Postural tachycardia syndrome (POTS) is a disorder of chronic orthostatic intolerance that disproportionately affects women of childbearing age. It is characterized by symptoms (including palpitations, lightheadedness, chest discomfort, shortness of breath, blurred vision, and mental clouding) that occur during standing but resolve with sitting or lying down.1–3 A most striking feature of this disorder is the excessive increase in heart rate (HR) that occurs on standing.4 Many patients with POTS have increased sympathetic nervous system tone measured with direct nerve recordings5 or biochemically with an elevated plasma norepinephrine on standing.6–8 POTS is associated with a very poor quality of life and significant functional disability9; there are a paucity of effective therapies. Because of the striking tachycardia that is central to this disorder, these patients are often referred to cardiologists for diagnosis and treatment.

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Given that excessive tachycardia is a cardinal feature of this syndrome, a logical treatment strategy would be to reduce the HR with β-adrenergic blockade. β-Blockers have been reported to improve symptoms in case reports10,11 and open-label studies12,13 and can decrease plasma norepinephrine levels in a hyperadrenergic state.14 Unfortunately, in experimental models of orthostatic intolerance, neither propranolol15,16 nor esmolol17 was found to improve orthostatic tolerance. One reason for the limited effectiveness of β-blockade might be that patients with POTS have a low stroke volume and might require an elevated HR to maintain their cardiac output.
output. Conversely, a lower HR might allow for improved cardiac filling and increased stroke volume.

Given the conflicting data on the effectiveness of β-blockers in POTS, we conducted a short-term single-blind crossover trial to test the hypothesis that low-dose propranolol would reduce orthostatic tachycardia and improve upright symptoms in patients with POTS. After the initial study, we conducted a second protocol to test the hypothesis that a higher dose of propranolol would be more effective in controlling HR and improving symptoms than a lower dose of propranolol in patients with POTS.

**Methods**

**Subjects**

Patients referred to the Vanderbilt University Autonomic Dysfunction Center with POTS between November 2003 and September 2008 were candidates for inclusion in this study. Patients were recruited for protocol 1 (see Drug Trials below) during the entire time interval and for protocol 2 between January 2007 and September 2008. Individual patients were eligible to participate in both protocols. Patients met criteria for POTS in that they developed symptoms of orthostatic intolerance accompanied by a HR rise ≥ 30 min−1 within the first 10 minutes of standing, in the absence of orthostatic hypotension (a fall in blood pressure [BP] > 20/10 mm Hg). All patients had at least a 6-month history of symptoms in the absence of an additional chronic debilitating disorder or prolonged bed rest, were at least 18 years of age, were not taking fludrocortisone for at least 5 days before testing. The diet was free of caffeine-containing beverages. HR, systolic BP (SBP), diastolic BP (DBP), and fractionated plasma catecholamines were assessed after overnight rest with the patient in the supine position and again after standing up to 30 minutes (as tolerated) as part of baseline characterization. For catecholamine measurements, blood was collected in plastic syringes, immediately transferred to chilled vacuum tubes with sodium heparin (BD, Franklin Lakes, NJ), and placed on ice. Plasma was separated by centrifugation at −4°C and stored at −70°C in collection tubes with 6% reduced gluthathione (Sigma-Aldrich Inc, St Louis, Mo) until the assay was performed. Concentrations of norepinephrine and epinephrine were measured by batch alumina extraction followed by high-performance liquid chromatography for separation with electrochemical detection and quantification. Plasma norepinephrine and epinephrine values are reported in SI units. To convert from nmol/L to μg/dL, multiply by 169.18 for norepinephrine (1 nmol/L=169.18 μg/dL) or by 183.2 for epinephrine (1 nmol/L=183.2 μg/dL).

