A Prospective, 1-Year Follow-up Study of Postural Tachycardia Syndrome

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Abstract

Objective: To prospectively evaluate patients who met standard criteria for postural tachycardia syndrome (POTS), at baseline and 1-year follow-up, using standard clinical and laboratory methods to assess autonomic function.

Methods: Fifty-eight patients met the study criteria (orthostatic symptoms and a heart rate increment of ≥ 30 beats/min on head-up tilt) and completed 12 months of follow-up. All patients were enrolled and completed the study from January 16, 2006, through April 15, 2009. Patients underwent standardized autonomic testing, including head-up tilt, clinical assessment, and validated questionnaires designed to determine the severity of autonomic symptoms.

Results: Patients were predominantly young females ($n=49$, 84%), with 20 patients (34%) reporting an antecedent viral infection before onset of symptoms. More than one-third (37%) no longer fulfilled tilt criteria for POTS on follow-up, although heart rate increment on head-up tilt did not differ significantly at 1 year (33.8 ± 15.1 beats/min) compared with baseline (37.8 ± 14.6 beats/min) for the entire cohort. Orthostatic symptoms improved in most patients. Autonomic dysfunction was mild as defined by a Composite Autonomic Severity Score of 3 or less in 55 patients (95%) at baseline and 48 patients (92%) at 1 year.

Conclusion: To our knowledge, this is the first prospective study of the clinical outcomes of patients with POTS. Orthostatic symptoms improved in our patients, with more than one-third of patients no longer fulfilling tilt criteria for POTS, although the overall group change in heart rate increment was modest. Our data are in keeping with a relatively favorable prognosis in most patients with POTS.

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Postural tachycardia syndrome (POTS) is defined by symptoms of orthostatic intolerance associated with heart rate increments greater than 30 beats/min on head-up tilt (HUT), with the more severe cases reaching standing heart rates of greater than 120 beats/min.¹ Symptoms related to orthostatic changes most often include light-headedness, palpitations, presyncope, and symptom exacerbations caused by heat or exercise.² The disorder begins primarily between 15 and 50 years of age (with a mean age at onset of 30 years) and is characterized by a strong female predominance.¹⁻⁵

The pathophysiologic and etiologic mechanisms of POTS are heterogeneous in nature. Several important subtypes of primary POTS have been described. Neuropathic POTS describes a subgroup with length-dependent denervation of sympathetic fibers in the lower extremity.⁶ In keeping with this denervation, these patients have impaired norepinephrine spillover, resulting in isolation to the legs.³ Approximately half of patients diagnosed as having primary POTS manifest this restricted autonomic neuropathy pattern.^{2,7} A second hyperadrenergic subtype has been defined by increased systolic blood pressure during HUT (≥ 10 mm Hg) and an elevated

plasma norepinephrine level (≥ 600 pg/mL [to convert to pmol/L, multiply by 5.911]).⁸ These patients have episodes of tachycardia and hypertension associated with prominent symptoms of anxiety, sweatiness, tremulousness, and palpitations related to sympathetic overactivation.⁴ Other mechanisms, including but not limited to excessive venous pooling, hypovolemia, and deconditioning, have been implicated in POTS and are described in more detail elsewhere.⁹

The prognosis of patients with POTS is favorable on the basis of prior retrospective studies, which found that 80% of patients improved and 60% had minimal residual symptoms during approximately 5 years.⁷ To our knowledge, no current prospective studies have dealt with the prognosis of patients with POTS. Data regarding the prognosis of patients with POTS are limited to retrospective evaluations.^{2,7} Therefore, a prospective, longitudinal study was undertaken with the following objectives. The first objective was to determine how autonomic parameters as measured by standardized autonomic testing can change from baseline to 1-year follow-up in patients with POTS. The second objective was to determine, using standardized clinical instruments and questionnaires, how the clinical features of

POTS can evolve over time from baseline evaluations to 1-year follow-up.

