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DECREASED ORTHOSTATIC ADRENERGIC REACTIVITY IN NON-DIPPING POSTURAL TACHYCARDIA SYNDROME

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Abstract

Whether non-dipping - the loss of the physiologic nocturnal drop in blood pressure - among patients with postural tachycardia syndrome (POTS) is secondary to autonomic neuropathy, a hyperadrenergic state, or other factors remains to be determined. In 51 patients with POTS (44 females), we retrospectively analyzed 24-hour ambulatory blood pressure recordings, laboratory indices of autonomic function, orthostatic norepinephrine response, 24-hour natriuresis and peak exercise oxygen consumption. Non-dipping (< 10% day-night drop in systolic blood pressure) was found in 55% (n=28). Dippers and non-dippers did not differ in: 1) baseline characteristics including demographic and clinical profile, sleep duration, daytime blood pressure, 24-hour natriuresis, and peak exercise oxygen consumption; 2) severity of laboratory autonomic deficits (sudomotor, cardiovagal and adrenergic); 3) frequency of autonomic neuropathy (7/23 vs. 8/28, $P=0.885$); 4) supine resting heart rate (75.3 ± 14.0 bpm vs. 74.0 ± 13.8 bpm, $P=0.532$); or 5) supine plasma norepinephrine level (250.0 ± 94.9 pg/ml vs. 207.0 ± 86.8 pg/ml, $P=0.08$). However, dippers

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differed significantly from non-dippers in that they had significantly greater orthostatic heart rate increment (43 ± 16 bpm vs. 35 ± 10 bpm, $P=0.007$) and significantly greater orthostatic plasma norepinephrine increase (293 ± 136.6 pg/ml vs. 209 ± 91.1 pg/ml, $P=0.028$). Our data indicate that in patients with POTS, a non-dipping blood pressure profile is associated with a reduced orthostatic sympathetic reactivity not accounted for by autonomic neuropathy.

Keywords

Postural tachycardia syndrome; orthostatic intolerance; circadian blood pressure rhythm; dipping; ambulatory blood pressure

INTRODUCTION

Postural tachycardia syndrome (POTS) is a disorder of orthostatic intolerance without evidence of orthostatic hypotension (OH) characterized by symptoms of cerebral hypoperfusion and sympathetic activation associated with excessive tachycardia when assuming an erect posture (Schondorf et al., 1993). The etiology remains unknown but is likely heterogeneous. Putative pathophysiologic mechanisms include a hyperadrenergic state (Jacob et al., 1997; Schondorf et al., 1993), peripheral adrenergic denervation (Jacob et al., 2000), hypovolemia (Jacob et al., 1997); venous pooling (Schondorf et al., 1993); deconditioning (Masuki et al., 2007); and possible central autonomic dysregulation (Novak et al., 1998).

An attenuation of the physiologic drop in blood pressure (BP) during nighttime (i.e., non-dipping), has recently been recognized in a subgroup of patients with POTS (Sato et al., 2009). The clinical relevance of this finding in POTS is highlighted by its common occurrence combined with the growing evidence of its association with a higher risk of end-organ damage among both normotensive (Kohara et al., 1995; Kurpesa et al., 2002; Sherwood et al., 2002; Sica, 1999) and hypertensive individuals (Cuspidi et al., 2004; Ohkubo et al., 1997). The mechanisms of non-dipping in POTS are poorly understood and a possible association with underlying autonomic impairment, hyperadrenergic state, and other factors remains to be determined.

The objectives of this study were to assess the frequency and potential autonomic mechanisms of non-dipping in POTS. We hypothesized that the loss of nocturnal BP drop in POTS relates either to autonomic denervation, as seen in patients with early diabetic autonomic neuropathy (Jermendy et al., 1996; Spallone et al., 1996) or to a hyperadrenergic state. We reasoned that if autonomic mechanisms mediate non-dipping in POTS, daytime autonomic evaluation would be predictive of the presence of a nocturnal blood pressure drop among patients with POTS, as reported in diabetic autonomic neuropathy (Spallone et al., 1996).

