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Distal Sudomotor Findings in Postural Tachycardia Syndrome

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Abstract

Postural tachycardia syndrome (POTS) is a heterogeneous disorder characterized by excessive orthostatic tachycardia in the absence of orthostatic hypotension and by sympathetic nervous system activation. Postganglionic sudomotor deficits have been used to define a neurogenic postural tachycardia POTS subtype. Norepinephrine levels above 600 pg/ml have also been used to delineate patients with a hyperadrenergic state. This study aims to determine the relationship of sudomotor abnormalities to other aspects of dysautonomia in POTS. Autonomic function was quantified in thirty women through tests of cardiovagal, adrenergic, and sudomotor function including quantitative sudomotor axon reflex testing (QSART) and spectral indices. Differences between patients with and without sudomotor dysfunction as defined by QSART and between patients with and without hyperadrenergic POTS were assessed with Mann Whitney U test and Mantel-Haenszel Chi-Square test using a p value of 0.01 for significance. Spearman correlation coefficients were used to test raw sweat volume correlations with other variables. Of thirty women (ages 20–58), seventeen patients (56%) had an abnormal QSART which was typically patchy and involved the lower extremity, while thirteen patients had normal QSART results. Other autonomic tests, catecholamines or spectral indices did not correlate with QSART results. No differences in autonomic tests or spectral indices were observed between hyperadrenergic and non-hyperadrenergic POTS. Our findings confirm that a large subset of POTS patients have sudomotor abnormalities which are typically patchy in distribution but do not correlate with other tests of autonomic function. Further studies are needed to determine the best method of endophenotyping patients with POTS.

Keywords

orthostatic intolerance; tachycardia; POTS; sudomotor; autonomic neuropathy; sweating

Introduction

Postural tachycardia syndrome (POTS) is a common cause of orthostatic sinus tachycardia and orthostatic intolerance which affects an estimated 500,000 persons in the United States (1). POTS is defined by a heart rate increase of 30 beats per minute (bpm) with standing from a supine position without a significant associated drop in blood pressure. Patients chronically have symptoms that are worse with upright posture and that improve with

recumbence. Symptoms often include orthostatic intolerance such as dizziness, fatigue, excessive sweating, and occasionally heat intolerance, diarrhea, constipation, and urinary urgency.

POTS is a heterogeneous disorder with several different recognized subtypes. Some patients have been found to be hyperadrenergic (2), some have a low blood volume (3), and rare cases associated with a low titer of an antibody targeting the ganglionic acetylcholine receptor have been reported (4).

POTS may be an attenuated form of pandysautonomia as quantitative sudomotor axon reflex testing (QSART) was abnormal in 6/16 patients and several patients noted antecedent viral infections (5). Some patients may have a “neuropathic” etiology, with a significant decrease in norepinephrine levels in femoral veins vs. antecubital veins, suggesting a possible distal sympathetic neuronal denervation causing excessive venous pooling and reflex tachycardia (6). More recently, a series of 152 patients with 68% having abnormal quantitative sudomotor axon reflex test (QSART) and 27% with a history of preceeding illness, and reduced low frequency component in blood pressure and R-R intervals was reported, suggesting an abnormal sympatho-vagal balance (7;8). The finding of abnormal postganglionic sudomotor activity in POTS patients has not been found to be correlate with other measurements of autonomic function (9;10).

Given both the multiple physiological abnormalities that have been documented in some patients with POTS, we assessed a well characterized inpatient cohort with POTS to determine the incidence of sudomotor abnormalities and the relationship between QSART findings and other biochemical and physiological measures of autonomic function.

Methods

Study Subjects

The study was approved by the Vanderbilt Institutional Review Board and all patients gave their written informed consent according to the principles of the Declaration of Helsinki. The diagnosis of POTS was confirmed upon admission and required: 1) minimum of six month history of daily orthostatic symptoms; 2) heart rate increase of 30 beats per minute (bpm) after standing from supine, without an orthostatic drop in blood pressure of 20/10 mm or greater, 3) absence of acute dehydration or other medical conditions, and 4) a standing norepinephrine value >100 pg/ml.

Between November 2005 and August 2007, 33 patients with POTS met criteria for inclusion in this study. Due to the minimal number of male patients (n=3) and gender differences in QSART findings, only the 30 female patients were included in the analyses here.