METHODS

Study Patients

Study patients needed to meet all 3 of the following criteria to be enrolled in the study: (1) males or females 13 to 50 years of age, (2) orthostatic heart rate increment of 30 beats/min within 5 minutes of HUT, and (3) symptoms of orthostatic intolerance, including weakness, light-headedness, blurred vision, nausea, palpitations, and difficulty with concentration and thinking for a period of greater than 3 months. The Mayo Clinic Institutional Review Board approved this study. All patients were enrolled and completed the study from January 16, 2006, through April 15, 2009.

Patients with one or more of the following exclusion criteria were eliminated from study: (1) pregnant or lactating females; (2) the presence of another cause of autonomic failure; (3) the presence of systemic illness or failure of other organ systems affecting the autonomic nervous system or the patient's ability to participate in the study, including but not limited to renal or hepatic disease, dementia, pheochromocytoma, severe alcoholism, anemia, malignant neoplasms, heart failure, hypertension, sympathectomy, hypothyroidism, or cerebrovascular accidents; (4) concomitant therapy with anticholinergic agents, α - and β -adrenergic antagonists, or other medication that could not be withheld before testing and could alter autonomic function; and (5) clinically significant coronary artery disease.

Autonomic Testing

Standardized testing of the autonomic nervous system was performed as previously described.^{10,11} The quantitative sudomotor axon reflex test evaluates postganglionic sympathetic sudomotor axon function. Sweat responses are obtained from the forearm, proximal aspect of the leg, distal aspect of the leg, and foot. Results were compared with normative data taken from studies on 223 healthy individuals aged 10 to 83 years.¹² Heart rate response to deep breathing and Valsalva ratio were used to assess cardiovagal function. The data were compared with normative results taken from 157 healthy individuals aged 10 to 83 years.¹² Cardiovascular adrenergic function was evaluated by measuring blood pressure and heart rate responses to Valsalva maneuver and HUT.^{10,11} The use of medications that potentially affect autonomic function was stopped for 5 half-lives before testing.

Laboratory Testing

Supine and standing plasma norepinephrine measurement and 24-hour urine volume and sodium collection were performed using standard protocols (Mayo Clinic, Rochester, MN).

Clinical Instruments

The Composite Autonomic Severity Score (CASS) is derived from the autonomic reflex screen and has been described previously.¹³ CASS is a measure of the severity and distribution of autonomic failure and has been previously validated.¹³ The 11-point CASS is further divided into 3 subscores: sudomotor (0-3), cardiovagal (0-3), and adrenergic (0-4). Each of the 3 subscores and the overall score are normalized for the confounding variables of age and sex.¹²

The Autonomic Symptom Profile is a validated self-report instrument designed to provide a measure of autonomic symptom severity.¹⁴ It yields a Composite Autonomic Symptom Score (COMPASS) that reflects overall severity of autonomic symptoms and 10 subscale scores that assess severity of symptoms within the following domains: orthostatic intolerance, gastroparesis, bladder dysfunction, secretomotor dysfunction, sexual failure, diarrhea, sleep disorder, constipation, vasomotor symptoms, and pupillomotor symptoms. The COMPASS Change Score is derived from a self-completed questionnaire on the basis of selected COMPASS domains to assess the change in autonomic symptoms over time, including orthostatic, secretomotor, male sexual dysfunction, urinary, gastrointestinal, pupillomotor, vasomotor, and sleep function, with a maximum score of 190 for women and 200 for men (10 points are added for male sexual dysfunction). A positive score indicates worsening and a negative score improvement of autonomic symptoms.

Statistical Analyses

Descriptive statistics are presented as mean $\pm$ SD. Paired data were analyzed using the Wilcoxon signed rank test to determine significant differences between 2 continuous variables. The χ^2 test and Spearman ρ test were used to determine significant correlation among variables. $P < .05$ was considered statistically significant. SPSS statistical software, version 15 for Windows (SPSS Inc, Chicago, IL), was used for all statistical analyses.