**Drug Trials**

All drug trials were started in the morning at least 2 hours after breakfast (to avoid any acute hemodynamic effects from eating) in a postvoid state. In protocol 1, the patients with POTS were given a tablet of propranolol 20 mg (Mylan Pharmaceuticals, Morgantown, WV) or placebo in a randomized single-blind, crossover fashion on separate days. This strength of propranolol represents a low dose. Placebo was prepared by the Vanderbilt Investigational Drug Services. The patients were seated comfortably in a chair for the duration of the data collection except during the prescribed periods of standing. Brachial cuff BPs and HRs were measured with an automated vital signs monitor (Dinamap Vital Signs Monitor, Critikon Corp) and digitally acquired into a custom-designed database (Microsoft Access, Microsoft Corporation, Redmond, Wash). Immediately before and every hour for 4 hours after study drug administration, each patient was asked to stand for 10 minutes while standing HRs and BPs were recorded. The degree of orthostatic stress is not as great when the subject is standing from a seated position compared with standing from a supine position. Although conducting the study while subjects are seated might decrease the magnitude of the orthostatic tachycardia, it provides a clinically relevant and reproducible scenario. In protocol 2, a high dose (80 mg) was compared with a low dose (20 mg) of propranolol (Mylan Pharmaceuticals, Morgantown, WV) in a randomized single-blind, crossover fashion on separate days, with study end points as in protocol 1.

**Symptoms**

Patients were asked to self-report their symptom burden immediately before and at 2 and 4 hours after study drug administration using the Vanderbilt POTS symptom score. The patients were asked to rate the severity of 9 symptoms on a scale of 0 to 10 (with 0 reflecting an absence of symptoms). The sum of the scores at each time point was used as a measure of symptom burden. The 9 symptoms were mental clouding, blurred vision, shortness of breath, rapid heart beat, tremulousness, chest discomfort, head-

### Table 1. Baseline Demographics and Postural Vital Signs and Catecholamines of the Subjects With POTS in the 2 Protocols

<table>
<thead>
<tr>
<th>Test</th>
<th>Protocol 1 (n=54)</th>
<th>Protocol 2 (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>49 (91)</td>
<td>16 (89)</td>
</tr>
<tr>
<td>Age, y</td>
<td>34±10</td>
<td>33±8</td>
</tr>
<tr>
<td><strong>Supine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, min−1</td>
<td>76±13</td>
<td>78±13</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>110±12</td>
<td>111±16</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>68±8</td>
<td>70±10</td>
</tr>
<tr>
<td>Norepinephrine, nmol/L</td>
<td>1.65±1.41</td>
<td>1.86±2.13</td>
</tr>
<tr>
<td>Epinephrine, nmol/L</td>
<td>0.15±0.14</td>
<td>0.19±0.19</td>
</tr>
<tr>
<td><strong>Standing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, min−1</td>
<td>122±26</td>
<td>130±29</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>115±22</td>
<td>118±24</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>74±14</td>
<td>79±16</td>
</tr>
<tr>
<td>Norepinephrine, nmol/L</td>
<td>4.94±3.35</td>
<td>3.93±2.21</td>
</tr>
<tr>
<td>Epinephrine, nmol/L</td>
<td>0.45±0.75</td>
<td>0.50±1.05</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. Reported P values are for paired t tests comparing supine and upright parameters. *P<0.001, †P<0.05.

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ache, lightheadedness, and nausea. This symptom score has been used previously by our center, and the symptoms were chosen because they reflect common complaints of patients with POTS.

Individual missing hemodynamic data points were interpolated by taking the within-individual mean for the parameter at the data point for the hour immediately before and immediately after the missing data point. Hemodynamic data were not interpolated if either the baseline or 4-hour (final) value was missing or if more than one consecutive hourly data point was missing. Only patients with complete hemodynamic data sets (after interpolation) were included in these analyses.

**Statistical Analysis**

Our primary end point was the change in HR on standing from a seated position ($\Delta$HR) 2 hours after study drug administration. The 2-hour time point was chosen because the peak effect of propranolol occurs at 90 minutes after a dose. We hypothesized that the 2-hour $\Delta$HR and 2-hour change in symptom score would be significantly lower on the propranolol day than the placebo day (protocol 1). We used a 2-tailed paired $t$ test that compared the $\Delta$HR 2 hours after propranolol and placebo administration, respectively.

Repeated-measures ANOVA was used to compare HR, SBP, DBP, and symptom scores over time on both the propranolol and placebo days. Repeated-measures ANOVA was performed with the use of a generalized estimating equation model with an identity link function and a normal random component. The variance-covariance matrix of the model’s parameters. Confidence intervals for the difference in patient responses to propranolol and placebo were derived from these models. Tests for day-treatment interactions were performed with the use of Wald tests of the appropriate interaction terms, and no significant day-treatment interactions were found.

