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Cardiac Origins of the Postural Orthostatic Tachycardia Syndrome

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Objectives The purpose of this study was to test the hypothesis that a small heart coupled with reduced blood volume contributes to the postural orthostatic tachycardia syndrome (POTS) and that exercise training improves this syndrome.

Background Patients with POTS have marked increases in heart rate during orthostasis. However, the underlying mechanisms are unknown and the effective therapy is uncertain.

Methods Twenty-seven POTS patients underwent autonomic function tests, cardiac magnetic resonance imaging, and blood volume measurements. Twenty-five of them participated in a 3-month specially designed exercise training program with 19 completing the program; these patients were re-evaluated after training. Results were compared with those of 16 healthy controls.

Results Upright heart rate and total peripheral resistance were greater, whereas stroke volume and cardiac output were smaller in patients than in controls. Baroreflex function was similar between groups. Left ventricular mass (median [25th, 75th percentiles], 1.26 g/kg [1.12, 1.37 g/kg] vs. 1.45 g/kg [1.34, 1.57 g/kg]; $p < 0.01$) and blood volume (60 ml/kg [54, 64 ml/kg] vs. 71 ml/kg [65, 78 ml/kg]; $p < 0.01$) were smaller in patients than in controls. Exercise training increased left ventricular mass and blood volume by approximately 12% and approximately 7% and decreased upright heart rate by 9 beats/min [1, 17 beats/min]. Ten of 19 patients no longer met POTS criteria after training, whereas patient quality of life assessed by the 36-item Short-Form Health Survey was improved in all patients after training.

Conclusions Autonomic function was intact in POTS patients. The marked tachycardia during orthostasis was attributable to a small heart coupled with reduced blood volume. Exercise training improved or even cured this syndrome in most patients. It seems reasonable to offer POTS a new name based on its underlying pathophysiology, the "Grinch syndrome," because in this famous children's book by Dr. Seuss, the main character had a heart that was "two sizes too small." (J Am Coll Cardiol 2010;55:2858–68) © 2010 by the American College of Cardiology Foundation

Young women are more susceptible to orthostatic intolerance than similarly aged men (1–3), and this sex difference is more dramatic in the postural orthostatic tachycardia syndrome (POTS) (also called *chronic orthostatic intolerance*), in which patients are unable to stand or remain upright for prolonged periods because of intolerable light headedness, weakness, and near syncope. This disorder affects more than 500,000 Americans (3), the vast majority of whom are pre-menopausal women. Severely affected patients are unable to work, to attend school, or to participate in recreational activities, resulting in substantial morbidity. However, the underlying mechanisms remain unknown and the effective therapy is uncertain.

Sex differences in orthostatic tolerance become more dramatic after spaceflight or a period of bed rest (4,5), in which deconditioning occurs. Numerous studies have shown that real or simulated microgravity exposure can elicit a POTS-like syndrome even in healthy, fit individuals. The induced tachycardia during orthostasis has been found to be associated with reduced stroke volume, which is attributable to cardiac atrophy and hypovolemia (6,7). Indeed, with chest roentgenographic and echocardiographic techniques, it was observed that the heart was much smaller in patients with chronic fatigue syndrome, a condition with substantial

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overlap with POTS, than in healthy controls (8). Decreases in blood volume also have been reported in many POTS patients (9,10). In addition, most of these patients have significant limitations to even low-intensity physical activity (11–13). Based on these observations, we speculated that POTS per se may be a consequence or signature of deconditioning, namely, cardiac atrophy and hypovolemia. However, this speculation needs to be verified.

Clarifying the pathophysiologic features of POTS is essential for determining optimal evidence-based therapy, particularly because many of these patients have disabling side effects with drug treatment. One nondrug therapy that has shown some promise is exercise training. For example, increased orthostatic tolerance after mild to moderate exercise training was reported in patients with unexplained syncope or orthostatic hypotension (14,15). Physical exercise training has been shown to increase plasma and blood volume (16). However, its effect on orthostatic tolerance in healthy individuals is controversial (17–19). Whether exercise training can be regarded as an effective therapy for patients with POTS needs to be determined. The primary objective of this study was to test the hypothesis that POTS would be attributable to a small heart coupled with reduced blood volume (i.e., deconditioning) and that exercise training could improve or even cure this syndrome by targeting the underlying pathophysiology.

Methods

Study population. The patient population consisted of 54 consecutive patients referred to our tertiary Autonomic Function Clinic between December 2004 and April 2008. Eight patients declined to participate immediately after we contacted them because they were not interested in participating in research. Forty-six patients were screened; 18 of them declined because they were not willing to be without medications for several months and to undergo all the comprehensive assessments before treatment. Twenty-eight patients (27 women, 1 man) eventually were enrolled in the study. The severity of POTS was not different between those who declined participation and those who were enrolled in the study. Among these 28 patients, 1 was diagnosed with Ehlers Danlos syndrome after baseline evaluations and thereafter was excluded from the study, because this syndrome may affect cardiac size and function (20). All patients met the inclusion without exclusion criteria for POTS (12) and had a heart rate (HR) rise of ≥30 beats/min or a rate that exceeded 120 beats/min that occurred after 10 min of standing without any evidence of orthostatic hypotension (9). Approximately 55% of them had mild POTS (i.e., an increase in HR ≤35 beats/min), whereas 45% had moderate to severe POTS (i.e., an increase in HR >35 beats/min). Most patients had been treated at some point with standard medications such as beta-blockers, volume expanders, and alpha$_1$-adrenergic agonists. Patients had stopped taking medications that could affect the autonomic nervous system 2 weeks or more before screening and testing.

