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## Diurnal Variability in Orthostatic Tachycardia: Implications for Postural Tachycardia Syndrome

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### Abstract

Patients with Postural Tachycardia Syndrome (POTS) have excessive orthostatic tachycardia (>30 bpm) when standing from a supine position. Heart rate (HR) and blood pressure (BP) are known to exhibit diurnal variability, but the role of diurnal variability in orthostatic changes of HR & BP is not known. In this study, we tested the hypothesis that there is diurnal variation of orthostatic HR & 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 & BP were obtained on the evening on the day of admission and in the following morning. Overall, standing HR was significantly higher in the morning than the evening (102±3 bpm [AM] vs. 93±2 bpm [PM]; P<0.001). Standing HR was higher in the morning in both POTS patients (108±4 bpm [AM] vs. 100±3 bpm [PM]; P=0.012) and controls (89±3 bpm [AM] vs. 80±2 bpm [PM]; P=0.005), when analyzed separately. There was no diurnal variability in orthostatic BP in POTS. More 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 to 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.

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## Keywords

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## Introduction

Postural tachycardia syndrome (POTS) is a disorder of chronic orthostatic intolerance characterized by excessive increase in heart rate upon standing in the absence of hypotension [8,12]. 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 [12]. 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 [1,2]. The pathophysiology underlying POTS is not completely understood; however, patients with POTS have been observed to have increased sympathetic nervous system tone upon standing[10], decreased total blood volume[16], and perturbations in the renin-aldosterone axis[13].

Blood pressure and heart rate exhibit considerable variation over a 24-hour period[3–5,9,17,24] as a result of diurnal variations in emotional and behavioral states[18,22], baroreflex sensitivity[5,13], renin-angiotensin system activity[23], plasma catecholamine levels[4,23], and adrenergic tone[11]. The measurement of blood pressure and heart rate in the supine and standing positions forms the basis of orthostatic testing, which is crucial to the evaluation of a number of neurocardiogenic disorders including syncope, autonomic failure, and POTS [12,26]. Given the diurnal variability in blood pressure and heart rate, one may expect to observe diurnal variation in orthostatic testing results that could affect whether patients meet the diagnostic criteria for POTS (>30 bpm orthostatic increase in heart rate [HR]).

In this small cohort study, we measured orthostatic vital signs (supine and standing heart rate and blood pressure) 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 this 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 to the evening.

## 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 [12,15]. Briefly, POTS patients developed symptoms of orthostatic intolerance accompanied by a heart rate (HR) rise  $\geq 30$  bpm that occurred within the first 10 minutes of standing or head-up tilt, without any evidence of orthostatic hypotension (fall in blood pressure [BP] of  $\geq 20/10$  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

hemodynamically significant medications for 5 half-lives prior to evaluation (or at least 5 days for fludrocortisone). Healthy control subjects ( $n=26$ ;  $27\pm 1$  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 of hemodynamically 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 2 groups for size and age. It should be noted that the primary comparisons in this study are not between groups, but within groups at different times of day.

### Measurement of Postural Vital Signs

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

### Evening & 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 this study. These times were chosen in order to maximize patient inclusion and to avoid confounding influence of other investigational drugs and procedures from other research protocols that may have started later in Day 2. HR, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the supine position and then upon standing upright for 5 minutes in the evening (~8pm) on the first day of admission for the research study (day 1) and then again the following morning (~8am; day 2), after an overnight fast. No medications or treatments were employed in the interval period between measurement of the evening and morning vital signs.