General Protocol

All patients were free from medications could alter autonomic tone for at least 5 half-lives. Before testing, all subjects were placed on a caffeine-free, low monoamine diet with controlled sodium (150 mEq /day) and potassium (70 mEq/day). All patients underwent a standard autonomic testing battery (see below) and a QSART. Supine and standing orthostatic vital signs and plasma catecholamine levels were drawn after being supine overnight and standing for 30 minutes.

Autonomic Function Testing (AFT)

All patients had EKG, pulse oximetry, respiration and blood pressure monitoring during autonomic function tests which included both brachial cuff blood pressure measurement

(Dinamap 1646XS, Critikon, Tampa, FL) and continuous non-invasive finger blood pressure measurement (Finapres monitor, Ohmeda, Englewood, Colorado). Initially, five minutes of resting supine heart rate and blood pressure data were recorded for spectral analysis. Patients had sixty seconds of rest or longer between tests to ensure patients were back to baseline before next examination. Patients underwent controlled deep breathing (6 cycles/minute) for 90 seconds in which the longest and shortest R-R interval, inverted to a heart rate in beats per minute (bpm), was calculated as a sinus arrhythmia (SA) ratio. Heart rate and blood pressure measurement were recorded during hyperventilation for 30 seconds. Each patient also performed a Valsalva maneuver that was sustained for 15 seconds. In order to force the patient to maintain a continuous sustained pressure, they blew into a mouthpiece connected to a closed manometer tube with a 22 gauge hole and were asked to maintain generate 40 mm Hg of Valsalva pressure. For sustained hand grip, a maximal voluntary contraction was measured using a dynometer. The patient was asked to grip using 1/3 maximal hand grip pressure for isometric exercise (Model 76618, Lafayette Instrument Co., Indiana) for 3 minutes. Cold pressor test consisted of the right hand placed in ice water for 60 seconds.

Standing Study with Catecholamines

Posture studies were performed after overnight fast. Subjects had an IV placed into an antecubital vein, and then lay supine for 30 minutes. Blood was drawn for supine plasma catecholamine measurements, plasma rennin activity and serum aldosterone. Patients were then asked to stand for up to 30 minutes or as long as they comfortably could, with heart rate and blood pressure measurements periodically for 30 minutes. At the end of 30 minutes or before sitting, blood was drawn for standing plasma catecholamine measurements. Plasma catecholamines were immediately transferred to chilled tubes containing EDTA, centrifuged and the plasma was transferred to storage tubes with reduced glutathione prior to freezing at −80C.

Catecholamine Measurements

In addition to norepinephrine, epinephrine and dopamine, the deaminated metabolites dihydroxyphenylglycol and DOPAC, as well as the precursor DOPA were measured. Plasma catechols were isolated by adsorption onto acid-washed alumina and then separated and quantified by reverse phase high-performance liquid chromatography with electrochemical detection, according to a modification of the procedure of Goldstein et al (11). Plasma renin activity was quantified by transformation of angiotensinogen to angiotensin I measured by radioimmunoassay. Plasma aldosterone was also quantified using radioimmunoassay techniques.

QSART

QSART testing was performed using the QSweat device (WR Electronics, Rochester, MN) using the technique of Low et al.(12). Capsules were placed at four standard sites: distal forearm, proximal leg, distal leg, and foot. 10% acetylcholine solution was iontophoresed using a current of 2.0 mA. Results were recorded in microliters of sweat volume. A study was determined to be abnormal if one or more sites were below the 5^{th} percentile for age and gender using previously published normative data, or if there was a proximal distal gradient with a distal site <1/3 the volume of the proximal leg site. Results were also analyzed by raw sweat volume and compared in hyperadrenergic and on hyperadrenergic patients.

Spectral Analysis

Signals were recorded with the WINDAQ data acquisition system (DI220; DATAQ, Akron, Ohio, USA; 14 Bit, 500 Hz) and were digitized at a sampling rate of 500 Hz and processed with user software (Visual Numerics Inc., Houston, TX). Spectral analysis was performed

using methods we have previously described and detailed below (13). Heart rate variability in the time domain was evaluated by standard deviation (SD RRI), root mean squared of successive differences of R–R intervals (RMSSD RRI) and percentage of interval changes greater than 50 milliseconds to normal sinus R–R intervals (PNN50) (14). Beat-to-beat values of detected R–R intervals and BP values were interpolated, low-pass filtered (cutoff 0.5 Hz) and re-sampled at 4 Hz. Data segments of 300 seconds were used for spectral analysis. Linear trends were removed and power spectral density was estimated with the FFT-based Welch algorithm using segments of 256 data points with 50% overlapping and Hanning window (15). The power in the frequency range of low frequencies (LF: 0.04–0.15 Hz) and high frequencies (HF: 0.15–0.40 Hz) was calculated following Task Force recommendations (16).