Abbreviations and Acronyms

BP = blood pressure
HR = heart rate
MRI = magnetic resonance imaging
MSNA = muscle sympathetic nerve activity
POTS = postural orthostatic tachycardia syndrome

Healthy controls were recruited from the Dallas-Fort Worth area. Approved flyers were posted in an advertisement format in locations such as local recreational centers, churches, grocery stores, colleges, and shopping centers. Potential subjects were asked to contact our recruiting staff to inquire about the study. Our experienced recruiting nurse performed initial telephone screening. If they did not have any exclusion criteria and seemed to have a sincere interest after explanation of the study purpose and requirements, they were invited to our laboratory for a formal screening. Sixteen healthy controls (15 women, 1 man) eventually were enrolled. Matching of groups was used in this study with the goal for the patient group and the control group to be comparable with regard to demographics and confounders; the groups had approximately the same mean age, sex, height, weight, and body mass index.

All participants were nonsmokers. None was an endurance-trained athlete (19,21). All were screened with a careful medical history, physical examination, 12-lead electrocardiogram, and a 10-min stand test. All participants were informed of the purpose and procedures used in the study and gave their written informed consent to a protocol approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas.

Study design. BASELINE ASSESSMENTS. All participants completed baseline evaluations, which included: 1) autonomic function tests and blood volume measurements; 2) neurohumoral regulation during 2-h standing (data to be reported elsewhere); and 3) cardiac magnetic resonance imaging (MRI) assessments. Ten female POTS patients and 11 healthy women who had normal menstrual cycles and were not taking or had not been taking oral contraceptives for 6 months or more were studied twice, once during the early follicular phase (when both estrogen and progesterone are low) and once during the mid-luteal phase (when both sex hormones are high), with the order counterbalanced. Patients then were assigned randomly to a beta-blocker versus placebo drug intervention trial before participation in exercise training (22). For the sake of simplicity, the beta-blocker trial and the effect of the menstrual cycle data will be reported separately.

SHORT-TERM EXERCISE TRAINING. Twenty-five patients (24 women, 1 man) participated in an optimized exercise training program for 3 months with 19 completing the program, and these patients were evaluated again after exercise training during the mid-luteal phase of the menstrual cycle. Because of the complexity of the overall study design, we only report here data obtained from baseline

assessments in all participants and after exercise training in POTS patients in this paper.

Autonomic function tests. All participants were provided with an isocaloric constant diet consisting of 200 mEq sodium, 100 mEq potassium, and 1,000 mg calcium, and fluid intake was ad libitum 2 days before testing. Women were tested during the mid-luteal phase (i.e., 19 to 22 days after the onset of menstruation) of their menstrual cycles. They took a pregnancy test and showed negative results on the testing day.

The experiments were performed in the morning 2 h or more after a light breakfast, and 48 h or more after the last caffeinated or alcoholic beverage in a quiet, environmentally controlled laboratory with an ambient temperature of approximately 25°C. An intravenous catheter was inserted into an antecubital vein of the nondominant arm, and a small recording electrode was placed in the peroneal nerve at the popliteal fossa for obtaining muscle sympathetic nerve activity (MSNA) signals (23). After 30 min or more of quiet rest in the supine position, baseline data were collected for 6 min. After that, a Valsalva maneuver (40 mm Hg, 20 s) was performed, followed by a cold pressor test for 2 min and static handgrip sustained to fatigue at 40% maximal voluntary contraction force (dominant arm), with 2 min of post-exercise circulatory arrest. After a sufficient recovery, the subject was tilted passively to 30° upright for 6 min and 60° upright for 45 min or until pre-syncope.

HR (electrocardiogram), blood pressure (BP) (Portapres, Finapres Medical Systems BV, Amsterdam, the Netherlands), MSNA (microneurography) (23), and respiratory rate (nasal cannula) were recorded continuously. Arm BP (SunTech, Jiangsu Province, People's Republic of China) was measured intermittently for the calculation of steady-state hemodynamics. Cardiac output (acetylene rebreathing) (24) was measured supine, at the end of 30° tilt, and after 5, 10, 20, 30, and 40 min of 60° tilt. Both stroke volume and total peripheral resistance were calculated (1,25). Blood samples were obtained in the supine position and after 5 and 20 min of 60° tilt. The subject was returned to the supine position for recovery either after completing 45 min of tilting or the development of pre-syncope. Blood volume was measured by a modified carbon monoxide rebreathing technique (26,27), with a typical error (expressed as coefficient of variation) of 4% to 5% in our laboratory.

Cardiac MRI. Cardiac MRI was acquired by a 1.5-T MRI scanner. After completing the standard imaging protocol for the assessment of mass and volume (28), gradient echo, cine long- and short-axis MRI sequences with a temporal resolution of approximately 42 ms, a repetition time of approximately 4 ms, an echo time of approximately 2 ms, and a flip angle of 55° were obtained. The heart was sectioned in 6-mm slices with a gap of 4 mm spanning from the apex to the base, and the image resolution was 256 × 256 with a 330-mm field of view. One observer who was blinded to the study read the MRI results. Short-axis slices were used for left ventricular volume and mass calculations using the MRI Analytical Software System (MEDIS, Leiden, the Netherlands). The typical error of the intraoperator variability of the manual planning of cardiac MRI in our laboratory was 1.6% for left ventricular mass and 1.3% for left ventricular end-diastolic volume assessments.

