Diurnal variability in orthostatic tachycardia: implications for the postural tachycardia syndrome

Jordan A. BREWSTER*†‡, Emily M. GARLAND*†‡, Italo BIAGGIONI*†‡§, Bonnie K. BLACK*†‡, John F. LING†, Cyndya A. SHIBAO*†‡§, David ROBERTSON*†‡§¶ and Satish R. RAJ*†‡§

*Division of Clinical Pharmacology, Vanderbilt University School of Medicine, AA3228 Medical Center North, 1161 21st Avenue South, Nashville, TN 37232-2195, U.S.A., †Autonomic Dysfunction Center, Vanderbilt University School of Medicine, AA3228 Medical Center North, 1161 21st Avenue South, Nashville, TN 37232-2195, U.S.A., ‡Department of Medicine, Vanderbilt University School of Medicine, AA3228 Medical Center North, 1161 21st Avenue South, Nashville, TN 37232-2195, U.S.A., §Department of Pharmacology, Vanderbilt University School of Medicine, AA3228 Medical Center North, 1161 21st Avenue South, Nashville, TN 37232-2195, U.S.A., ¶Department of Neurology, Vanderbilt University School of Medicine, AA3228 Medical Center North, 1161 21st Avenue South, Nashville, TN 37232-2195, U.S.A.

ABSTRACT

Patients with POTS (postural tachycardia syndrome) have excessive orthostatic tachycardia (>30 beats/min) when standing from a supine position. HR (heart rate) and BP (blood pressure) are known to exhibit diurnal variability, but the role of diurnal variability in orthostatic changes of HR and BP is not known. In the present study, we tested the hypothesis that there is diurnal variation of orthostatic HR and BP in patients with POTS and healthy controls. Patients with POTS (n = 54) and healthy volunteers (n = 26) were admitted to the Clinical Research Center. Supine and standing (5 min) HR and BP were obtained in the evening on the day of admission and in the following morning. Overall, standing HR was significantly higher in the morning (102 ± 3 beats/min) than in the evening (93 ± 2 beats/min; P < 0.001). Standing HR was higher in the morning in both POTS patients (108 ± 4 beats/min in the morning compared with 100 ± 3 beats/min in the evening; P = 0.012) and controls (89 ± 3 beats/min in the morning compared with 80 ± 2 beats/min in the evening; P = 0.005) when analysed separately. There was no diurnal variability in orthostatic BP in POTS. A greater number of subjects met the POTS HR criterion in the morning compared with the evening (P = 0.008). There was significant diurnal variability in orthostatic tachycardia, with a great orthostatic tachycardia in the morning compared with the evening in both patients with POTS and healthy subjects. Given the importance of orthostatic tachycardia in diagnosing POTS, this diurnal variability should be considered in the clinic as it may affect the diagnosis of POTS.

INTRODUCTION

POTS (postural tachycardia syndrome) is a disorder of chronic orthostatic intolerance characterized by excessive increase in HR (heart rate) upon standing in the absence of hypotension [1,2]. The disorder typically affects women of childbearing age and is associated with a variety of chronic symptoms, including palpitations, chest...
discomfort, dyspnea, blurred vision, mental clouding and syncope that are worse in the standing position and improve upon sitting or lying down [2]. These symptoms are chronic (>6 months) and occur in the setting of an excessive orthostatic tachycardia. POTS is often disabling and associated with a poor quality of life [3,4]. The pathophysiology underlying POTS is not completely understood; however, patients with POTS have been observed to possess increased sympathetic nervous system tone on standing [5], decreased total blood volume [6] and perturbations in the renin–aldosterone axis [7].

BP (blood pressure) and HR exhibit considerable variation over a 24 h period [8–13] as a result of diurnal variations in emotional and behavioural states [14,15], baroreflex sensitivity [7,10], renin–angiotensin system activity [16], plasma catecholamine levels [9,16] and adrenergic tone [17]. The measurement of BP and HR in the supine and standing positions forms the basis of orthostatic testing, which is crucial for the evaluation of a number of neurocardiogenic disorders including syncope, autonomic failure and POTS [2,18]. Given the diurnal variability in BP and HR, one may expect to observe diurnal variation in orthostatic testing results that could affect whether patients meet the diagnostic criteria for POTS (>30 beats/min orthostatic increase in HR).