Symptom Evaluation

All patients were surveyed for 37 common symptoms such as racing heart rate, headache, dizziness, fainting, etc. on a scale of 1 to 5 (1 equivalent to never happens, 5 equivalent to happens daily) prior to admission. Seven of these symptoms; dizziness, fatigue, headaches, palpitations, GI symptoms, anxiety, and syncope were chosen for analysis as they corresponded to symptoms reported elsewhere (17).

Statistical Analysis

Descriptive analyses including mean, median, and range were performed for each variable. Two sets of analyses were performed. Based on a null hypothesis that there was no correlation between sweat volumes at each site and other variables, Spearman correlation coefficients were calculated for the sweat volume at each site for each variable. Spearman's rank correlation test was performed using sweat volumes for each site.

The second hypothesis was that there was a significant difference between "hyperadrenergic"(standing norepinphrine greater than 600 pg/ml) and non-hyperadrenergic POTS patients. Patients were grouped based on catecholamine results and Wilcoxan Rank-Sum test was used to compare variables between the two groups. Because of the large number of variables analyzed, a p value of 0.01 was used to denote significance to correct for multiple comparisons. The SAS program was used to perform all statistical analyses (SAS Institute).

Results

Clinical Characteristics

All patients were white, non-hispanic with a mean age of 35 (range 20–58) and average BMI was 24 (range 18–41) (Table 1). Most patients experienced symptoms for years before diagnosis and evaluation (median 3.5). One patient had signs and symptoms of peripheral neuropathy on examination, otherwise neurological examination was normal. Six patients out of 28 with detailed medical histories recalled an antecedent injury or illness. Two of the six noted symptoms started after pregnancy or miscarriage.

There were no significant differences in age or body-mass index (BMI) between subjects with or without abnormal QSARTS. Thirteen women had a normal QSART, mean age 33 (20–58), mean bmi 25 (19– 29). Seventeen women had an abnormal QSART, mean age 39 ± 11, bmi 22.7 (18–41). Age was the only variable which was significantly different when comparing patients with hyperadrenergic POTS [11] and non-hyperadrenergic POTS [19] (table 2). Older patients were more likely to be hyperadrenergic (p=.0003). There were no significant differences between hyperadrenergic and non-hyperadrenergic POTS patients for typical symptoms such as dizziness, racing heart rate, headaches, anxiety, fainting, and

fatigue. Symptoms were considered significant if patient reported them to occur at least on a weekly basis. Palpitations, dizziness, syncope and fatigue were the most common symptoms reported (73%, 73%, 66%, and 66% respectively) followed by GI symptoms (41%). More non-hyperadrenergic POTS patients had gastrointestinal symptoms such as constipation, diarrhea, bloating (36% vs. 6%), this was not statistically significant (p=0.06). Headache or migraine symptoms were reported by 50% of patients. Anxiety was reported by 30% of patients.

QSART results

Sweat volumes obtained at the four standard sites were: forearm, mean 0.69 μl (range 0.04–2.22 μl); proximal leg 0.57 μl (0.02–1.7 μl); distal leg 0.60 μl (0.04–2.8 μl); and foot 0.38 (0.02–1.4 μl). 17 patients had abnormal QSART results (57%). The foot and proximal leg sites were the most likely to be abnormal, followed by the distal leg site. The forearm site was abnormal in only 3 patients. Patients with an abnormal QSART typically had only one or two sites abnormal. Only four patients had a severe deficit with 3 or more sites abnormal, although no patient had complete loss of sweat such as that seen in pure autonomic failure. When comparing each site, the foot response was the most dissimilar in POTS patients with abnormal QSART results compared to POTS patients with normal QSART (0.31 μL compared to 0.65 μl in patients with normal sudomotor function, p=0.03). The forearm sweat volumes were similar in both groups (0.86 μl in normal POTS vs. 0.82 μl in POTS patients with abnormal QSART). The most common pattern seen if there was more than one site decreased was patchy, with either proximal leg and distal leg, or proximal leg and foot sites decreased in volume.

Autonomic function test results

Autonomic function test results demonstrated significant tachycardia upon standing (mean 37, maximum 75 bpm difference between supine and standing for 30 minutes). There was no correlation between sweat volumes and autonomic function test parameters. There were no differences in autonomic test results in POTS patients with and without elevated standing norepinephrine.