### Posture Study

A diagnostic “posture study” was performed in the patients with POTS, and was done as a part of our routine POTS evaluation in our center. This study was performed following an overnight fast on our Clinical Research Center. Using an indwelling intravenous catheter, supine HR & BP were assessed and plasma catecholamines were drawn. The patients were then asked to stand for up to 30 minutes (or as long as tolerated). At the end of the standing period, HR & BP and plasma catecholamines were re-measured. Posture studies were performed within 48 hours of the reported evening and morning orthostatic vital signs, and usually within 24 hours. Medications were not given between these 2 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

Data are expressed as mean  $\pm$  SEM (unless otherwise noted). Groups were compared with the Student's  $t$  test. The 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  $t$  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 (SPSS Inc., Chicago, IL). All of the tests were 2-sided, and  $P < 0.05$  was considered statistically significant.

## Results

### Orthostatic Hemodynamics 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 than in the prior evening ( $102 \pm 3$  bpm [AM] vs.  $93 \pm 2$  bpm [PM];  $P < 0.001$ ). The standing SBP was slightly lower in the morning than in the prior evening ( $112 \pm 2$  mmHg [AM] vs.  $116 \pm 2$  mmHg [PM];  $P = 0.004$ ), but the DBP was not significantly different ( $72 \pm 1$  mmHg [AM] vs.  $74 \pm 1$  mmHg [PM];  $P = 0.129$ ). Supine HR did not differ with time of day, and this resulted in a larger orthostatic (supine to standing 5 minutes) tachycardia in the morning than in the prior evening ( $31 \pm 2$  bpm [AM] vs.  $22 \pm 2$  bpm [PM];  $P < 0.001$ ). Neither supine nor orthostatic changes in SBP or DBP differed with the time of day.

### Orthostatic Hemodynamics 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 ( $34 \pm 3$  bpm [AM] vs.  $27 \pm 2$  bpm [PM];  $P = 0.011$ ) and control subjects ( $26 \pm 2$  bpm [AM] vs.  $13 \pm 2$  bpm [PM];  $P = 0.001$ ; Figure 1a). The standing HR was also significantly higher in the morning than in the evening in both the POTS patients ( $108 \pm 4$  bpm [AM] vs.  $100 \pm 3$  bpm [PM];  $P = 0.012$ ) and control subjects ( $89 \pm 3$  bpm [AM] vs.  $80 \pm 2$  bpm [PM];  $P = 0.005$ ; Figure 1b). The supine HR was not different at the 2 time points in the POTS patients ( $74 \pm 2$  bpm [AM] vs.  $74 \pm 2$  bpm [PM];  $P = 0.694$ ), and was slightly lower in the morning than in the evening in the control subjects ( $68 \pm 2$  bpm [AM] vs.  $63 \pm 2$  bpm [PM];  $P = 0.011$ ; 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 prior evening ( $5 \pm 2$  mmHg [AM] vs.  $1 \pm 2$  mmHg [PM];  $P = 0.156$ ; 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 [AM] vs.  $-1 \pm 2$  mmHg [PM];  $P = 0.684$ ). The standing SBP was slightly lower in the morning than in the prior 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 2 time points ( $P = 0.807$ ; Figure 2c), but was slightly lower in the morning in the controls subjects ( $P = 0.028$ ).

There were no significant differences in DBP between morning and the prior evening in either body position (Figure 2d–2f).

### POTS Orthostatic Tachycardia Criterion

An increase in HR  $> 30$  bpm from lying to standing is used as a HR criterion in the definition of POTS [8,12]. There was a significant increase in the number of subjects who met the POTS HR criterion in the morning compared with the evening (McNemar  $P = 0.008$ ; 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

The key finding in this study is that orthostatic tachycardia is significantly higher first thing in the morning when compared to 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. While 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 hypovolemic state resulting from the overnight fast and morning diuresis. This seems unlikely to be the primary explanation. In prior medications trials [14], 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 performed in a post-absorptive state at least 2 hours 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 create orthostatic intolerance. This model has caused blood volume redistribution with resultant central hypovolemia and cardiac atrophy [7,19,20,25]. These studies, however, have required prolonged durations of bed rest (42–120 days). In contrast to 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 [17,24]. HR was maximal in the morning (10 am) 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 rise again [17]. 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 [6,11,27]. Thus, the increased morning orthostatic tachycardia and standing HR observed in this study could result from increased adrenergic tone in the early morning hours, although our 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 hemodynamic 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 this study during the evening and early morning evaluations, so 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 in the day.