In the present small cohort study, we measured orthostatic vital signs (supine and standing HR and BP) in a group of patients meeting the diagnostic criteria for POTS and in a group of normal, healthy volunteers during the evening and morning in order to study diurnal variability in orthostatic vital signs in these groups. The overall goal of the present study was to characterize the diurnal variation in orthostatic HR in subjects under controlled conditions. Our hypothesis was that POTS patients would have a greater increase in HR on standing in the morning as compared with the evening.

**MATERIALS AND METHODS**

**Subjects**

Patients with POTS and normal healthy volunteers between 18 and 60 years of age were admitted to the Vanderbilt University Clinical Research Center between 1998 and 2006. The Vanderbilt University Investigational Review Board approved each individual study, and written informed consent was obtained from each subject before the study began.

Patients with POTS (n = 54; 35 ± 2 years; 85 % female) met the conventional criteria [2,19]. Briefly, POTS patients developed symptoms of orthostatic intolerance accompanied by an increase in HR of >30 beats/min that occurred within the first 10 min of standing or head-up tilt, without any evidence of orthostatic hypotension (fall in BP of >20/10 mmHg). Patients had at least a 6 month history of symptoms, in the absence of another chronic debilitating disorder or prolonged bed rest. POTS patients stopped haemodynamically significant medications for 5 half-lives (t1/2) prior to evaluation (or at least 5 days for fludrocortisone). Healthy control subjects (n = 26; 27 ± 1 years; 58 % female) were individuals who volunteered for participation as control subjects for clinical studies, who did not meet criteria for POTS and who were free from haemodynamically active medications. Healthy control subjects responded to local advertisements seeking volunteers for a series of clinical research protocols. All subjects underwent a detailed history and physical examination, including assessment of blood chemistry and complete blood count (Table 1). There were slight differences between the two groups for size and age. It should be noted that the primary comparisons in the present study are not between groups, but within groups at different times of the day.

**Measurement of postural vital signs**

Orthostatic vital signs were measured with the subject supine and then standing for 5 min. An automatic oscillometric BP cuff was used to determine the SBP (systolic BP) and DBP (diastolic BP). HR was derived automatically from the BP recording. MBP (mean BP) was calculated as MBP = (1/3 SBP + 2/3 DBP). A 5 min stand was chosen as this is the standard duration of orthostatic vital signs measurement in our institution.

**Evening and morning orthostatic vitals**

Orthostatic vital signs were obtained at regular periods during the day as part of the standard protocol in the Clinical Research Center. We obtained postural vital sign data from the evening on the day of admission (day 1) and in the following morning (day 2) to include in

<table>
<thead>
<tr>
<th>Parameter</th>
<th>POTS patients</th>
<th>Healthy controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female/male)</td>
<td>46/8</td>
<td>15/11</td>
<td>0.007</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35 ± 2</td>
<td>27 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169 ± 1</td>
<td>174 ± 2</td>
<td>0.026</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71 ± 3</td>
<td>78 ± 3</td>
<td>0.077</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.6 ± 0.7</td>
<td>25.5 ± 1.0</td>
<td>0.494</td>
</tr>
<tr>
<td>Leucocytes (cells/µl)</td>
<td>(6.5 ± 0.2) × 10^9</td>
<td>(5.7 ± 0.3) × 10^9</td>
<td>0.037</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>13.5 ± 0.2</td>
<td>13.2 ± 0.3</td>
<td>0.287</td>
</tr>
<tr>
<td>Serum sodium (mmol/l)</td>
<td>139 ± 0.3</td>
<td>139 ± 0.4</td>
<td>0.811</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>4.0 ± 0.04</td>
<td>4.1 ± 0.07</td>
<td>0.188</td>
</tr>
<tr>
<td>Serum chloride (mmol/l)</td>
<td>104 ± 2</td>
<td>102 ± 2</td>
<td>0.003</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.74 ± 0.02</td>
<td>0.93 ± 0.04</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 1: Demographics, haematology and blood chemistry results for POTS patients and healthy control subjects

Continuous data are presented as means ± S.E.M. and were analysed using Student’s t tests, whereas dichotomous data were analysed using Fisher’s exact test.
the present study. These times were chosen in order to maximize patient inclusion and to avoid the confounding influence of other investigational drugs and of procedures from other research protocols that may have started later on day 2. HR, SBP and DBP were measured in the supine position and then on standing upright for 5 min in the evening (20:00 hours) on the first day of admission for the study (day 1) and then again in the following morning (08:00 hours; day 2), after an overnight fast. No medications or treatments were employed in the interval between measurements of the evening and morning vital signs.