The van Elteren test was used to assess differences in symptom scores of patients on propranolol and placebo stratified by time since baseline evaluation. Because symptom score data were not normally distributed, paired comparisons between groups were performed with the nonparametric Wilcoxon signed rank test.

A similar data analysis plan was used for protocol 2. We hypothesized that the 2-hour $\Delta$HR and 2-hour change in symptom scores of patients on propranolol and placebo stratified by time since baseline evaluation. Because symptom score data were not normally distributed, paired comparisons between groups were performed with the nonparametric Wilcoxon signed rank test.
score would be significantly lower on the high-dose (80 mg) propranolol day than the low-dose (20 mg) propranolol day. Furthermore, the changes in the individual component symptoms over 2 hours after each dose of propranolol were assessed with a paired t test to determine whether the change was different from 0.

Values are reported as mean and SD unless noted otherwise. Total symptom scores are reported as median (25th percentile, 75th percentile). P values of \( P < 0.05 \) were considered statistically significant, and all tests were 2-tailed. Statistical analyses were performed with SPSS for Windows (version 16.0; SPSS), with the exception of the generalized estimating equation and the van Elteren test, which were performed with Stata Statistical Software (release 10; StataCorp LP). Prism for Windows 4 (version 4.02; GraphPad Software Inc) was used for graphical presentation.

### Results

#### Patient Characteristics

Demographic data and supine and standing parameters for each protocol are presented in Table 1. In protocol 1 (propranolol versus placebo), 54 subjects with POTS had complete paired data sets suitable for analyses, as did 18 subjects in protocol 2 (propranolol 80 mg versus propranolol 20 mg). As expected, subjects in both protocols were predominantly female, with a mean age of 33 to 34 years.

Supine HR and BP were comparable in both protocols, and supine plasma norepinephrine and epinephrine values were within the normal range in both groups (norepinephrine <2.81 nmol/L [<475 pg/mL] and epinephrine <0.41 nmol/L [<75 pg/mL]). On standing of the subjects, there was a marked increase in HR (protocol 1: 122±26 min\(^{-1}\), \( P < 0.001 \); protocol 2: 130±29 min\(^{-1}\), \( P < 0.001 \)) and norepinephrine (protocol 1: 4.94±3.35 nmol/L, \( P < 0.001 \); protocol 2: 3.93±2.21 nmol/L, \( P = 0.015 \)) compared with respective supine values. The DBP also increased on standing (protocol 1: 68±8 mm Hg supine versus 74±14 mm Hg standing, \( P = 0.001 \); protocol 2: 70±11 mm Hg supine versus 79±16 mm Hg standing, \( P = 0.031 \)). The mean differences and SDs of the mean differences are shown in Table 1.

#### Protocol 1: Seated and Standing HR and BP Measurements With Propranolol 20 mg Versus Placebo

The summary of data from protocol 1 is presented in Table 2 and Figure 1. Standing HR before study drug administration was not different between placebo and propranolol 20 mg (117±19 versus 114±17 min\(^{-1}\); \( P = 0.199 \); Figure 1A). Standing HR started to decrease by 1 hour after study drug in both groups, the first assessment after baseline. Compared with placebo, propranolol 20 mg effected a lower standing HR at 1 hour (90±13 versus 110±18 min\(^{-1}\); \( P < 0.001 \)), and this difference was maintained at \( P < 0.001 \) for the 4 hours after study drug administration. When the effect of propranolol 20 mg versus placebo on standing HR was analyzed over time, there was a significant difference in response based on study drug (\( P < 0.001 \)). Standing SBPs were similar at baseline for propranolol 80 mg (110±17 mm Hg) and placebo (110±18 mm Hg; \( P = 1.0 \)). By 1 hour after study drug, propranolol 20 mg had significantly lowered the standing SBP compared with placebo (102±15 versus 109±14 mm Hg; \( P = 0.009 \); Figure 1D), and it remained...
Table 3. Orthostatic Hemodynamics and Symptoms With Low-Dose Propranolol (20 mg) vs High-Dose Propranolol (80 mg) (Protocol 2) in Patients With POTS (n=18)