METHODS

Participants

After Institutional Review Board approval, we identified a total of 51 consecutive patients with POTS seen at Mayo Clinic in Rochester, MN, from 2006 to 2009. All had undergone a standardized evaluation that included 24-hour ambulatory BP recording and full autonomic testing. Extensive cardiologic evaluation including electrocardiogram, Holter monitoring and echocardiogram revealed an absence of specific cardiac arrhythmias or structural heart disease. Patients fulfilled predetermined inclusion criteria for POTS: 1) onset between the ages of 16 and 50 years; 2) symptoms of orthostatic intolerance; 3) orthostatic heart rate increase of at least 30 beats per minute (bpm); and 4) absence of OH. Patients were excluded if (1) they had another cause of autonomic failure; (2) took medications that interfered with autonomic function that could not be withheld before testing; or (3) had a concurrent illness that could affect autonomic function such as hypertension, severe anemia, renal or hepatic disease, and pheochromocytoma.

Prospective standardized data collection of the entire patient population presenting to the same clinic during a defined time interval maximized data accuracy and minimized selection bias. To avoid inter-rater variability and assessment bias during the retrospective chart review process a single data abstractor blinded to dipping status was used. Use of standard definitions ensured data abstraction reliability. Among clinical variables, fatigue was defined as lack of physical energy that interferes with function. Sleep disturbance was defined as difficulty falling or staying asleep that required the use of sleep aids or need for daytime naps.

Circadian and Hemodynamic Measurements

A 24-hour ambulatory BP monitor (SpaceLabs Medical Inc., California, USA) was placed as previously reported (Metoki et al., 2010). The cuff was attached to the non-dominant arm. Recordings were obtained every 15 minutes during daytime and every 30 minutes during nighttime for a 24-hour period. The patient was sent home with instructions to hold the arm immobile at the time of measurements, keep a diary of daily activities and quality of night rest. Nighttime period was defined as the interval between bedtime onset (considered as sleep onset) and morning waking based on patient diaries and not on a predefined nighttime period. The number of hours between bedtime onset and morning waking as documented on patient diaries was used to quantify sleep duration. No participant was a shift worker or was engaged in activities that might lead to a reversed circadian rhythm. Participants with a daytime average BP less or equal to 135/85 mmHg were considered normotensive.

The magnitude of dipping was expressed as the percentage of drop in nocturnal systolic blood pressure (BP) calculated as follows: $\text{decline in nighttime systolic BP (\%)} = (\text{average daytime systolic BP} - \text{average nighttime systolic BP}) \times 100 / \text{average daytime systolic BP}$. A standard definition of dipping status was used as follows. Individuals who showed a minimum of 10% reduction in systolic BP were classified as “dippers” and individuals with less than 10% reduction were classified as “non-dippers” (Hoshida et al., 2003).

Autonomic Function Tests

Standardized autonomic testing routinely used in clinical practice was performed as previously described (Low, 2003). Autonomic testing was used to assess the severity and distribution of sudomotor, cardiovagal and adrenergic deficits (Low, 1993). Sudomotor function was assessed using quantitative sudomotor axon reflex test (QSART) and, when available, thermoregulatory sweats test (TST). QSART, measured at proximal and distal standard sites, was used to assess the integrity of the sympathetic postganglionic sudomotor axon and the pattern of involvement (e.g. length-dependent) (Low, 2003). TST assessed the integrity of both central and peripheral sudomotor pathways involved in thermoregulatory response to changes in environmental temperature (Fealey et al., 1989). Cardiovagal function was assessed with the beat-to-beat heart rate responses to deep breathing and the Valsalva maneuver (respiratory sinus arrhythmia, Valsalva ratio and cardiovagal baroreflex sensitivity). Adrenergic function was assessed with the beat-to-beat blood pressure responses to the Valsalva maneuver (late phase II reflex vasoconstriction in response to impediment of venous return, phase IV pressure recovery time after impediment has been released, and adrenergic baroreflex sensitivity), beat-to-beat blood pressure recording to head-up tilt (HUT), and serum norepinephrine (NE) levels (supine and standing) (Low, 1993).

