume-pressure curve in high flow POTS patients, but esmolol had no effect (Figure 4). Low-flow patient data were segregated into 2 subgroups: one had no change in the volume-pressure relation with medication, and the second had the largest changes in the volume-pressure relation of any patients with phenylephrine (only). These patients accounted for the entire response to phenylephrine in low-flow POTS subjects. This is fundamentally different from results from high-flow POTS patients, who had a uniform downward shift in the volume-pressure relation in every patient.

**Upright Results**

**Effects of Medication on Heart Rate and Blood Pressure Variability During Upright Tilt**

With phenylephrine administration, indices of arterial blood pressure and heart rate variability were increased and blood pressure variability was unchanged during tilt (Figure 5). Heart rate decreased compared with baseline values. Esmolol had no effect during tilt. Changes in parameters were not different from tilts of these same patients while unmedicated. Thus, blood pressure variability increased, heart rate increased \( \approx 40\% \) to \( 50\% \), LF/HF ratio significantly decreased, and baroreceptor transfer gain decreased.

**Effects of Medication on Peripheral Vascular Responses During Upright Tilt**

The capacitance could not be calculated accurately or in sufficient numbers of patients during esmolol infusion because of orthostatic intolerance (Figure 6). Compared with nonmedicated tilt, phenylephrine tended to blunt the increase in arm and leg \( P_r \). \( P_c \) increased in low-flow POTS patients during esmolol infusion, which further increased the already elevated resting \( P_c \). Flow was decreased and peripheral arterial resistance was increased with phenylephrine. Esmolol had no effects on flow or peripheral resistance.
Discussion
We investigated the short-term effects of a representative α-1 adrenergic agonist and a β-1 adrenergic antagonist, which are commonly used in the treatment of orthostatic intolerance. Long-term drug administration may yield different results. The results indicate that POTS patients become orthostatically tolerant during phenylephrine infusion and orthostatically intolerant during esmolol infusion. A relatively small number of patients were studied with esmolol, and further studies were abandoned for reasons of patient safety. Nevertheless, on the basis of current data, one might infer that β-1 blockade is not a favorable choice of therapy for chronic orthostatic intolerance with POTS, whereas α-1 adrenergic agonist therapy with an oral agent such as midodrine might prove useful in POTS treatment.

Supine Data

Unmedicated Heart Rate and Blood Pressure Data
Data were consistent with earlier experiments indicating an overall decrease of heart rate variability in POTS, whereas baroreflex gain was decreased, as reported by Farquhar and colleagues. This has been interpreted as consistent with vagal withdrawal related to absolute or redistributive thoracic hypovolemia. Experimentally produced hypovolemia gives similar results. Our LF/HF data are different from adult data. In the present study, LF/HF is increased in POTS primarily because of a decrease in the HF component. This is consistent with previous data and highlights differences in the vagal responsiveness of adolescents and adults. Thus, standing in normal children also increases LF/HF primarily through a decrease in HF, whereas in adults an increase in LF is the rule.

Unmedicated Peripheral Vascular Results
POTS patients were partitioned into 2 groups, low and high flow, as previously shown. High-flow POTS patients with impaired vasoconstriction correspond closely to the adult subjects studied by Jacob et al. We previously partitioned patients on the basis of P. Increased P may be the consequence rather than the cause of low flow. A potential explanation for increased P is provided by the work of Johnson and colleagues showing that the low flow of blood, but not acellular media, results in progressive increases in venous resistance related to axial cell migration at low shear rates.

Effects of Medical Therapy on Heart Rate, Blood Pressure, and Variability
Heart rate variability during phenylephrine administration is predictable for systems with an intact baroreflex, producing bradycardia with little change in blood pressure. This may represent rightward movement along the heart rate/blood pressure baroreflex curve or a rightward shift in the curve itself.