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>2 Hours After</th>
<th>4 Hours After</th>
<th>P, Repeated-Measures ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>βHR (standing-seated), min⁻¹</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Propranolol low dose</td>
<td>29.9±14.4</td>
<td>19.2±9.8</td>
<td>20.8±9.1</td>
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<tr>
<td>Propranolol high dose</td>
<td>37.2±14.4</td>
<td>11.9±6.4</td>
<td>12.4±5.8</td>
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</tr>
<tr>
<td>P (between drugs)</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Standing HR, min⁻¹</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol low dose</td>
<td>116.3±20.0</td>
<td>89.9±14.5</td>
<td>90.9±15.0</td>
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<tr>
<td>Propranolol high dose</td>
<td>120.5±20.3</td>
<td>78.3±8.5</td>
<td>79.1±9.9</td>
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</tr>
<tr>
<td>P (between drugs)</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Seated HR, min⁻¹</strong></td>
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<td></td>
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<tr>
<td>Propranolol low dose</td>
<td>86.3±10.5</td>
<td>70.6±11.3</td>
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<td>Propranolol high dose</td>
<td>83.3±11.2</td>
<td>66.4±7.7</td>
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<tr>
<td>P (between drugs)</td>
<td>NS</td>
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<td>NS</td>
<td>0.980</td>
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<td><strong>βSBP (standing—seated), mm Hg</strong></td>
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<tr>
<td>Propranolol low dose</td>
<td>4.8±14.2</td>
<td>-0.6±10.9</td>
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<tr>
<td>Propranolol high dose</td>
<td>-0.9±15.5</td>
<td>3.0±10.8</td>
<td>-0.6±10.4</td>
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</tr>
<tr>
<td>P (between drugs)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.052</td>
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<tr>
<td><strong>Standing SBP, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol low dose</td>
<td>108.1±18.3</td>
<td>97.4±12.4</td>
<td>104.8±11.3</td>
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<tr>
<td>Propranolol high dose</td>
<td>103.7±17.0</td>
<td>99.9±13.2</td>
<td>96.1±14.0</td>
<td></td>
</tr>
<tr>
<td>P (between drugs)</td>
<td>NS</td>
<td>0.05</td>
<td>NS</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Sitting SBP, mm Hg</strong></td>
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<tr>
<td>Propranolol low dose</td>
<td>103.3±11.6</td>
<td>97.9±10.6</td>
<td>101.0±9.3</td>
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</tr>
<tr>
<td>Propranolol high dose</td>
<td>104.6±11.3</td>
<td>96.9±9.8</td>
<td>96.7±8.8</td>
<td></td>
</tr>
<tr>
<td>P (between drugs)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.347</td>
</tr>
<tr>
<td><strong>Symptom score, AU (n=16)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Propranolol low dose</td>
<td>17.5 (8, 27.5)</td>
<td>7 (1.5, 13.25)</td>
<td>6 (3, 11.75)</td>
<td></td>
</tr>
<tr>
<td>Propranolol high dose</td>
<td>12 (3.5, 26.5)</td>
<td>8 (2, 18)</td>
<td>5 (1, 13.5)</td>
<td></td>
</tr>
<tr>
<td>P (between drugs)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.527 (van Elteren test)</td>
</tr>
</tbody>
</table>

For hemodynamic parameters, data are presented as mean±SD. Repeated-measures ANOVA was used to determine the P value for the overall change between high and low doses of propranolol, and paired comparisons were made with within-model contrasts. Symptom data are presented as median (25th percentile, 75th percentile) and were analyzed with the van Elteren test overall and with the Wilcoxon signed rank test for paired data. P<0.05 was considered significant. NS indicates not significant.

significantly lower for 3 hours after study drug. When analyzed over time, standing SBP was lowered more with propranolol 20 mg than placebo (P=0.001). Standing DBPs were similar at baseline but were lowered more with propranolol 20 mg than placebo (P=0.037) (all DBP data are presented in Table I in the online-only Data Supplement).

Immediately before administration of the study drug, there was no difference in seated HR between the placebo day (87±12 min⁻¹) and the propranolol day (87±13 min⁻¹; P=0.977; Figure 1B). Seated HR at 1 hour decreased significantly with propranolol 20 mg (84±14 min⁻¹) compared with placebo (74±12 min⁻¹; P<0.001) and remained significantly lower for the 4 hours of follow-up. A repeated-measures ANOVA model also found that seated HR was lower over time after propranolol 20 mg (P<0.001). Seated SBPs were similar at baseline for propranolol 20 mg (104±13 mm Hg) and placebo (106±14 mm Hg; P=0.249). By 2 hours after study drug, propranolol 20 mg had significantly lowered seated SBP compared with placebo (98±11 versus 107±15 mm Hg; P=0.001; Figure 1E), and it remained significantly lower up to 4 hours after study drug. When analyzed over time, seated SBP was lowered more with propranolol 20 mg than placebo (P=0.002). Seated DBP was lower more with propranolol 20 mg than placebo (P<0.001) when analyzed over time.