Exercise training. A modified Astrand-Saltin incremental treadmill protocol was used to determine each patient's peak exercise capacity before training. Based on the maximal steady-state HR and resting HR, 3 training zones were determined (i.e., recovery, base pace, and maximal steady state). To quantify the training stimulus, we used the method of Banister et al. (29) for the calculation of the training impulse.

Most of the training sessions, particularly during the early phases, were prescribed as base training, with the target HR equivalent to approximately 75% to 85% of maximal. Initially, patients trained 2 to 4 times per week for 30 to 45 min/session by using a recumbent bike, rowing, or swimming. The use of only semirecumbent exercise at the beginning was a critical strategy, allowing patients to exercise while avoiding the upright posture that elicits their symptoms. As the patients became relatively fit, the duration of the base training sessions was prolonged, and subsequently sessions of increased intensity (i.e., maximal steady state) were added first once and then twice per week, and were always followed by recovery sessions. Upright exercise was added gradually as tolerated, although usually not until the second or third month. By the end of the training, patients were exercising 5 to 6 h per week, and they were encouraged to use an upright bike, to walk on the treadmill, or to jog. In addition to the endurance training, resistance training such as weight lifting was also used. Weight lifting started from once weekly, 15 to 20 min/session and gradually increased to twice weekly, 30 to 40 min/session. Additionally, patients were encouraged to increase their daily salt intake to 6 to 8 g/day and water intake to 3 to 4 l/day and to elevate the head of the bed during sleeping at night. Patients were encouraged to continue to train at the same level indefinitely after the study so as to maintain their fitness and heart health. Patient quality of life was assessed using the 36-item Short-Form Health Survey (30) before and after training.

Data analysis. Sympathetic bursts were identified by a computer program (31) and then were confirmed by a microneurographer. The integrated neurogram was normalized by assigning a value of 100 to the largest amplitude of a burst during baseline. All bursts for that trial were then normalized against that value (32). Burst areas of the integrated neurogram and systolic and diastolic pressures were measured simultaneously on a beat-to-beat basis. Total activity of the burst was defined as the burst area of the rectified and integrated neurogram. The number of bursts per minute (burst frequency), the number of bursts per 100 heart beats (burst incidence), and total activity were used as quantitative indexes.

Sympathetic baroreflex sensitivity was assessed by relating all sympathetic bursts occurring during the 20-s straining

period of the Valsalva maneuver to the maximum fall of diastolic pressure (33), and cardiovagal baroreflex sensitivity was assessed during early phase II and phase IV (34). Data were averaged for 1 min at baseline and during the cold pressor test. Data were averaged for 1 min of the initial handgrip, the last 30 s of handgrip before fatigue, the intermediate period after the initial 1 min and before the last 30 s of handgrip, and for each 1 min of post-exercise circulatory arrest. During 30° upright tilt, data were averaged from the second to the fifth min. During 60° tilt, data were averaged from the second to the fifth min, seventh to 10th min, 17th to 20th min, 26th to 29th min, 36th to 39th min, and 42nd to 45th min. Because some subjects had pre-syncope during tilting and the tilt test was terminated at different time points, we used the last stable data carry forward method for imputing missing values (35).

Statistical analysis. Data are expressed as median [25th, 75th percentiles]. Physical characteristics, baseline variables, and baroreflex sensitivity between groups were compared using the nonparametric Mann-Whitney rank-sum test. Sympathetic and cardiovascular responses during the autonomic function tests were analyzed using the Friedman repeated measures analysis of variance on ranks, and the Student-Newman-Keuls method was used post hoc for multiple comparisons within groups. A 2-way repeated measures analysis of variance was used to verify whether responses to various interventions during autonomic function tests were different between groups, and the interaction in the model was used for comparisons of group responses. In the case of a significant difference between groups, the Holm-Sidak method was used post hoc for multiple comparisons. Survival analysis with the log-rank test was used to compare time without pre-syncope during 45-min 60° tilt between groups. Effects of training on hemodynamic variables, blood volume, cardiac size and mass, and 36-item Short-Form Health Survey scores were analyzed using Wilcoxon signed-rank tests. All statistical analyses were performed with a personal computer-based analysis program (Sigma Stat, SPSS, Inc., Chicago, Illinois). A p value <0.05 was considered statistically significant.

Results

Physical characteristics. Table 1 depicts physical characteristics of POTS patients and healthy controls. Both supine and 10-min standing HR as well as changes in HR were significantly greater in patients than controls. Approximately 55% of the patients had an increase in HR of 35 beats/min or less, whereas 45% had greater increases (>35 beats/min), with 7 patients having increases of 40 beats/min or more; the largest increase in HR was 60 beats/min, and the highest standing HR was 165 beats/min. Blood and plasma volumes were reduced markedly in patients. The POTS patients had much smaller left ventricular mass compared with healthy sedentary controls.