**Posture study**
A diagnostic ‘posture study’ was conducted in patients with POTS and this was as a part of our routine POTS evaluation in our centre. The present study was performed following an overnight fast in our Clinical Research Center. Using an indwelling intravenous catheter, supine HR and BP were assessed and plasma catecholamines were drawn. The patients were then asked to stand for up to 30 min (or as long as tolerated). At the end of the standing period, HR and BP and plasma catecholamines were re-measured. Posture studies were conducted within 48 h of the reported evening and morning orthostatic vital signs, and usually within 24 h. Medications were not given between these two evaluations. Posture study values for the patients with POTS are shown in Table 2. Control subjects did not undergo a formal ‘posture study’.

**Statistical analysis**
Results are expressed as means ± S.E.M. (unless otherwise noted). Groups were compared using a Student’s t test. A Mann–Whitney U test was also used to confirm the results obtained from the Student’s t test, and the significance of the reported parameters was not different between the two tests. Within-group comparisons were performed using paired Student’s t tests and confirmed using a Wilcoxon signed rank test. Paired categorical comparisons were performed using McNemar’s test. Statistical analyses were carried out using the statistical software SPSS for Windows, version 19.0. All the tests were two-sided, and P < 0.05 was considered statistically significant.

**RESULTS**

**Orthostatic haemodynamics in combined cohort**
Table 3 displays the evening and morning orthostatic vital signs for the two study groups combined. The standing HR was significantly higher in the morning (102 ± 3 beats/min) than in the previous evening (93 ± 2 beats/min; P < 0.001). The standing SBP was slightly lower in the morning (112 ± 2 mmHg) than in the previous evening (116 ± 2 mmHg; P = 0.004), but the DBP was not significantly different (72 ± 1 mmHg in the morning compared with 74 ± 1 mmHg in the evening; P = 0.129). Supine HR did not differ with the time of the day, and this resulted in a larger orthostatic (supine to standing 5 min) tachycardia in the morning (31 ± 2 beats/min) than in the previous evening (22 ± 2 beats/min; P < 0.001). Neither supine nor orthostatic changes in SBP or DBP differed with the time of the day.

**Orthostatic haemodynamics in POTS and control subjects**
When broken down by group, the orthostatic tachycardia was greater in the morning than in the evening for both POTS patients (34 ± 3 beats/min in the

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**Table 2** Diagnostic supine and standing haemodynamic parameters and catecholamines in patients with POTS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Supine</th>
<th>Standing (up to 30 min)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>76 ± 2</td>
<td>120 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>111 ± 1</td>
<td>114 ± 3</td>
<td>0.392</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>69 ± 1</td>
<td>72 ± 2</td>
<td>0.041</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>83 ± 1</td>
<td>86 ± 2</td>
<td>0.097</td>
</tr>
<tr>
<td>Noradrenaline (pg/ml)</td>
<td>323 ± 31</td>
<td>974 ± 68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adrenaline (pg/ml)</td>
<td>31 ± 5</td>
<td>71 ± 12</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 3** Supine and standing haemodynamic parameters of combined cohort in the admission evening and in the following morning