Composite Autonomic Severity Score (CASS)

The CASS is a well validated measure of severity and distribution of autonomic failure that has been derived from the autonomic reflex screen (QSART, heart rate response to deep breathing, Valsalva maneuver and head-up tilt) (Low, 1993). Overall laboratory evidence of autonomic failure (CASS total) is graded as follows: 0, absent; 1–3 mild and limited in distribution; 4–6 moderate; and 7–10 severe and widespread failure. CASS total is divided into three subscores: CASS sudomotor (range, 0–3), CASS cardiovagal (range, 0–3), and CASS adrenergic (range, 0–4). Each score has been normalized for age and gender (Low et al., 1997).

Baroreflex Sensitivity (BRS)

We used validated indices of cardiovagal and adrenergic BRS derived from the Valsalva maneuver. Cardiovagal BRS was expressed as the slope of regression of heart period over systolic BP during early phase II of the Valsalva maneuver (Schrezenmaier et al., 2007; Vogel et al., 2005). Pressure recovery time (PRT) was defined as time in seconds from the valley of phase III until systolic BP returned to baseline during the phase IV of the Valsalva maneuver (Vogel et al., 2005). Adrenergic BRS was defined as the systolic BP decrement associated with early phase II and phase III divided by the PRT on the Valsalva maneuver as previously described (Schrezenmaier et al., 2007).

Phenotypic classification

It has become increasingly common to classify patients with POTS based on findings on autonomic function tests that would suggest the presence of a specific underlying pathomechanism. The two most commonly accepted phenotypes, neuropathic and hyperadrenergic, have been well defined. In order to explore for an association between

dipping and POTS phenotype, we also defined POTS phenotypes follows: Hyperadrenergic POTS was defined by standing serum norepinephrine (NE) concentration ≥ 600 pg/ml and an orthostatic increase in systolic BP ≥ 10 mmHg. Neuropathic POTS required at least one evidence of sympathetic denervation on autonomic function tests as follows: 1) Thermoregulatory anhidrosis of both lower extremities involving feet; 2) QSART foot volume $< 2.5^{\text{th}}$ percentile or less than a third of the distal leg value; or 3) absent late phase II or pressure recovery time > 6 seconds on the Valsalva maneuver.

Laboratory Tests

The increase in plasma catecholamine concentrations from supine to standing was measured to assess orthostatic adrenergic reactivity. Salt and fluid intake were estimated by 24-hour urine sodium excretion and urine volume. Oxygen consumption during exercise [peak VO_2 % predicted] was used to assess exercise capacity and physical conditioning. All tests were obtained using standard clinical laboratory protocols (Mayo Clinic Rochester, MN).

Statistical Analysis

Data were analyzed using JMP version 10. Continuous and categorical variables were compared between dippers and non-dippers. Values were expressed as mean $\pm$ standard deviation and percentages. Mean values were compared between groups using the non-parametric Mann-Whitney test. Proportion values were compared between groups using Chi-squared test. Given the exploratory nature of statistical testing in this study, $P < 0.05$ was considered significant without correction for multiple comparisons (O'Brien, 1983). Regression analysis between selected cardiovascular parameters was performed using Pearson's correlation and multivariate models where appropriate.

RESULTS

We studied 51 normotensive patients with POTS (44 women and 7 men). Mean age was 29.0 ± 8.0 years, and mean BMI, 23.8 ± 4.2 kg/m². Twenty nine (57%) patients had laboratory evidence of autonomic deficits which were generally mild (CASS total all patients, 0.9 ± 1.2) and involved sudomotor, adrenergic or cardiovagal functions in different combinations among patients. Fifteen (29%) had laboratory evidence of sympathetic denervation consistent with neuropathic POTS. In 10 (20%) of 49 patients, the orthostatic catecholamine profile was consistent with hyperadrenergic POTS. Twenty eight (55%) patients had a non-dipping BP profile. The magnitude of the nocturnal systolic BP fall relative to the daytime systolic BP in non-dippers was approximately half of that seen in dippers ($6.1 \pm 3.8\%$ vs. $13.9 \pm 3.3\%$; $P < 0.001$).