RESULTS

Patient Characteristics

Fifty-eight patients met the criteria for POTS, were enrolled in the current study, and completed 1 year of follow-up. Fifty-four patients were followed up at

1 year. The remaining patients completed their forms but did not return for the follow-up visit. One patient was pregnant. Most patients were female (49) and young (27.4 ± 10.9 years of age). Patients were symptomatic with the disorder for a mean of 3.4 years, 14 (24%) of patients had a history of remote orthostatic intolerance or syncope before the onset of persistent symptoms, and 4 (7%) of patients had a family history of orthostatic intolerance. The onset of symptoms was acute (maximal in <1 month), subacute (maximal in 1-3 months), and insidious (maximal in >3 months) in 20 (34%), 14 (24%), and 29 (34%) of patients, respectively. A total of 20 (35%) of patients reported an antecedent viral infection before symptoms. Patient characteristics are presented in Table 1.

Patients were counseled on optimal conservative measures to treat their orthostatic symptoms at baseline assessment and re-reviewed at the 1-year follow-up. Specific recommendations included appropriate fluid hydration, reasonable sodium intake, compression garments, exercise regimens, and safety issues related to orthostasis. Twenty (35%) patients were taking β -blockers at baseline (metoprolol was used most, followed by propranolol, atenolol, and nadolol) and 28 (54%) at 1 year. Ten (17%) patients took midodrine at baseline and 11 (21%) at 1 year. Fourteen (24%) took fludrocortisone at baseline and 8 (15%) at 1 year. One (2%) took pyridostigmine at baseline and 8 (15%) at 1 year. The dosages were not significantly different at 1 year when compared with those at baseline.

Autonomic Symptoms Profile

As expected on the basis of the inclusion criteria, the major autonomic symptom reported by patients was orthostatic intolerance. On the basis of COMPASS at baseline (30.2 ± 7.1 ; $n=53$) and COMPASS Change Score at follow-up (-14.4 ± 30.8 ; $n=56$), a clinically significant improvement was seen in orthostatic intolerance during the follow-up period (Table 2); 39 (70%) underwent an improvement and only 17 (30%) experienced worsening. The remainder of autonomic domains studied, including syncope, vasomotor, secretomotor, gastrointestinal, diarrhea, constipation, neurogenic bladder, pupillomotor, and sleep, produced minimal involvement and modest change (Table 2).

Clinical Autonomic Testing

Heart rate increment during HUT at baseline (37.8 ± 14.6 beats/min) did not significantly differ from that at 1-year follow-up (33.8 ± 15.1 beats/min) ($P=.12$; Figure). However, 20 (38%) of the patients no longer fulfilled criteria for POTS. Auto-

TABLE 1. Characteristics of the 58 Study Patients (49 Females and 9 Males)^a

Characteristic	Finding
Age (y), mean $\pm$ SD	
All patients	27.4 $\pm$ 10.9
Female	27.8 $\pm$ 10.7
Male	25.3 $\pm$ 12.3
Symptom duration (mo), mean $\pm$ SD	
All patients	41.0 $\pm$ 52.8
Female	43.8 $\pm$ 56.9
Male	26.0 $\pm$ 14.6
History of orthostasis	
Yes	14 (24)
No	40 (69)
Unknown	4 (7)
Family history of orthostasis	
Yes	4 (7)
No	50 (86)
Unknown	4 (7)
Symptom onset	
Acute (<1 mo)	20 (34)
Subacute (1-3 mo)	14 (24)
Insidious (>3 mo)	20 (34)
Unknown	4 (7)
History of preceding illness	
Yes	27 (47)
No	29 (50)
Unknown	2 (3)
Preceding illness type	
Viral, gastrointestinal	5 (9)
Viral, upper respiratory tract infection	10 (17)
Viral, unspecified	5 (9)
Postoperative	1 (2)
Other	7 (12)
Unknown	30 (52)

^a Data are presented as No. (percentage) unless indicated otherwise.

autonomic dysfunction was mild at both baseline and follow-up with CASS of 3 or lower in 55 patients (95%) and 48 patients (92%), respectively (Table 3). This mild autonomic impairment was characterized by sudomotor denervation in the lower limbs (CASS sudomotor subscore ≥ 1 : baseline, 18 [31%]; follow-up, 19 [36%]) and mild peripheral adrenergic dysfunction (CASS adrenergic subscore ≥ 1 : baseline, 12 [21%]; follow-up, 14 [27%]; Table 3). Cardiovascular parasympathetic dysfunction (CASS cardiovascular subscore ≥ 1) was minimal at baseline (4 [8%]) and follow-up (2 [4%]) (Tables 3 and 4).