Catecholamine Results

One patient did not have catecholamine levels drawn. Seventeen patients had standing norepinephrine levels of 600 pg/mL or greater. Change in DHPG after standing was also significantly different (p=0.01) between the hyperadrenergic and normal POTS groups. Two patients with two abnormal sweat responses had an elevated standing norepinephrine level, the patient with three abnormal sites did not. There was no correlation between QSART and any of the catecholamine results.

Heart Rate Variability Results

Patients had a mean resting heart rate of 76 bpm (standard deviation 12.8). Mean standard deviation of the RRI (RR interval) was 50.4 ms (range 16–128). The mean total power was 2190 ms^2 (189–11,426 ms^2). Both low frequency (LF) and high frequency (HF) mean power of RRI was significantly lower than normal published values (18). (LF (non-respiratory frequency) power of RRI was 750 ms^2 (98–2889 ms^2). HF (respiratory frequency) power of RRI was 556.3 ms^2 (33–4103 ms^2). Resting LF/HF ratio was 2.54 (0.49–7.02) which is higher than normal, similar to that reported previously (19). There was no significant difference in LF, HF power or LF/HF ratio between patients with normal and abnormal QSART testing or patients with normal or elevated norepinephrine levels.

Discussion

The results of this study in addition to previous data (20–23) confirm that although sudomotor responses have been used to support a distal autonomic neuropathy as a cause of POTS, they do not correlate with other cardiac autonomic function tests, spectral analysis of heart rate variability and blood pressure, or plasma catecholamine levels. Sudomotor results do not appear to have any significant correlation with symptom measurements.

QSART specifically measures integrity of postganglionic cholinergic sudomotor fibers. In a distal predominant autonomic neuropathy, it is conceivable that central cardiac autonomic and baroreflexes are relatively spared compared to peripheral fibers. Previous studies have demonstrated a decrease in norepinephrine in the leg compared to arm (24). However, evaluation of muscle sympathetic nerve traffic show increased frequency of firing in response to head up tilt or Valsalva maneuver, in POTS patients compared to controls without increase in mean burst area in addition to increased vascular resistance suggesting increased sympathetic outflow (25–28). Analysis of peripheral somatic C-fibers in a small group of POTS patients with abnormal QSART revealed normal intra-epidermal nerve fiber density measurements (29;30) suggesting that POTS may be selective for autonomic fibers; however these findings have not been replicated in a larger population.

The lower extremity sweat responses, especially in the foot are significantly lower than the forearm in POTS patients. However, the pattern is not the typical length-dependent pattern seen in “dying-back” axonal neuropathies and but rather is patchy in distribution. Only one patient had significant loss of sweat at 3 sites and none had complete loss of sweating, the pattern observed in patients with pure autonomic failure. This finding is less suggestive of a distal predominant polyneuropathy primarily affecting sudomotor nerves, but rather suggests an inflammatory etiology. About 50% of patients describe an acute “viral” illness preceding their symptoms, which suggest a post-infectious etiology. A consistent infectious cause has not been described in this population (31;32). In our population, only 6 patients (out of 28 patients with detailed medical histories) specifically recalled an injury or illness preceding their symptoms which is less than that previously described.

This study suggests that endophenotyping based on only one type of autonomic testing may be inappropriate at this time. We did not find any differences in “hyperadrenergic” POTS vs. non-hyperadrenergic” POTS patients in regards to sweat output, symptoms, length of symptoms, autonomic testing, or heart rate and blood pressure variabilities. There were no significant differences between patients with abnormal QSART testing and normal QSART testing. It is possible that our negative findings may be secondary to the small sample size but our results are consistent with larger studies.

One limitation of our study is that despite the extensive testing that was performed, numerous other “peripheral” autonomic tests were left unperformed including whole body or segmental norepinephrine spillover, skin biopsy, peripheral blood flow, and microneurography which may correlate better with QSART than the “cardiac” autonomic tests that were performed. Thermoregulatory sweat testing showed distal, patchy anhidrosis in a small group of patients (6 of 8 POTS patients studied), but could be used to confirm distal sudomotor abnormalities (33).

Age was the only significant variable found in this analysis. It is interesting that older patients were more likely to have significantly higher catecholamine levels than younger patients. This may suggest that greater catecholamine secretion is required to maintain blood pressure with postural standing in older patients with POTS. However, given that plasma catecholamine levels rise with age, this is most likely not a pathologic association (34).