Effects of Medical Therapy on Peripheral Vascular Flow and Resistance
Arm and leg blood flow were decreased by phenylephrine, but arterial resistance was increased. High-flow POTS patients resemble the subjects discussed by Jacob et al. in whom there is partial denervation of the leg sympathetic vasoconstrictor system. Such patients might expect to benefit from α-1 replacement therapy. Differential effects of phenylephrine on the lower compared with upper limbs is consistent with estimated enhanced numbers of lower limb α-1 receptors in these patients. Esmolol had little effect on vascular parameters.
Effects of Medical Therapy on Volume-Pressure Relations and Capacitance

Venous return to the heart during orthostasis is compromised by abnormally increased venous capacity and is facilitated, at least in the short-term, by decreased venous capacity. Conditions such as skin heating and prolonged standing, which increase the peripheral pooling of blood, worsen orthostatic tolerance. Short-term downward shifts in the volume-pressure relation and decreased capacity should therefore favor orthostatic tolerance. The data indicate that phenylephrine but not esmolol produces such a favorable response. Venoconstriction occurs supine and may contribute to the observed shift in the baroreflex curve.

Uniform venoconstriction occurred in high-flow POTS patients, but nonuniform venoconstriction occurred in low-flow POTS patients, who segregate into subgroups with and without a venoconstrictive response to phenylephrine. Results imply that α hypersensitivity may exist in certain low-flow
patients and that insensitivity may exist in others. This observation is consistent with the hypothesis propounded by Jacob et al9 that certain POTS patients have “denervated” lower extremities. It might be physiologically more reasonable to redesignate subjects as “responders” or “nonresponders” to phenylephrine related to the individual α-adrenergic receptor and baroreflex sensitivity,28 apart from flow status.

Upright Results

Effects of Medication on Heart Rate and Blood Pressure Variability During Upright Tilt

Phenylephrine, but not esmolol, improved heart rate and blood pressure variability; results are most striking when upright. Decreased heart rate variability and unstable blood pressure (increased blood pressure variability) are characteristic of POTS and reflect an inability of baroreflex coordination,29 which may be centrally or peripherally mediated.13 With esmolol, blood pressure variability increased, heart rate increased (40% to 50%) during tilt, the LF/HF ratio increased, and baroreceptor transfer gain decreased, indicating continued sympathovagal instability. Jacob et al30 also found improvement in orthostatic tolerance and in autonomic measures of sympathovagal balance using α-1 adrenergic agonists and also by volume expansion.

Effects of Medication on Peripheral Vascular Responses During Upright Tilt

Phenylephrine but not esmolol produced decreased flow and increased peripheral arterial resistance, thus normalizing the vasoconstrictive defect in high-flow POTS.

Limitations

We focused on short-term effects of medication using short-lived intravenous infusions of medications. Results cannot be freely generalized to long-term medication effects. Acutely induced changes in vascular properties are functional changes only. Potentially important structural remodeling could occur with long-term treatment.

The study was limited to forearm and calf vascular properties. It is almost certain that other regional circulations are involved in POTS. We do not know how the splanchnic or pelvic regional circulations respond to medications. Prior work indicates that splanchnic arterial inflow is abnormal in POTS.31 However, the lower extremities and buttocks are important pooling reservoirs during orthostasis.32

A β-1 selective antagonist was used. It is likely that nonselective agents might have favorably affected arterial and venous vascular properties through β-2 blockade. Nevertheless, β-1 antagonists are commonly used treatments, and the data support their discontinuation in the treatment of POTS.

Steady states were studied for practical reasons. There could be potentially useful information that was missed. It was evident from our data that arterial vasoconstriction occurred rapidly, thus justifying a steady approach. A similar time course for venoconstriction might be expected.

Age limitations to generalizability may exist. Our conclusions are only justified across a maturational age range. However, cardiovascular structure and function are mature by puberty, and results can be regarded as at least qualitatively similar to older age groups.

A majority of subjects fulfilled criteria for chronic fatigue syndrome, thus potentially limiting the generalizability of results. We have found, however, that most adolescent females with chronic fatigue syndrome have POTS and, conversely, that many patients who are significantly impaired with POTS fulfill criteria for chronic fatigue syndrome.

Acknowledgments

Supported by grant 5RO1HL66007 from the National Heart, Lung, and Blood Institute of the National Institutes of Health.

References


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Circulation. 2002;106:2946-2954; originally published online November 18, 2002; doi: 10.1161/01.CIR.0000040999.00692.F3
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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