<table>
<thead>
<tr>
<th>Parameter</th>
<th>In the evening of admission</th>
<th>In the following morning</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>72 ± 1</td>
<td>70 ± 2</td>
<td>0.395</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>114 ± 2</td>
<td>112 ± 1</td>
<td>0.177</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>68 ± 1</td>
<td>67 ± 1</td>
<td>0.668</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>83 ± 1</td>
<td>82 ± 1</td>
<td>0.356</td>
</tr>
<tr>
<td>Noradrenaline (pg/ml)</td>
<td>1 0.097</td>
<td>1 0.394</td>
<td></td>
</tr>
<tr>
<td>Adrenaline (pg/ml)</td>
<td>1 0.129</td>
<td>1 0.395</td>
<td></td>
</tr>
</tbody>
</table>
morning compared with $27 \pm 2$ beats/min in the evening; $P = 0.011$) and control subjects ($26 \pm 2$ beats/min in the morning compared with $13 \pm 2$ beats/min in the evening; $P = 0.001$) (Figure 1A). The standing HR was also significantly higher in the morning than in the evening in both the POTS patients ($108 \pm 4$ beats/min in the morning compared with $100 \pm 3$ beats/min in the evening; $P = 0.012$) and control subjects ($89 \pm 3$ beats/min in the morning compared with $80 \pm 2$ beats/min in the evening; $P = 0.005$) (Figure 1B). The supine HR was not different at the two time points in the POTS patients ($74 \pm 2$ beats/min in the morning compared with $74 \pm 2$ beats/min in the evening; $P = 0.694$), and was slightly lower in the morning than in the evening in the control subjects ($68 \pm 2$ beats/min in the morning compared with $63 \pm 2$ beats/min in the evening; $P = 0.011$) (Figure 1C).

POTS patients experienced a small increase in SBP from supine to standing, but this was not significantly different in the morning than in the previous evening ($5 \pm 2$ mmHg in the morning compared with $1 \pm 2$ mmHg in the evening; $P = 0.156$) (Figure 2A). In contrast, control subjects had a small decrease in SBP at both time points, but these were not different from each other ($0 \pm 2$ mmHg in the morning compared with $-1 \pm 2$ mmHg in the evening; $P = 0.684$). The standing SBP was slightly lower in the morning than in the previous evening in both the POTS patients ($P = 0.041$; Figure 2B) and control subjects ($P = 0.036$). The supine SBP was unchanged in the POTS patient at the two time points ($P = 0.807$; Figure 2C), but was slightly lower in the morning in the control subjects ($P = 0.028$).

There were no significant differences in DBP between morning and the previous evening for either body position (Figures 2D–2F).

**POTS orthostatic tachycardia criterion**

An increase in HR $>30$ beats/min from lying to standing is used as an HR criterion in the definition of POTS [1,2]. There was a significant increase in the number of subjects who met the POTS HR criterion in the morning compared with the evening (McNemar’s test; $P = 0.008$; Figure 3). This threshold HR was exceeded in the evening by 42% of POTS patients and 4% of control subjects. In the morning, the percentages increased to 60% of POTS patients and 31% of control subjects.

**DISCUSSION**

A key finding of the present study is that orthostatic tachycardia is significantly higher first thing in the morning when compared with the evening. This diurnal variability in orthostatic tachycardia is driven largely by diurnal variability in the standing HR, while the supine HR changes only minimally. Although the absolute HR increase is higher among patients with POTS (as would be expected given this diagnosis), this diurnal orthostatic
variability is seen both in POTS patients and healthy control subjects. These data suggest that this increase in morning standing HR is a normal physiological phenomenon that is exaggerated in patients with POTS. To our knowledge, this phenomenon has not been reported previously.

**Pathophysiology underlying diurnal variability of orthostatic tachycardia**

Morning vital signs were measured after an overnight fast and after the patient had remained in bed overnight. One possible explanation for the exaggerated standing HR in the morning is a transient hypovolaemic state resulting from the overnight fast and morning diuresis. This seems unlikely to be the primary explanation. In previous medication trials [20], we have found that orthostatic tachycardia was diminished in mid-morning compared with early morning baseline assessment, even in the absence of further fluid ingestion and even in the placebo arm. Those studies were all conducted in a post-absorptive state at least 2 h after breakfast. We could not exclude a ‘placebo-effect’ as the explanation for that finding.

Prolonged head-down bed rest is a well-recognized model to recreate a microgravity environment and to create orthostatic intolerance. This model has caused blood volume redistribution with resultant central hypovolaemia and cardiac atrophy [21–24]. These studies, however, have required prolonged durations of bed rest (42–120 days). In contrast with those heroic studies, our subjects experienced only a brief period of recumbence (overnight) in a neutral supine (and not head-down) position. It seems unlikely that the body position is contributing greatly to the exaggerated orthostatic tachycardia.