## Implications for Diurnal Variability in Orthostatic Tachycardia on Diagnosis of POTS

This observation is important because it suggests that the time of day may affect the accurate diagnosis of POTS. While multiple criteria are required for the diagnosis of POTS [12], the key hemodynamic criterion requires a HR increase of at least 30 bpm within 10 minutes of standing from a supine position [12]. When the orthostatic tachycardia was assessed dichotomously (using the 30 bpm 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 bpm 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 minutes instead of 5 minutes.

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 likely relates to work by David HP Streeten in which he defined an increase of 27 beats/min as the upper 95% confidence interval for orthostatic tachycardia in normal subjects [21]. 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 the assessment of orthostatic tachycardia, whether in the early morning or later in the day. Ignoring the diurnal variability could account for both missed diagnoses of POTS and increased “noise” in clinical research studies involving orthostatic heart rates.

## Conclusion

We have observed that there is a significant increase in orthostatic tachycardia in the morning compared to the evening both in patients with POTS and 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 study.

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## Abbreviations

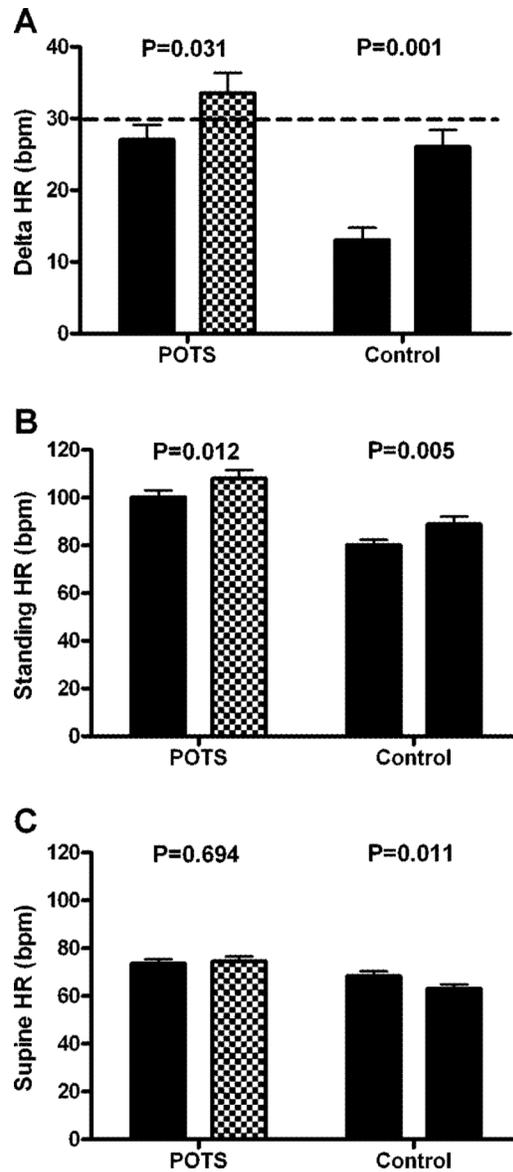
<b>POTS</b>	Postural Tachycardia Syndrome
<b>HR</b>	heart rate
<b>BP</b>	blood pressure
<b>SBP</b>	systolic blood pressure
<b>DBP</b>	diastolic blood pressure
<b>MBP</b>	mean blood pressure
<b>AM</b>	morning