TABLE 2. Selected Autonomic Symptoms at Baseline and 1-Year Follow-up^a

Symptom	Baseline COMPASS			1-Year COMPASS Change Score		
	Score	No. of patients	Overall range	Score	No. of patients	Overall range
Orthostatic intolerance	30.2±7.1	53	0-40	-14.4±30.8	56	-60 to 60
Syncope	1.4±2.2	53	0-20	NA	56	NA
Vasomotor	4.1±3.3	55	0-10	0.4±3.3	56	-10 to 10
Secretomotor	5.8±3.6	55	0-20	1.7±8.3	56	-25 to 25
Gastrointestinal	2.2±2.3	55	0-10	0.4±3.9	56	-10 to 10
Diarrhea	4.3±4.9	55	0-20	0.5±3.5	56	-10 to 10
Constipation	1.7±2.5	55	0-10	0.3±2.9	56	-10 to 10
Neurogenic bladder	1.8±2.8	55	0-20	1.2±3.4	56	-30 to 30
Pupillomotor	1.9±1.4	55	0-5	0.4±3.0	56	-10 to 10
Sleep	2.1±2.2	53	0-15	0.5±5.5	56	-25 to 25
Total	54.5±16.8	51	0-170	-9.2±42.5	56	-190 to 190

^aThe degree of autonomic dysfunction is indicated by higher values on the Autonomic Symptom Profile at baseline and the follow-up evaluation using Composite Autonomic Symptom Score (COMPASS) Change Score at 1 year. The overall range for each domain is indicated. The apparent discrepancies in the number of patients reflect domains that were omitted or incompletely filled out by the participant. COMPASS (ie, total) includes 10 domains (excludes male sexual function questions). COMPASS Change Score (ie, total) includes 9 domains (excludes male sexual function questions). NA = not applicable.

Postural plasma norepinephrine levels were measured at baseline and follow-up. A total of 11 patients (20%; n=55) at baseline and 2 patients at follow-up (6%; n=35) had standing norepinephrine levels greater than 600 pg/mL, which is compatible with a hyperadrenergic state (Table 4). No significant association was found between peripheral sudomotor denervation (defined as a CASS su-

domotor subscore of ≥ 1) and standing norepinephrine levels of 600 pg/mL or higher ($P=.25$, χ^2 test). However, heart rate increment with HUT was positively correlated with a standing norepinephrine level of 600 pg/mL or greater ($P=.03$, Spearman test ρ).

Urinary sodium excretion was measured using 24-hour urine collection. A total of 18 patients (38%; n=48) at baseline and 12 patients (27%; n=45) at follow-up had a 24-hour sodium excretion of less than 100 mEq, possibly compatible with a hypovolemic state (Table 4).¹⁵ No significant association was found between 24-hour sodium excretion and standing norepinephrine levels ($P=.26$, χ^2 test).

DISCUSSION

The main findings of our study were that overall symptoms and functional status (Autonomic Symptom Profile averaged over time) improved and 20 (38%) no longer met orthostatic heart rate criteria for POTS. Other key points are as follows. First, our cohort of patients with POTS consisted of predominantly young females with a variable onset of symptoms, with approximately one-third reporting an antecedent viral infection before the onset of symptoms. Second, heart rate increment on HUT for the entire cohort did not significantly differ during the 1-year follow-up period, presumably reflecting heterogeneity of responses. Third, the autonomic dysfunction in these patients was mild (total CASS ≤ 3) at baseline and at the 1-year follow-up period.