Before study drug administration, the POTS patients had a large acute postural increase in HR with standing from a seated position (ΔHR), a cardinal hemodynamic feature of the syndrome (propranolol 20 mg day, 27±16 min⁻¹ versus placebo day, 30±16 min⁻¹; P=0.193; Figure 1C). ΔHR decreased in both groups but significantly more at 1 hour after propranolol 20 mg (16±11 min⁻¹) than placebo (26±17 min⁻¹; P=0.004) and remained significantly lower with propranolol at each hour during follow-up (the primary study end point was ΔHR at 2 hours after study drug [P=0.033]).
When analyzed over time, there was a trend to a lower ΔHR after propranolol 20 mg than placebo ($P=0.076$). There was a similar nonsignificant effect of propranolol on ΔSBP compared with placebo ($P=0.057$; Figure 1F). There was no difference in ΔDBP between the 2 groups over time ($P=0.148$).

**Protocol 2: Comparison of Low-Dose Propranolol (20 mg) Versus High-Dose Propranolol (80 mg)**

The summary of the data from protocol 2 can be found in Table 3 and Figure 2. Standing HR before study drug administration was not different between low-dose and high-dose propranolol (116±20 versus 121±20 min$^{-1}$; $P=0.366$; Figure 2A). Standing HR at 1 hour was lower with high-dose (84±12 min$^{-1}$) than low-dose propranolol (93±15 min$^{-1}$; $P<0.001$), and this significant difference persisted through the 4-hour follow-up. When the effect of propranolol dose on standing HR was analyzed over time, there was a significantly lower HR with high-dose propranolol ($P<0.001$). Standing SBPs were similar at baseline for both low-dose (108±18 mm Hg) and high-dose propranolol (104±17 mm Hg; $P=0.216$; Figure 2D). Although standing SBP after propranolol decreased for both low-dose and high-dose propranolol, this was significantly greater for the high dose ($P<0.001$). Standing DBP was not different between doses at baseline, and although there was a slight trend to a lower DBP with high-dose propranolol, this was not statistically significant ($P=0.080$).

Seated HR was not significantly different between high-dose and low-dose propranolol at any time point or when analyzed over time ($P=0.981$; Figure 2B). Seated SBPs were similar at baseline for high-dose (105±11 mm Hg) and low-dose propranolol (103±12 mm Hg; $P=0.604$; Figure 2E). When analyzed over time, the effects of propranolol dose over time on seated SBP were not statistically significant ($P=0.347$). Seated DBP was not different between doses at baseline, and although there was a slight trend to a lower DBP with high-dose propranolol, this was not statistically significant ($P=0.125$).

Before study drug administration, there was a trend toward a larger change in HR with high-dose propranolol (37±14 min$^{-1}$) than low-dose propranolol (30±14 min$^{-1}$; $P=0.052$; Figure 2C). Although ΔHR decreased in both groups, it was significantly lower at 1 hour after high-dose propranolol (13±7 min$^{-1}$) than low-dose propranolol (19±7 min$^{-1}$; $P=0.001$) and remained significantly lower with high-dose propranolol (at $P<0.002$). The primary end point in this protocol was ΔHR at 2 hours after study drug (high dose: 12±6 min$^{-1}$ versus low dose: 19±10 min$^{-1}$; $P<0.001$). When analyzed over time, the orthostatic increase in HR was significantly lower after high-dose propranolol than low-dose propranolol ($P<0.001$). The effect of propranolol dose on orthostatic change in SBP did not achieve statistical significance ($P=0.052$; Figure 2F). There were no differences in orthostatic changes in DBP by the propranolol dose.