Another possibility is that the observed diurnal variability is due to intrinsic circadian variability. Continuous ambulatory HR monitoring has previously shown that HR undergoes diurnal variation [12,13].

HR was maximal in the morning (10.00 hours) with a subsequent progressive decline throughout the day until a nadir in the early morning hours just prior to waking, after which HR begins to increase again [12]. This variability might be an adaptive advantage to allow the human to rise in the morning to meet the challenges of a new day. A relative increase in adrenergic tone, in part through vagal withdrawal, seems to underlie this phenomenon. The increased frequency of myocardial infarction in the early morning hours has been attributed in part to this effect [17,25,26]. Thus the increased morning orthostatic tachycardia and standing HR observed in the present study could result from increased adrenergic tone in the early morning hours, although our present study was not designed to test this directly.

The MBP increased with standing from a supine position, both in the evening and in the following morning (Table 3). Therefore the orthostatic tachycardia is not due to a failure of vasoconstriction. The increase in MBP, however, was blunted in the early morning, and this was associated with the exaggerated increase in HR.

The possibilities underlying this haemodynamic pattern include a relative reduction in vascular resistance in the early morning or a reduced stroke volume in the morning with an exaggerated reflex tachycardia that maintains cardiac output.

We did not assess symptoms in the present study during the evening and early morning evaluations; hence we cannot state conclusively whether or not the diurnal differences in orthostatic tachycardia tracked with diurnal variability in symptom burden. Anecdotally, many patients do report that their symptoms of palpitation and lightheadedness are worse in the morning, while some other symptoms (such as fatigue) are worse later during the day.

**Implications for diurnal variability in orthostatic tachycardia on diagnosis of POTS**

This observation is important because it suggests that the time of the day may affect the accurate diagnosis of POTS. Although multiple criteria are required for the diagnosis of POTS [2], the key haemodynamic criterion requires an HR increase of at least 30 beats/min within 10 min of standing from a supine position [2]. When the orthostatic tachycardia was assessed dichotomously (using the 30 beats/min criterion), significantly more subjects met this criterion in the morning than in the evening (P = 0.008). There was an absolute increase of 18% in POTS patients meeting the 30 beats/min criterion in the morning than in the evening. Only 42% of the POTS patients met the HR criterion in the evening assessment. It is possible that more POTS patients would have met the HR criterion at both time points if the stand duration were 10 min instead of 5 min.
These data suggest that the diagnosis of POTS may be missed in some patients with POTS if orthostatic tachycardia is assessed only later in the day and not in the early morning. It may be questioned whether it is better to diagnose more patients (early morning assessment) or fewer patients (evening assessment) with POTS. The 30 beats/min orthostatic tachycardia criterion for POTS probably relates to the book by Streeten [27] in which he defined an increase of 27 beats/min as the upper 95% confidence interval for orthostatic tachycardia in normal subjects. This is based on his physiological studies that would have been conducted in the mornings in a fasting state. Ultimately, it is important to standardize the time of assessment of orthostatic tachycardia, whether in the early morning or later during the day. Ignoring the diurnal variability could account for both missed diagnoses of POTS and increased ‘noise’ in clinical research studies involving orthostatic HRs.

Conclusions

We found that there is a significant increase in orthostatic tachycardia in the morning compared with the evening, both in patients with POTS and in healthy subjects. Given the importance of orthostatic tachycardia to the diagnostic criteria for POTS, this phenomenon may affect the diagnostic accuracy of POTS if assessments are performed only later in the day. The pathophysiology underlying this diurnal variability requires further investigation.

AUTHOR CONTRIBUTION

Bonnie Black and Satish Raj conceived and designed the study; John Ling, Jordan Brewster and Emily Garland acquired the data; David Robertson, Italo Biaggioni, Satish Raj and Cyndya Shibao analysed and interpreted the data; Satish Raj and Jordan Brewster performed the statistical analysis of the data; Jordan Brewster and Satish Raj drafted the paper; Emily Garland, John Ling, Italo Biaggioni, David Robertson, Bonnie Black and Cyndya Shibao revised the paper; Satish Raj, David Robertson and Italo Biaggioni obtained funding for the study; and Satish Raj supervised the study.

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REFERENCES


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