FIGURE. Comparison of heart rate increment on head-up tilt at baseline and 1-year follow-up. Heart rate increment during head-up tilt did not significantly differ at baseline vs the follow-up period (2-related sample Wilcoxon signed rank test, $P=.12$). Heart rate increment was obtained as the maximum increase with tilt during a 5-minute period.

TABLE 3. Autonomic Dysfunction on Clinical Autonomic Testing at Baseline and 1-Year Follow-up^a

Test score	No. (%) of patients		P value
	Baseline (N=58)	1 Year (N=52)	
CASS (sudomotor)			.07
0	40 (69)	33 (64)	
1	10 (17)	10 (19)	
≥2	8 (14)	9 (17)	
CASS (cardiovagal)			>.99
0	54 (93)	50 (96)	
1	2 (3)	1 (2)	
≥2	2 (3)	1 (2)	
CASS (adrenergic)			.24
0	46 (79)	38 (73)	
1	8 (14)	9 (17)	
≥2	4 (7)	5 (10)	
CASS (total)			.07
0	35 (60)	27 (52)	
1	6 (10)	9 (17)	
2	10 (17)	6 (12)	
3	4 (7)	6 (12)	
4	3 (5)	3 (6)	
7	0 (0)	1 (2)	

^aP values for Composite Autonomic Severity Score (CASS) comparisons (ie, baseline and 1-year follow-up) on the basis of a 2-related sample Wilcoxon signed rank test due to skewness of the data set.

Fourth, orthostatic intolerance was the most severe autonomic symptom reported in this patient group at baseline and produced significant improvement at follow-up.

The characteristics of the patients in our study were in keeping with previously published data with respect to age and sex. Specifically, our study revealed female predominance, with an approximate female-male ratio of 4:1 and a mean age of 27 years, which is comparable to previously published data.¹⁻⁵ In addition, the reported antecedent viral infection before the onset of symptoms was 20 (35%), which is comparable to the 42 (28%) previously reported.² Similarly, the baseline heart rate increment of 37.8 beats/min was in keeping with the 44.0 beats/min previously described.² The percentage of patients in our study (38%, n=18) classified as hypovolemic (sodium excretion <100 mEq/24 h) was slightly higher than in comparable studies (29%, n=30), and the percentage classified as hyperadrenergic was slightly lower (20%, n=11 vs 29%, n=27 previously reported).² However, the variation among studies was less than 10% and still indicative of similar patient populations. Overall, our patient characteristics at baseline are comparable to those in previously published data, supporting the assertion that our prospective follow-up is representative of patients with POTS in general.

It was interesting that the patients in our study reported overall improved symptoms related to their orthostatic intolerance but mean orthostatic heart rate increment remained increased. On follow-up, more than 1 in 3 patients (37%) had a heart rate increment less than 30 beats/min (no longer fulfilling criterion for POTS), so the lack of significant mean heart rate increment for the group indicates heterogeneity. The improvement in orthostatic symptoms supports improvement over time and is consistent with prior studies.^{2,7} In this cohort, POTS was rela-

TABLE 4. Summary of Autonomic and Laboratory Data^a

Variable	Baseline	1 Year	P value
HRDB (beats/min), mean ± SD ^b	24.5±8.8 (n=58)	23.3±8.9 (n=53)	.04
Valsalva ratio, mean ± SD	2.2±0.4 (n=58)	2.3±0.4 (n=53)	.49
Supine norepinephrine (pg/mL), mean (IQR)	178.3 (158) (n=55)	163.5 (127) (n=35)	.02
No. (%) of patients with supine norepinephrine >100 pg/mL	48 (87) (n=55)	28 (80) (n=35)	
Standing norepinephrine (pg/mL), mean (IQR)	437.0 (249) (n=55)	343.8 (125) (n=35)	.001
No. (%) of patients with standing norepinephrine >600 pg/mL	11 (20) (n=55)	2 (6) (n=35)	
24-Hour urine sodium (mEq/24 h), mean ± SD	122.1±67.6 (n=48)	156.3±90.0 (n=45)	.04
No. (%) of patients with urine sodium excretion <100 mEq/24 h	18 (38) (n=48)	12 (27) (n=45)	

^aIQR = interquartile range.