Table 1 Subject Characteristics

Variables	POTS Patients (n = 26 Women, 1 Man)	Healthy Controls (n = 15 Women, 1 Man)
Age (yrs)	26 (21, 33)	28 (23, 35)
Height (cm)	163 (161, 172)	166 (162, 172)
Weight (kg)	64 (57, 70)	63 (56, 68)
Body mass index (kg/m^2)	23 (22, 26)	22 (21, 24)
Screening supine heart rate (beats/min)	88 (77, 93)*	72 (64, 77)
10-min stand heart rate (beats/min)	114 (108, 131)*	89 (77, 99)
Changes in heart rate (beats/min)	32 (24, 38)*	17 (10, 22)
Supine hematocrit (%)	39 (37, 40)	38 (36, 40)
Blood volume (ml/kg)	60 (54, 64)*	71 (65, 78)
Plasma volume (ml/kg)	39 (36, 43)*	49 (44, 52)
Left ventricular mass (g/kg)	1.26 (1.12, 1.37)*	1.45 (1.34, 1.57)
Left ventricular end-diastolic volume (ml/m^2)	60 (52, 65)	64 (57, 70)

Values are presented as median (25th, 75th percentiles). *$p < 0.01$ versus healthy controls.
POTS = postural orthostatic tachycardia syndrome.

Autonomic function. UPRIGHT TILT. MSNA increased at 30° and further increased at 60° tilt in all subjects (both $p < 0.01$). Total activity was significantly greater ($p = 0.04$) in patients than controls after 10 min of 60° tilt, and burst frequency followed a similar trend ($p = 0.07$) (Fig. 1). Table 2 shows hemodynamic responses during upright tilt. Systolic BP increased in patients but remained unchanged in controls, whereas diastolic BP increased in all subjects during tilting; these responses did not differ between groups. Both supine and upright HR was markedly greater in patients than in controls. Patients had smaller cardiac output and stroke volume in both supine and upright postures. Total peripheral resistance was greater in patients than controls in the supine position and during tilting. Pre-syncope developed in 14 (52%) of 27 patients and 6 (38%) of 16 controls during the 45-min 60° tilting, but the time to pre-syncope was not significantly different between groups ($p = 0.31$, log-rank test).

VALSALVA MANEUVER. Sympathetic baroreflex sensitivity, as assessed by relating all sympathetic bursts occurring during the 20-s straining period of the Valsalva maneuver to the maximum fall in diastolic pressure, did not differ between patients and controls (−0.75 bursts/20 s/mm Hg [−1.05, −0.55 bursts/20 s/mm Hg] vs. −0.83 bursts/20 s/mm Hg [−1.21, −0.45 bursts/20 s/mm Hg]; $p = 0.85$). Cardiovagal baroreflex sensitivity assessed during early phase II (i.e., a hypotensive stimulus) of the Valsalva maneuver was comparable in patients and controls (4.61 ms/mm Hg [3.01, 5.76 ms/mm Hg] vs. 4.45 ms/mm Hg [3.42, 6.88 ms/mm Hg]; $p = 0.80$). It was not different between groups during phase IV (i.e., a hypertensive stimulus, 10.01 ms/mm Hg [6.91, 14.05 ms/mm Hg] vs. 10.80 ms/mm Hg [7.48, 13.43 ms/mm Hg]; $p = 0.83$). These results are consistent with the findings of Masuki et al. (36), suggesting that tachycardia in POTS patients is not the result of abnormal baroreflex control of HR.

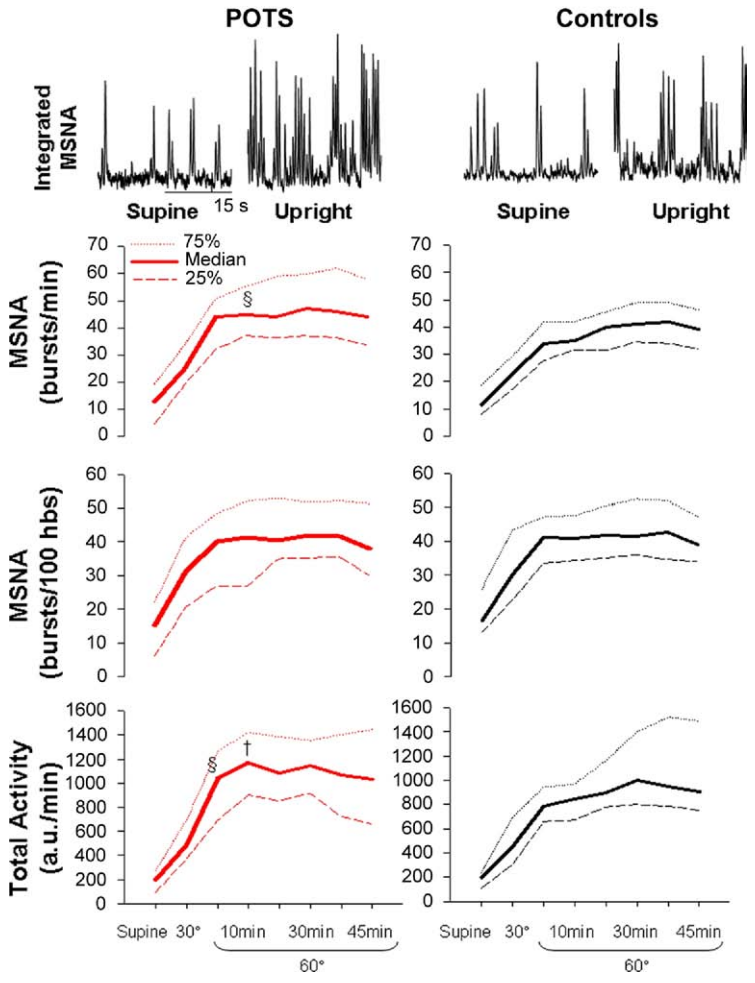

Figure 1 **Muscle Sympathetic Nerve Activity Responses During Graded Upright Tilt**

Values are expressed as median (25th, 75th percentiles). †$p < 0.05$ and §$p < 0.10$ compared with controls after 5 and 10 min of 60° upright tilt.