**Symptoms**

In protocol 1, the symptom scores were completed for both propranolol and placebo by 36 patients with POTS, who comprised the analysis pool. Data are shown in Table 2 and
In protocol 2, all 18 patients completed the symptom scores at baseline and 2 hours after propranolol dose, but only 16 patients completed the 4-hour symptom score. Both low-dose and high-dose propranolol lowered total symptoms over time (Table 3), but there was no significant overall difference in symptom burden between low- versus high-dose propranolol (P=0.527). In contrast to the effect of propranolol dose on HR response, the decrease in total symptom burden from baseline to 2 hours after study drug was significantly greater with low-dose (20 mg) propranolol than high-dose (80 mg) propranolol (Δ-6 [−21.5, −2.5] versus −2 [−12.5, 1.5] AU; P=0.041; Figure 3B).

To better understand the contribution of changes to the individual component symptoms to the overall improvement in symptom score with propranolol, the 2-hour change in score for each of the 9 component symptoms was compared with a reference change of 0 (presented in Table II in the online-only Data Supplement for both low- and high-dose propranolol). Palpitation and tremulousness decreased significantly with both high- and low-dose propranolol, whereas chest pains, headache, nausea, and visual disturbance did not change significantly with either dose of propranolol. Interestingly, 3 symptoms (lightheadedness, mental clouding, and shortness of breath) improved significantly only with low-dose (20 mg) propranolol but not with high-dose (80 mg) propranolol.

**Discussion**

This report is the first placebo-controlled trial of a β-blocker in patients with POTS. We found that (1) low doses of propranolol significantly decreased the standing HR and orthostatic tachycardia of patients with POTS acutely compared with placebo, and this was associated with a symptomatic improvement; (2) higher-dose propranolol (more complete β-blockade) can further restrain HR and orthostatic tachycardia but does not further improve symptoms in patients with POTS; and (3) some symptoms (mental clouding, lightheadedness, and dyspnea) improved after patients received low-dose propranolol but not after they received higher-dose propranolol.

**Hemodynamic Arguments Against Acute Use of Propranolol Are Incorrect**

Hemodynamic arguments can be made for why β-adrenergic receptor blockers, such as propranolol, could be beneficial or deleterious in patients with POTS. At its most basic level, the disorder is associated with a sometimes striking increase in HR in response to upright posture. It has been recognized for many years that β-blockade will lower HR. The value of controlling HR, however, will depend on whether an elevated HR is needed to maintain hemodynamic stability. Masuki et al18 reported that patients with POTS have a lower stroke volume than healthy control subjects both at rest and in response to exercise. Their data suggest that the excessive HR seen in patients with POTS might be required to maintain an adequate cardiac output in the setting of a diminished stroke volume. Supporting this line of reasoning, Stewart et al17 reported that intravenous esmolol does not improve orthostatic tolerance during tilt table testing in patients with POTS.

Our present data with propranolol demonstrate a marked clinical improvement in patients with POTS. Although orthostatic tolerance was not formally assessed as an end point (because we only asked subjects to stand for 10 minutes), the symptom scores significantly improved with propranolol compared with placebo. This was in the setting of a significant reduction in HR. These data suggest that not all of the orthostatic HR increase seen in POTS is needed to avoid a hemodynamic collapse.
Less Is More: Benefits of Low-Dose Propranolol

There are many anecdotal reports from our patients with POTS that they have “failed” or not tolerated β-blockers. Consequently, the magnitude of improvement in both hemodynamics and in reported symptoms in our first protocol comparing a low dose of propranolol with placebo was surprising. This raised questions about whether the anecdotal patient reports related to the use of excessive β-blockade. We chose to compare our low dose of 20 mg of propranolol with a high dose of 80 mg, which is the highest dose available in a single tablet.22 The higher dose of propranolol further restrained orthostatic tachycardia in the patients with POTS, but there was no further improvement in symptoms. In fact, the relationship between propranolol dose and symptoms is more complicated. Some individual symptoms improved with high-dose propranolol (such as palpitations and tremulousness; Table II of online-only Data Supplement), whereas other symptoms did not improve (lightheadedness, mental clouding, and shortness of breath). These data suggest that symptoms in POTS are not just due to orthostatic tachycardia or an elevated HR. One possibility is that the elevated HR does not cause symptoms directly but that both the HR and the symptoms are worsened by a common underlying cause (such as norepinephrine). Another possibility is that an underlying cause worsens some symptoms directly, whereas other symptoms are mediated through the elevated HR. In this case, more effective β-blockade might help the HR-mediated symptoms but not the other symptoms.