<b>PM</b>	evening
<b>SEM</b>	standard error of the mean

## Reference List

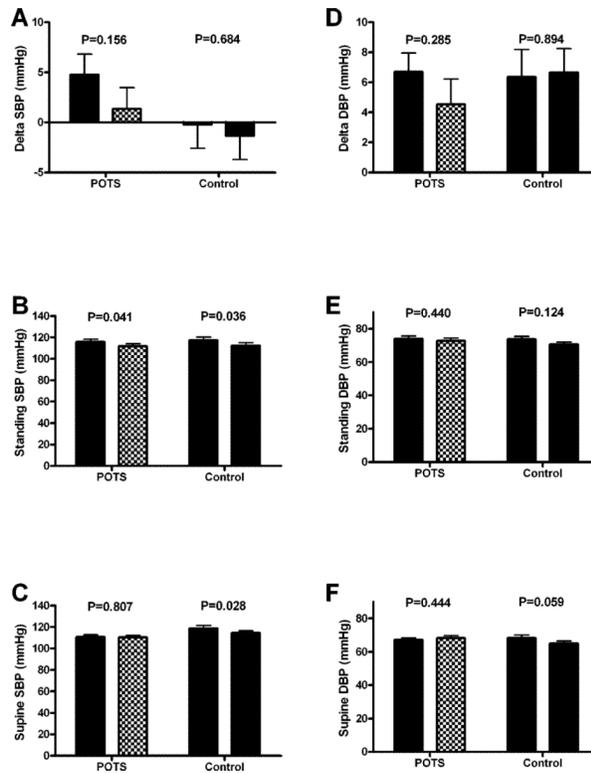
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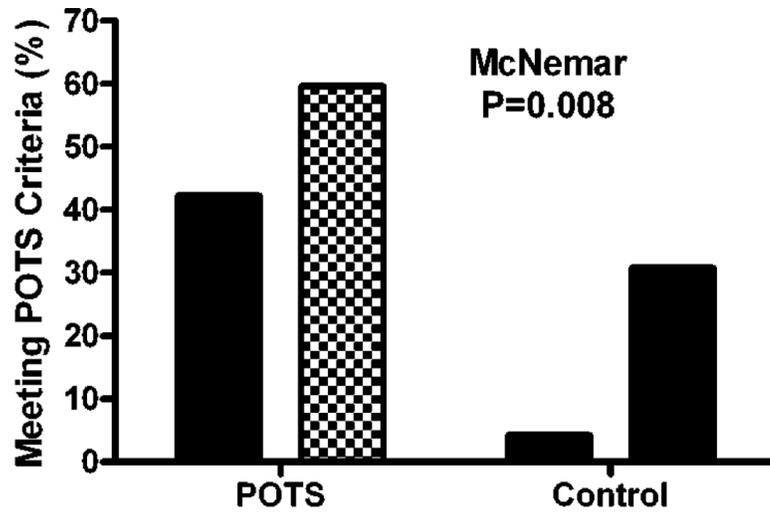
**Figure 1. Evening and Morning Heart Rate Parameters**

Orthostatic increase in heart rate (delta heart rate [HR]) from supine to standing (Panel A), standing HR at 5 minutes (Panel B) and supine HR (Panel C) are shown for patients with Postural Tachycardia Syndrome (POTS; black bars) and Control subjects (gray bars) in the evening (solid bars) and the morning (hashed bars). Reported P values were generated using paired t-tests.



### Figure 2. Evening and Morning Blood Pressure Parameters

Orthostatic changes in systolic blood pressure (delta systolic blood pressure [SBP]) from supine to standing (Panel A), standing SBP (Panel B) and supine SBP (Panel C) are shown for patients with Postural Tachycardia Syndrome (POTS; black bars) and Control subjects (gray bars) in the evening (solid bars) and the morning (hashed bars). Similar data for diastolic blood pressure (DBP) is shown in Panels D–F. Reported P values were generated using paired t-tests.