COLD PRESSOR TEST AND STATIC HANDGRIP. Cardiovascular and sympathetic responses during the cold pressor test did not differ between groups, even though HR was consistently greater in patients (Table 3). These results indicate that the integrity of central vasomotor processes and their efferent pathways was intact in POTS patients. Table 4 depicts responses to handgrip. At the same relative fatiguing force, the peak BP during handgrip did not differ between groups. Although absolute values of HR were consistently greater in patients than in controls, the contraction-induced rises in HR were not different between groups ($p = 0.67$). Contraction-evoked peak MSNA responses were similar in patients and controls ($p = 0.85$ for total activity). MSNA during post-exercise circulatory arrest was also similar between groups ($p = 0.64$). These data suggest that modulation of the sympathetic nerve system by the muscle metaboreflex, mechanoreflex, and central command was intact in POTS patients.

Exercise training effects. Twenty-five patients initiated the exercise training program, including all of the sickest and most debilitated patients, with 19 completing the 3-month training. The dropout rate was 24% in this study. The reasons for these dropouts were that: 1) 2 patients were too busy with work and no longer had time to exercise; 2) 2 patients became injured (one injured her ankle falling down the stairs, and the other one was in a car accident and injured her legs); 3) 1 patient was diagnosed with seizures in addition to POTS; and 4) 1 patient had an arrhythmia, which was not related to the training. HR was similar between those who dropped out and those who completed the program in the supine position (80 beats/min [72, 90 beats/min] vs. 85 beats/min [72, 90 beats/min]; $p = 0.98$) and after 10 min of standing (114 beats/min [108, 126 beats/min] vs. 120 beats/min [103, 122 beats/min]; $p = 0.85$), suggesting that the severity of POTS was not the cause for the dropout.

Exercise training increased peak oxygen uptake (26.8 ml/kg/min [24.1, 29.0 ml/kg/min] before training vs. 28.9 ml/kg/min [26.7, 32.7 ml/kg/min] after training; $p < 0.01$),

Table 2 Hemodynamic Responses During Graded Upright Tilt

	POTS Patients (n = 27)					Healthy Controls (n = 16)			
			60° Tilt				60° Tilt		
Variables	Supine	30° Tilt	5 min	20 min	40 min	Supine	30° Tilt	5 min	20 min	40 min
SBP (mm Hg)	105 (98, 114)	112* (105, 120)	113* (109, 124)	112* (105, 118)	114* (106, 120)	109 (106, 115)	116 (105, 123)	116 (109, 122)	114 (107, 116)	112 (109, 115)
DBP (mm Hg)	66 (60, 69)	70† (63, 74)	77† (67, 81)	76† (68, 83)	72† (67, 81)	63 (59, 69)	69† (66, 75)	72† (70, 82)	73† (70, 77)	75† (71, 77)
HR (beats/min)	77‡ (70, 90)	84‡‡ (75, 94)	104‡‡ (96, 111)	107†‡ (102, 122)	110†‡ (103, 125)	68 (61, 76)	70† (65, 82)	83† (77, 93)	87† (82, 99)	87† (83, 108)
CO (l/min)	5.0‡ (4.3, 5.4)	4.4‡‡ (4.0, 5.0)	3.6†‡ (3.3, 4.4)	3.5†‡ (3.1, 3.8)	3.2†‡ (2.9, 3.8)	6.8 (5.9, 7.3)	5.9† (5.0, 6.9)	5.1† (4.5, 6.1)	4.4† (4.0, 5.2)	4.2† (3.9, 4.7)
SV (ml)	59‡ (50, 66)	47†‡ (38, 56)	36†‡ (28, 42)	30†‡ (25, 37)	29†‡ (23, 35)	86 (74, 100)	76† (60, 102)	60† (45, 76)	47† (39, 64)	42† (36, 56)
TPR (dyn · s · cm^{-5})	1,284‡ (1,106, 1,501)	1,566†‡ (1,328, 1,735)	1,867†‡ (1,573, 2,314)	1,959†‡ (1,788, 2,336)	2,137†‡ (1,805, 2,493)	944 (859, 1,057)	1,063† (957, 1,504)	1,309† (1,130, 1,623)	1,475† (1,346, 1,799)	1,635† (1,362, 1,790)

Values are expressed as median (25th, 75th percentiles). *p < 0.05 versus and †p < 0.01 versus supine baseline within the same group. ‡p < 0.01 versus healthy controls.
CO = cardiac output; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure; SV = stroke volume; TPR = total peripheral resistance; other abbreviations as in Table 1.

blood volume (Fig. 2), and plasma volume (39 ml/kg [34, 42 ml/kg] vs. 41 ml/kg [37, 43 ml/kg]; $p < 0.01$) in these patients. Left ventricular mass also increased significantly after training in POTS patients and was no longer different from controls (Fig. 2). Both supine and 10-min standing HR decreased markedly after short-term exercise training (Fig. 3). Ten of 19 patients no longer met POTS criteria after the training, although as a group, standing HR was still greater in these patients compared with controls (Fig. 3). Quality of life was improved significantly after training in all patients (Fig. 4).