Propranolol is a nonselective β-blocker with good penetration of the blood-brain barrier. From our data, we cannot conclude whether the beneficial effects of propranolol are due purely to its peripheral effects on the heart and vasculature or whether some of the benefits of low-dose propranolol stem from central effects in lowering sympathetic activity and hence peripheral norepinephrine14 (this latter effect is controversial23). If all of the benefits are due to peripheral actions, then other β-blockers that do not cross the blood-brain barrier might be preferable because they may be less likely to cause some central adverse effects. This hypothesis, however, remains to be tested.

Vanderbilt POTS Symptom Score

We used the Vanderbilt POTS symptom score to assess orthostatic symptom burden in our patients with POTS. This score has been used in prior studies by our group.6 It involves subjective rating by the patient at multiple time points for a number of symptoms that were commonly reported among our patients with POTS. Because there is no objective anchor to these symptoms, one individual’s rating may vary greatly from that of another individual (eg, one person’s rating of 4 may reflect more severe symptoms than another person’s rating of 6). Like serial chest pain rating scales, however, we expect serial intrapatient reports to use a more constant frame of reference. This is 1 reason that all of our symptom-based analyses were done with the use of paired comparisons within an individual. There are historical disease-specific (Orthostatic Grading Scale24) and general health-related quality of life tools available (Short Form-3625 or EurQol26), but these are not designed for repeated assessments over hours, as were performed in these protocols.
Clinical Significance
These are the first blinded data comparing oral β-blocker therapy with placebo in POTS. Low doses (20 mg) of propranolol were very effective in reducing HR and orthostatic tachycardia in patients with POTS. This is physiologically noteworthy. Of more clinical importance, however, is that low doses of propranolol also significantly improved symptom burden in these patients. The clinician should be careful not to be too aggressive by targeting complete cally noteworthy. Of more clinical importance, however, is static tachycardia in patients with POTS. This is physiologi-
propranolol were very effective in reducing HR and ortho-
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Limitations
Our studies were conducted with the patient and the principal investigator blind to study drug order until after an individual’s study completion, but the research center nurse was not blind to the intervention. The study was thus single-blind and not double-blind. It is noteworthy, however, that the research center nurse did not directly collect the data presented in this report. The hemodynamic data were collected by an automated oscillometric BP cuff that was connected to a personal computer for digital data collection, and the symptoms were all self-reported by the blinded patient.

Another limitation of this study is the relatively small sample of patients in protocol 2, although it is comparable to other reported POTS trials. The sample size in protocol 1 is, in fact, quite large by the standard of interventional trials in POTS.

The short duration of follow-up in this study (4 hours) makes it difficult to intelligently project the long-term efficacy of this treatment. Although our anecdotal clinical experience is that low-dose propranolol is well tolerated in this patient population, a longer-duration clinical trial would be required to show long-term efficacy.

Conclusion
We have found that low-dose propranolol is a highly effective agent in immediately decreasing orthostatic tachycardia and improving symptoms in patients with POTS. Symptoms did not further improve with higher doses of propranolol, suggesting that caution should be used by clinicians in titrating up the propranolol dose.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Postural tachycardia syndrome (POTS) is a disorder of chronic orthostatic intolerance that disproportionately affects women of childbearing age. It is characterized by a constellation of symptoms that occur during standing but resolve with sitting or lying down. A most striking feature of this disorder is the excessive increase in heart rate that occurs on standing in the absence of hypotension. Given the striking tachycardia, β-adrenergic blockers would seem like ideal treatments, but prior anecdotal and experimental experience has been disappointing. We report the first placebo-controlled trial of propranolol in POTS. A low dose of propranolol (20 mg) immediately decreased heart rate and orthostatic tachycardia and improved the orthostatic symptoms in patients with POTS. A higher dose of propranolol (80 mg) elicited more complete β-blockade with a further lowering of heart rate but did not further improve symptoms and may have made some symptoms worse. These data suggest that although low doses of propranolol are of benefit in POTS, higher doses might be counterproductive. These data also offer a potential explanation for the conflicting prior results of β-blockers in POTS.

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Satish R. Raj, Bonnie K. Black, Italo Biaggioni, Sachin Y. Paranjape, Maricelle Ramirez, William D. Dupont and David Robertson

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