Clinical Characteristics

Dippers and non-dippers were evenly balanced on all demographic and clinical characteristics, including fatigue, sleep disturbances, and sleep duration and daytime "activity" as measured by diary recording. Average daytime blood pressure and heart rate were comparable between groups. (Table 1)

Autonomic Function Tests, BP monitoring, and Laboratory Data

There were no statistically significant differences between the two groups in terms of the autonomic deficits (Table 2). Dippers and non-dippers displayed similar severity and distribution of autonomic deficits as measured by CASS total score and subscores (sudomotor, adrenergic and cardiovagal), frequency of impaired late phase II pressure recovery during Valsalva maneuver or prolonged phase IV pressure recovery time following Valsalva maneuver, indices of baroreflex sensitivity, and frequency and degree of distal anhidrosis. Exercise peak oxygen consumption, 24-hour urine volume, and 24-hour sodium excretion were comparable between groups (Table 2).

Dippers and non-dippers displayed comparable baseline supine resting heart rate and plasma NE during head-up tilt testing. However, dippers differed significantly from non-dippers in that they had greater orthostatic HR increment (43 ± 16 bpm vs. 35 ± 10 bpm, $P=0.007$) and greater orthostatic plasma NE increase (293 ± 137 pg/ml vs. 209 ± 91 pg/ml, $P=0.028$, Table 3). Accordingly, there was a trend toward a higher frequency of hyperadrenergic POTS among dippers (Table 3).

There was a significant association between the HR response to tilt as well as standing NE levels and the degree of nocturnal dipping (Figure 1). A multivariate regression model using both of these variables predicted the magnitude of nocturnal BP dipping quite well ($R=0.67$, $p<0.0001$, Figure 1).

While the nocturnal fall in HR was not associated with the HR response to head-up tilt, there was a weak but significant association between the nocturnal fall in blood pressure and the nocturnal fall in HR (Figure 2).

Daytime systolic BP correlated well with nocturnal systolic BP ($R=0.79$, $p<0.0001$), but not with the magnitude of dipping.

DISCUSSION

To our knowledge, this is the first systematic investigation addressing the association between autonomic function and phenotype of patients with POTS and the presence of a non-dipping blood pressure profile. Our main findings are: 1) non-dipping is prevalent in POTS; 2) there is no difference in neuropathic findings between dippers and non-dippers; and 3) dippers are distinguished from non-dippers in that they have greater orthostatic HR increment and greater orthostatic NE increase. Contrary to our initial hypothesis, we found that 1) non-dippers have lower adrenergic reactivity rather than a hyperadrenergic profile; and 2) that this difference is not accounted for by a difference in severity and distribution of autonomic failure, particularly peripheral sympathetic denervation.

A higher prevalence of non-dipping in POTS (10 out of 15 patients) compared to normal controls (1 out of 8 patients) and lower muscle sympathetic nerve activity on superficial peroneal nerve microneurography at 30 degrees tilt in non-dippers compared to dippers in POTS have recently been reported (Sato et al., 2008; Sato et al., 2009). This information led us to study non-dipping in POTS using a larger sample ($n=51$) with an extensive laboratory

evaluation of autonomic deficits for quantification of autonomic neuropathy and hyperadrenergic states. We found no differences in baroreflex sensitivity between dippers and non-dippers in POTS. Although the relationship between BRS and circadian arterial blood pressure pattern is not clear, previous studies among hypertensive individuals suggest little or no association (Mancia et al., 1986; Vaile et al., 1996).

The mechanism for a more modest adrenergic response in non-dipping POTS cannot be directly inferred from our results as 1) our findings do not support a difference in severity and distribution of autonomic failure between dippers and non-dippers, 2) although we did not directly measure plasma volume, surrogate markers of volume status also did not differ between dippers and non-dippers, and 3) our hemodynamic studies show that all our patients were normotensive, and that there was no tendency for higher baseline blood pressure in non-dippers. Considering the association between nocturnal fall in HR and BP one could hypothesize that a central CNS mechanism may be responsible for the non-dipping phenomenon. An obvious mechanism of this kind would be lighter or lower quality sleep in non-dippers, but we did not find differences in sleep or fatigue history to support that theory, though formal polysomnograms or standardized questionnaires for sleep disorders, migraine, chronic fatigue or fibromyalgia were not performed. Another theory that could be deducted from our findings would be that the more prevalent hyperadrenergic state among dippers during waking hours results in a greater nocturnal BP fall when external stimuli are minimized and the body is at rest. The problem with that theory, however, is that it would explain the normal phenomenon of dipping with an abnormal hyperadrenergic state while the abnormal nocturnal non-dipping would be seen without such abnormalities.