**Figure 3. POTS Heart Rate Criterion Met by Time of Day**

These histograms show the percentage of subjects with an increase in heart rate >30 bpm with a 5 minute stand (from a supine body position) and not the 10 minute stand that is used to diagnose Postural Tachycardia Syndrome (POTS). Data are shown for patients with POTS (black bars) and Control subjects (gray bars) in the evening (solid bars) and the morning (hashed bars). McNemar's test was used to determine if there was a difference in the number of combined subjects meeting this criterion between the 2 time points.

**Table 1**

Demographics, Hematology and Blood Chemistry results in patients with Postural Tachycardia Syndrome and Healthy Control Subjects

	<b>POTS</b>	<b>Healthy Controls</b>	<b>P</b>
Gender (F/M)	46 / 8	15 / 11	0.007
Age (years)	35 ± 2	27 ± 1	<0.001
Height (cm)	169 ± 1	174 ± 2	0.026
Weight (kg)	71 ± 3	78 ± 3	0.077
Body Mass Index (kg/m <sup>2</sup> )	24.6 ± 0.7	25.5 ± 1.0	0.494
White Blood Cells (thou/ $\mu$ l)	6.5 ± 0.2	5.7 ± 0.3	0.037
Hemoglobin (g/dL)	13.5 ± 0.2	13.2 ± 0.3	0.287
Serum Sodium (mEq/L)	139 ± 0.3	139 ± 0.4	0.811
Serum Potassium (mEq/L)	4.0 ± 0.04	4.1 ± 0.07	0.188
Serum Chloride (mEq/L)	104 ± 2	102 ± 2	0.003
Creatinine (mg/dL)	0.74 ± 0.02	0.93 ± 0.04	<0.001

Continuous data are presented as the mean ± SEM, and were analyzed using Student t-tests and dichotomous data analyzed using a Fisher's Exact test. POTS – Postural Tachycardia Syndrome.

**Table 2**

Diagnostic supine and standing hemodynamic parameters and catecholamines in patients with Postural Tachycardia Syndrome

	Supine	Stand (up to 30 min)	P
Heart Rate (bpm)	76 ± 2	120 ± 3	<0.001
Systolic Blood Pressure (mmHg)	111 ± 1	114 ± 3	0.392
Diastolic Blood Pressure (mmHg)	69 ± 1	72 ± 2	0.041
Mean Blood Pressure (mmHg)	83 ± 1	86 ± 2	0.097
Norepinephrine (pg/ml)	323 ± 31	974 ± 68	<0.001
Epinephrine (pg/ml)	31 ± 5	71 ± 12	<0.001

Continuous data are presented as the mean ± SEM, and were analyzed using paired t-tests.

**Table 3**

Supine and standing hemodynamic parameters of combined cohort on the Admission Evening and on the following Morning.

	Evening of Admission	Following Morning	P
<b>Supine</b>			
Heart Rate (bpm)	72 ± 1	70 ± 2	0.395
Systolic Blood Pressure (mmHg)	114 ± 2	112 ± 1	0.177
Diastolic Blood Pressure (mmHg)	68 ± 1	67 ± 1	0.668
Mean Blood Pressure (mmHg)	83 ± 1	82 ± 1	0.356
<b>Standing</b>			
Heart Rate (bpm)	93 ± 2	102 ± 3	<0.001 **
Systolic Blood Pressure (mmHg)	116 ± 2	112 ± 2	0.004 *
Diastolic Blood Pressure (mmHg)	74 ± 1	72 ± 1	0.129
Mean Blood Pressure (mmHg)	88 ± 1	85 ± 1	0.014 *
<b>Change from Supine to Standing</b>			
Heart Rate (bpm)	22 ± 2	31 ± 2	<0.001 **
Systolic Blood Pressure (mmHg)	3 ± 2	0 ± 2	0.150
Diastolic Blood Pressure (mmHg)	7 ± 1	5 ± 1	0.394
Mean Blood Pressure (mmHg)	6 ± 1	4 ± 1	0.162

Continuous data are presented as the mean ± SEM, and were analyzed using paired t-tests.

\* P<0.05;

\*\* P≤0.001.