Exercise training lowered HR significantly during upright tilt in all patients ($p = 0.02$). Based on the median value of MSNA burst frequency for healthy controls during acute upright tilt (i.e., fifth min of 60° tilt), we separated patients into 2 subgroups before training, namely, hyperadrenergic group (i.e., MSNA ≥45 bursts/min) and normadrenergic group (i.e., MSNA <45 bursts/min). Upright MSNA decreased in the hyperadrenergic group (n = 9; fifth min of 60° tilt, 51 bursts/min [50, 60 bursts/min] before training vs. 41 bursts/min [38, 47 bursts/min] after training; $p = 0.02$), but not in the normadrenergic group (n = 10; 36 bursts/min [24, 42 bursts/min] vs. 35 bursts/min [31, 44 bursts/min]; $p = 0.57$) after training. Exercise training did not alter BP responses during tilting. Both cardiovagal ($p = 0.55$ and 0.89 during early phase II and phase IV) and sympathetic ($p = 0.17$) baroreflex sensitivity remained unchanged after training. Although the absolute values of HR were markedly lowered by exercise training, the responses of MSNA and BP during the cold pressor test and static handgrip did not change.

Discussion

The major findings from this study are that: 1) cardiac size and mass and blood volume were much smaller in POTS patients compared with healthy sedentary controls; 2) HR was greater, whereas stroke volume was smaller, in patients than in controls during upright posture; 3) the function of the autonomic nervous system was intact in POTS patients; and 4) exercise training increased cardiac size and mass, expanded blood volume, and thus improved or even cured POTS syndrome. These results suggest that POTS per se is indeed a consequence of deconditioning (i.e., cardiac atrophy and hypovolemia) and that carefully prescribed exercise training can be used as a nondrug treatment for patients with POTS.

POTS and deconditioning. POTS is characterized by orthostatic tachycardia without significant hypotension (37). It has been demonstrated that the excessive tachycardia in POTS patients is not caused by anxiety (38). Patients with POTS often experience palpitations, light-headedness, dizziness, nausea, fatigue, exercise intolerance, or near syncope. It has been the focus of increasing clinical interest over the last 15 years (9,12,39). However, the pathophysiologic features of this disorder remain unclear. It is proposed

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Table 3 Cardiovascular and Sympathetic Responses During the Cold Pressor Test

	POTS Patients (n = 27)				Healthy Controls (n = 16)			
Variables	Baseline	CPT 1 min	CPT 2 min	Recovery	Baseline	CPT 1 min	CPT 2 min	Recovery
SBP (mm Hg)	110 (99, 118)	120* (113, 130)	127* (119, 137)	112 (101, 117)	114 (110, 121)	126* (121, 133)	130* (115, 138)	114 (110, 120)
DBP (mm Hg)	66 (63, 70)	80* (71, 88)	78* (73, 85)	66 (63, 68)	68 (65, 72)	82* (72, 86)	77* (71, 83)	69 (65, 73)
HR (beats/min)	79* (69, 87)	82†‡ (72, 97)	82‡ (70, 93)	72‡ (66, 86)	67 (62, 72)	79† (69, 87)	71 (63, 79)	64† (58, 70)
MSNA-BF (bursts/min)	9 (4, 15)	22* (16, 47)	30* (16, 36)	16† (6, 18)	7 (4, 13)	29* (15, 36)	24* (9, 38)	13† (6, 17)
MSNA-BI (bursts/100 heart beats)	9 (6, 18)	30* (15, 55)	38* (16, 44)	19* (7, 27)	11 (6, 19)	32* (20, 50)	35* (14, 47)	18† (11, 26)
Total activity (AU/min)	170 (99, 265)	560* (336, 1098)	612* (324, 876)	265 (121, 346)	123 (65, 211)	725* (216, 935)	533* (255, 808)	225† (169, 325)

Values are expressed as median (25th, 75th percentiles). *p < 0.01 and †p < 0.05 versus baseline within the same group. ‡p < 0.05 versus healthy controls.
AU = arbitrary unit; CPT = cold pressor test; MSNA-BF = muscle sympathetic nerve activity burst frequency; MSNA-BI = muscle sympathetic nerve activity burst incidence; other abbreviations as in Tables 1 and 2.

that POTS is heterogeneous in presentation and mechanisms (37). Previous investigations have shown that POTS patients have altered baroreflex function (40,41), hyperadrenergic activity (42), post-ganglionic sympathetic denervation and inadequate peripheral vasoconstriction (43), cardiac sympathetic dysautonomia (44), norepinephrine transporter deficiency (45), decreased blood volume (39), abnormal activation of the renin-angiotensin system (42), mast cell activation (46), muscle pump defects (47), or autoimmune autonomic neuropathy (48).

We assessed comprehensively the function of the autonomic nervous system in all patients, but did not find any evidence of abnormalities. However, blood and plasma volume were approximately 20% lower, whereas left ventricular mass was approximately 16% smaller in these patients compared with healthy sedentary controls. Similar observations can almost always be made after a period of microgravity exposure (e.g., bed rest or spaceflight) when deconditioning occurs (49,50). Previous work from our laboratory demonstrated that a smaller and less distensible heart in young women or in healthy individuals after bed rest deconditioning can result in a larger reduction in stroke volume during orthostasis as a function of the Frank-Starling mechanism, leading to an excessive increase in HR (50). Consistent with our previous preliminary observations reported in abstract format (51), upright stroke volume was markedly smaller in POTS patients than healthy controls in this study. The orthostatic tachycardia observed in these patients thus seemed to be a physiologic compensatory response to the smaller stroke volume (51,52), which was attributable to cardiac atrophy and reduced blood volume. POTS may occur alone (primary), or because of another medical condition (secondary) (53). However, almost all the patients have a history of physical inactivity (i.e., deconditioning) that subsequently elicits or exacerbates POTS symptoms.