In the end, the mechanism of non-dipping remains elusive.

This study had the strengths of a large sample size and extensive testing. Nevertheless, it has limitations. Several deserve mention. The study is a retrospective review and lacks a control group. Ambulatory blood pressure monitoring was performed only on one occasion in each subject, and classification of dipping status was carried out on the basis of this single measurement. Limited reproducibility of dipping measures has been reported (Manning et al., 2000; Omboni et al., 1998) suggesting that without repeat monitoring, findings should be interpreted with caution. Finally, although differences in 24-hour natriuresis between groups were not found, we did not explore day-to-night natriuresis ratios. Impaired ability to excrete sodium during the day has been proposed as a major determinant of the circadian rhythm of blood pressure (Burnier et al., 2007).

PERSPECTIVES

Our results confirm that non-dipping is prevalent in POTS, and suggest that a lower adrenergic reactivity and not peripheral sympathetic denervation or a hyperadrenergic state relates to non-dipping among patients with POTS. Considering peripheral adrenergic sparing and concordance of nocturnal BP and HR changes future studies on the etiology of non-dipping in POTS might explore central autonomic or neurohumoral mechanisms.

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Highlights

- A physiologic nocturnal drop in blood pressure (dipping) is frequently absent in POTS
- There is no difference in autonomic deficits between dippers and non-dippers
- Non-dippers have lower adrenergic reactivity rather than a hyperadrenergic profile

Figure 1.

The degree of the orthostatic sympathetic response is associated with the magnitude of nocturnal dipping. The correlation between orthostatic heart rate response and the nocturnal fall in blood pressure is shown in A, the correlation between standing norepinephrine and nocturnal fall in blood pressure is shown in B, and the predicted versus actual nocturnal blood pressure fall based on a multivariate regression model that includes both predictors (orthostatic heart rate response, standing norepinephrine) are shown in C.

Figure 2.

The nocturnal decrease in heart rate is not associated with the orthostatic heart rate response (A). In contrast, there is a weak but significant association between nocturnal fall in blood pressure and heart rate (B).

Table 1

Clinical and hemodynamic characteristics of study patients*

	Dippers n=23 (45%)	Non-dippers n=28 (56%)	p-value
Clinical			
Age (y)	29 ± 7.8	29.9 ± 8.7	0.842
Gender (F:M)	20 : 3	24 : 4	0.898
BMI (kg/m ²)	23.9 ± 4.3	23.7 ± 4.2	0.992
Disease duration (y)	3.3 ± 4.7	2.6 ± 2.5	0.769
Disease onset			
Acute or subacute (< 3 mo)	11 (48%)	10 (36%)	0.382
Preceding illness	12 (52%)	15 (54%)	0.921
Clinical manifestations			
Presyncope or syncope	17 (74%)	24 (86%)	0.291
Exercise intolerance	13 (57%)	14 (50%)	0.642
Migraine-like headache	9 (39%)	11 (39%)	0.991
Fatigue	9 (39%)	15 (54%)	0.304
Sleep disturbances	4 (17%)	5 (18%)	0.965
24-h BP monitoring			
Average nighttime BP and HR fall (%)			
SBP	13.9 ± 3.3	6.1 ± 3.8	< 0.001 [†]
DBP	22.3 ± 5.0	14.4 ± 4.7	< 0.001 [†]
HR	18.7 ± 11.7	13.1 ± 6.4	0.047 [†]
Average daytime BP and HR			
SBP (mmHg)	115.9 ± 8.5	116.2 ± 11.7	0.919
DBP (mmHg)	74.0 ± 6.1	73.9 ± 8.3	0.946
HR (bpm)	80.0 ± 23.3	83.8 ± 14.8	0.508
Average nighttime BP and HR			
SBP (mmHg)	99.7 ± 6.4	109.0 ± 9.7	0.001 [†]
DBP (mmHg)	57.4 ± 5.3	63.1 ± 7.1	0.003 [†]
HR (bpm)	66.3 ± 19.7	72.8 ± 14.1	0.195
Self-reported diary data			
Sleep duration (h)	8.7 ± 0.7	8.2 ± 1.8	0.104