^bHeart rate response to deep breathing (HRDB) is expressed as the mean difference between the maximal and minimal heart rate obtained during deep breathing for 1 minute at a rate of 6 cycles per minute.

tively mild, and part of the failure to meet criteria at 1 year could relate to variability in heart rate response. In considering natural history, it is important to consider other indices. The findings that fewer patients met the criteria at 1 year, 70% had improved scores, and fewer patients had a hyperadrenergic orthostatic norepinephrine response at 1 year (compared with baseline) support the conclusion that patients underwent an overall improvement in POTS.

The degree of autonomic dysfunction in our population was mild at baseline, with only 7 (12%) of patients with a CASS of 3 or higher compared with 10 (20%) at follow-up. The degree of autonomic dysfunction by clinical testing was mild, but the predominant abnormalities exhibited were postganglionic sudomotor denervation and/or adrenergic impairment. At both baseline and follow-up, these findings were present in approximately 30 of 58 patients (52%). These results are in keeping with our previous studies of a retrospective cohort of 152 patients, which reported the same findings in at least half of these patients.² Our study continues to support our prior assertions that a large proportion of patients with POTS have a limited autonomic neuropathy. Prior studies have also reported an association among peripheral adrenergic denervation, impaired sympathetic function in the lower limbs, and excessive elevation of standing norepinephrine levels.³ We have previously reported a lack of correlation between peripheral denervation and excessive standing norepinephrine levels and again in the current study have postulated that other mechanisms, such as hypovolemia and instability in the adrenergic nervous system, may account for these findings.^{2,7} Interestingly, we found no correlation between elevated norepinephrine levels and presumed hypovolemia (on the basis of 24-hour urine output) or 24-hour sodium excretion. There was, however, a positive correlation between heart rate increment on HUT and standing norepinephrine levels. This finding could suggest that the excessive increase in standing norepinephrine levels may result from impaired baroreflex-mediated vasoconstriction on standing in patients with POTS. Although there has been some disagreement in the literature, previously published studies have reported impaired arteriolar vasoconstriction in the lower extremities with increased venous adherence.^{16,17}

All patients were treated at Mayo Clinic, Rochester, MN, and received best medical management for POTS on the basis of the individual needs. However, we did not attempt to correlate individual patient treatment regimens to their clinical outcomes. Most patients enrolled in the trial had already undergone numerous treatments, including multiple drug therapies, at outside institutions that would have complicated any attempt at this evaluation in our patients. In a prior

retrospective analysis, patients with POTS were treated with multiple medications without significant effect on their clinical outcomes. Nevertheless, therapy based on autonomic principles (eg, volume expansion, compression garments, physical countermaneuvers) and countering altered physiologic mechanisms (eg, hyperadrenergic subgroup with β -blockers) would seem reasonable.

CONCLUSION

To our knowledge, the current study is the first large cohort of patients studied in a prospective manner with respect to clinical outcomes in POTS. Our patient group revealed improvement in their orthostatic symptoms with minimal mean change in heart rate increment on HUT. The autonomic dysfunction in our patients was mild but yielded evidence of sympathetic denervation in the lower limbs and mild adrenergic dysfunction in keeping with our prior assertion that many of these patients are characterized by a limited autonomic neuropathy. The findings on clinical autonomic testing indicative of this limited autonomic neuropathy did not change during the 1-year follow-up period. However, our study indicates that patients generally improve from a symptomatic standpoint, similar to the results of prior retrospective studies on POTS. Overall, the prognosis in POTS continues to be favorable.

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Abbreviations and Acronyms: CASS = Composite Autonomic Severity Score; COMPASS = Composite Autonomic Symptom Score; HUT = head-up tilt; POTS = postural tachycardia syndrome

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