The Grinch syndrome: a new name for POTS. Results from our laboratory have shown that there is a sex-specific difference in cardiac size and mass even in healthy humans and that women have a smaller (and therefore, less distensible) heart compared with men (2,54). It is possible that such a sex difference is exaggerated in POTS patients. This notion is supported by a recent study of Miwa and Fujita (8) showing that a considerable number of chronic fatigue syndrome patients had a small heart, as assessed by roentgenography and echocardiography. POTS is a frequent finding in patients with chronic fatigue syndrome (55). It is highly likely that the small heart contributes to the development of POTS and probably should be included in the genesis of this syndrome.

By using a cardiac MRI technique, we assessed precisely the heart size and mass in patients with POTS and found that the heart was approximately 16% smaller in these patients and more than 2 SDs smaller than the true mean for healthy sedentary controls. In the famous children's book *How the Grinch Stole Christmas* by Dr. Seuss (56), subsequently popularized by the movie of the same name (2000), the main character had a heart that was "two sizes too small." We suggest, then, that a more pathophysiologic name for POTS is the "Grinch syndrome," emphasizing

Table 4 Cardiovascular and Sympathetic Responses During Static Handgrip to Fatigue

	POTS Patients (n = 27)				Healthy Controls (n = 16)			
Variables	Baseline	HG Fatigue	PECA	Recovery	Baseline	HG Fatigue	PECA	Recovery
SBP (mm Hg)	117 (111, 132)	145* (133, 154)	137* (128, 148)	117 (109, 130)	129 (125, 138)	158* (131, 170)	148* (130, 159)	131 (121, 137)
DBP (mm Hg)	69 (60, 73)	91* (78, 98)	80* (68, 88)	67† (57, 73)	68 (63, 71)	85* (73, 93)	75* (73, 83)	66† (61, 70)
HR (beats/min)	75‡ (65, 84)	94*‡ (81, 107)	79‡ (67, 89)	76 (64, 85)	65 (61, 72)	79* (73, 92)	65 (60, 73)	64 (61, 74)
MSNA-BF (bursts/min)	9 (5, 19)	28* (24, 38)	23* (16, 31)	12† (7, 21)	10 (5, 24)	28* (20, 39)	23* (16, 28)	10 (8, 20)
MSNA-BI (bursts/100 heart beats)	13 (6, 25)	32* (25, 42)	31* (19, 43)	19* (9, 28)	15 (7, 31)	37* (25, 51)	35* (22, 44)	14 (12, 28)
Total activity (AU/min)	192 (107, 313)	774* (593, 974)	471* (372, 627)	274† (175, 366)	172 (102, 303)	814* (476, 1,121)	542* (368, 692)	173† (157, 360)

Values are expressed as median (25th, 75th percentiles). *p < 0.01 and †p < 0.05 versus baseline within the same group. ‡p < 0.05 versus healthy controls.
HG fatigue = static handgrip at fatigue; PECA = post-exercise circulatory arrest; other abbreviations as in Tables 1 to 3.

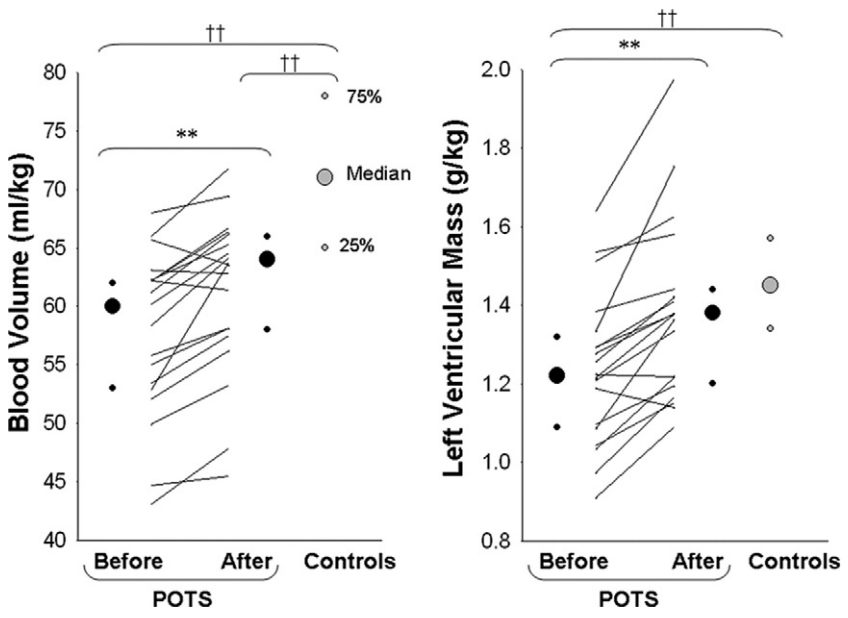

Figure 2 **Blood Volume and Left Ventricular Mass in POTS Patients Before and After 3 Months of Exercise Training as Well as in Controls**

Values are expressed as individuals and median (25th, 75th percentiles). **p < 0.01 compared with before training in the postural orthostatic tachycardia syndrome (POTS). ††p < 0.01 compared with controls.

that a small heart is the primary abnormality and target for therapy. A small heart coupled with reduced blood volume contributes to the small stroke volume, ultimately resulting in reflex tachycardia during orthostasis in these patients.