* Data expressed as mean ± SD, unless indicated otherwise

[†] Statistically significant

BP=blood pressure; bpm=beats per minute; DBP=diastolic blood pressure; F=female; h=hours; HR=heart rate; M=male; mo=months; n=number; SBP=systolic blood pressure; y=years

Table 2

Autonomic function tests and laboratory data*

	Dippers	Non-dippers	p-value
Neuropathic POTS (n/n)	7/23	8/28	0.885
CASS score	(n=23)	(n=28)	
Sudomotor	0.5 ± 0.6	0.6 ± 0.8	0.830
Cardiovagal	0.1 ± 0.3	0.1 ± 0.3	0.811
Adrenergic	0.4 ± 0.8	0.2 ± 0.4	0.272
Total	1.0 ± 1.4	0.9 ± 1.0	0.745
Thermoregulatory Sweat Test	(n=22)	(n=27)	
% Anhidrosis	1.1 ± 3.1	5.7 ± 18.8	0.117
Baroreflex indices [†]	(n=23)	(n=28)	
PRT (sec)	2.6 ± 2.7	2.5 ± 1.9	0.597
Adrenergic BRS (mmHg/s)	33.9 ± 22.2	27.9 ± 22.8	0.869
Vagal BRS (mmHg/s)	2.7 ± 1.2	3.2 ± 1.2	0.792
24 hour urine studies	(n=22)	(n=27)	
Volume (mL/24 h)	1725.5 ± 838.1	1605.2 ± 814.6	0.416
Sodium (nmol/24 h)	141.5 ± 75.6	131.4 ± 66.2	0.564
Maximal oxygen consumption	(n=19)	(n=25)	
% Predicted	58.1 ± 14.8	63.8 ± 13.2	0.169

* Data expressed as mean ± SD unless indicated otherwise.

[†] Baroreflex indices derived from Valsalva maneuver.

BRS=baroreflex sensitivity; CASS=composite autonomic severity score; HR=heart rate; n=number; PRT=pressure recovery time; POTS=postural orthostatic tachycardia syndrome

Table 3

Orthostatic autonomic response in study patients *

	Dippers	Non-dippers	p-value
Hyperadrenergic POTS (n/n)	7/22	3/27	0.074
Systolic blood pressure (mmHg)			
Supine (resting)	110.5 ± 9.0	114.2 ± 12.63	0.337
Standing (at 5 min head-up tilt)	105.8 ± 10.9	111.8 ± 14.5	0.136
Change (supine to standing)	-4.7 ± 10.2	-2.4 ± 9.3	0.258
Diastolic blood pressure (mmHg)			
Supine (resting)	70.3 ± 7.3	72.1 ± 8.5	0.628
Standing (at 5 min HUT)	75.0 ± 9.1	74.4 ± 9.8	0.739
Change (supine to standing)	4.6 ± 8.2	2.3 ± 5.1	0.313
Heart rate (bpm)			
Supine (resting)	75.3 ± 14	74 ± 13.8	0.532
Standing (at 5 min head-up tilt)	118.7 ± 24.3	109 ± 16.1	0.108
Change (supine to standing)	43.4 ± 16.4	35 ± 10	0.007
Serum norepinephrine (pg/dL)			
Supine (resting)	250 ± 94.9	207 ± 86.8	0.080
Standing (at 5 min head-up tilt)	543 ± 182.5	418.3 ± 140.3	0.007
Change (supine to standing)	293 ± 136.6	209.5 ± 91.1	0.028

* Data expressed as mean ± SD unless indicated otherwise

Bpm=beats per minute; n=number; POTS=postural orthostatic tachycardia syndrome.