In conclusion, sudomotor abnormalities are frequent in POTS and these abnormalities have a distinct pattern that is unlike that of multiple system atrophy, pure autonomic failure, peripheral neuropathies or other common causes of sudomotor dysfunction. The significance of these findings at the present time is unknown. It is unclear whether these correlate specifically with any of the previously described subtypes of POTS. Further work is needed in order to determine the optimal methods for endophenotyping patients with postural tachycardia syndrome.

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Table 1

Clinical Characteristics of POTS Patients

Measurements	Mean	SD	Range
Age	35	9.7	20–58
Body mass index (kg/m^2)	24.0	5.9	18–41.4
Symptom onset (years)	5.3	5.6	1–30
*Dizziness	4.7	.5	4–5
*Fatigue	4.7	.8	2–5
*GI	3.8	1.3	1–5
*Syncope	2.1	1.1	1–5
*Palpitations	4.5	.9	1–5
*Migraine	3.8	.9	1–5
*Anxiety	3.2	1.6	1–5

*Reported on a 1–5 scale, 1,Never; 2, <1=month;3, 2–4 times a month; 4, 5–7 times a month; 5 daily

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Table 2

Spearman Correlations Between QSART Volumes and Autonomic Test Results

	Spearman Correlations to Sweat Volume in Microliters				P-values			
	Forearm	**Proximal Leg**	**Distal Leg**	**Foot**	**Forearm**	**Proximal Leg**	**Distal Leg**	**Foot**
Age	−0.09	−.01	−.08	−.10	0.67	0.54	0.67	0.60
BMI	−0.02	−0.20	−0.29	−0.24	0.92	0.28	0.12	0.20
Symptom onset	0.22	0.16	0.07	−.02	0.23	0.40	0.71	0.91
Supine Norepinephrine	−0.12	−0.19	−0.35	−0.28	0.51	0.33	0.66	0.14
Upright Norepinephrine	0.08	−0.08	−0.04	−0.08	0.66	0.66	0.83	0.66
Change in heart rate on standing	0.32	0.09	0.03	−0.06	0.09	0.66	0.89	0.76
*Change in SBP with Handgrip	0.23	0.14	−0.09	−0.01	0.23	0.45	0.65	0.95
*Change in SBP with Cold pressor	−0.05	−0.26	−0.25	−0.16	0.79	0.16	0.19	0.41
Mean RRI	0.11	0.17	0.10	−0.08	0.57	0.37	0.62	0.69
Normalized low frequency power	0.25	−0.06	0.04	−0.07	0.21	0.78	0.84	0.86
Normalized high frequency	−0.37	−0.01	−0.02	0.06	0.05	0.97	0.92	0.74
LF/HF ratio	0.24	−0.06	0.04	−0.03	0.22	0.79	0.84	0.86

*SBP: Systolic blood pressure

Table 3

Comparison of Measures for POTS patients with elevated norepinephrine vs. Non-Hyperadrenergic POTS

	Normal POTS (10)		Hyper POTS (19)		p-value
Variable	**Mean**	**Range**	**Mean**	**Range**	
Age	26.8	20–32	40.8	29–58	0.0003†
BMI	22.0	18.5–29.4	25.5	18.4–41.4	0.22
Symptom onset (years)	4.8	1–11	5.8	1–30	0.75
Supine Norepinephrine (pg/ml)	140	95–272	396	120–1525	0.0009†
Upright Norepinephrine (pg/ml)	387	129–596	1175	611–2139	0.0000†
*Change in heart rate on standing (bpm)	43.2	18–75	38.6	15–75	0.83
**Change in SBP with Handgrip (mm Hg)	12.8	1–34	11.8	0–53	0.37
**Change in SBP with Cold pressor (mm Hg)	24.7	8–42	18.8	0–41	0.2
Mean RRI (ms)	789.7	559.8–1062	752.1	610–1008	0.56
Normalized low frequency power (ms^2)	63	35–75	64.5	33-86-7	0.86
Normalized high frequency (ms^2)	22.3	7.4–35.9	20.7	1.4–48.8	0.55
LF/HF ratio	2.5	0.5–7.0	2.5	0.5–6.5	0.85

*All patient required heart rate increase on at least two occasions to be greater than 30 bpm when standing. Two patients on formal testing had heart rate increases less than 30 on day of testing.

**SBP: Systolic blood pressure

†Significant at $p<0.01$