Exercise training for POTS. Treating POTS is difficult, because there are no effective pharmacologic therapies for POTS patients so far. Many patients have disabling side effects with standard drug treatments. For example, admin-

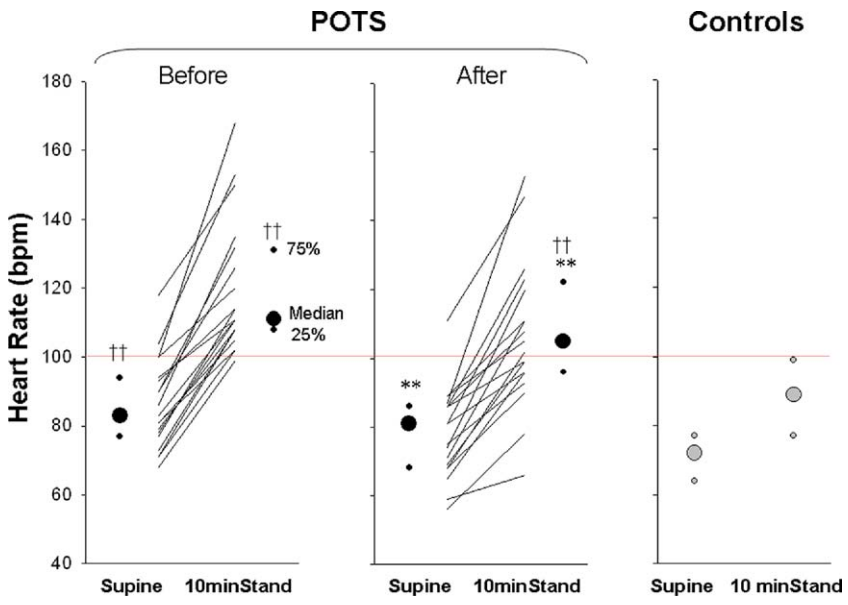

Figure 3 **Heart Rate Responses During 10-Min Stand in POTS Patients Before and After Exercise Training as Well as in Controls**

Values are expressed as individuals and median (25th, 75th percentiles). **p < 0.01 compared with before training in postural orthostatic tachycardia syndrome (POTS) in the same posture. ††p < 0.01 compared with controls in the same posture.

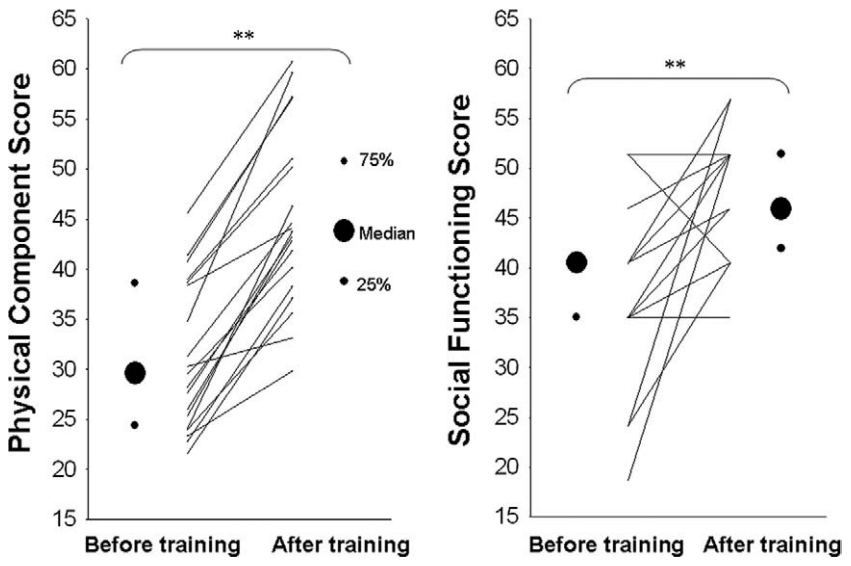

Figure 4 Effects of Training on Patients' Quality of Life Assessed by the 36-Item Short-Form Health Survey

Values are expressed as individuals and median (25th, 75th percentiles). **$p < 0.01$ compared with before training in postural orthostatic tachycardia syndrome.

istration of beta-blockers can reduce tachycardia; but, if the excessive reduction in stroke volume during orthostasis cannot be corrected, orthostatic hypotension and severe fatigue often occurs in these patients. Administration of volume expanders increases body fluids and vascular volume, which can result in a smaller reduction in stroke volume during orthostasis in POTS patients. However, leg edema may appear and hypokalemia may develop in some patients. Administration of alpha$_1$-adrenergic agonists also can decrease heart rate through the baroreflex mechanism. However, hypertension or other intolerable side effects may develop in some patients, which is quite common in these patients with prominent hypervigilance (37).

To avoid the side effects with drug therapies, we applied a nondrug treatment, namely, exercise training, to patients with POTS. It is important to emphasize that even the sickest patients participated in this program and that training was facilitated by avoiding upright exercise in the early stage. Endurance training has been shown to expand blood and plasma volumes (16), to increase cardiac size and mass (49) and to prevent cardiac atrophy, and increase orthostatic tolerance in healthy women after prolonged period of bed rest (49) as well as in patients with unexplained syncope or orthostatic hypotension. We found that 3 months of progressive exercise training in POTS patients increased maximal oxygen uptake by 11%, indicating an increase in physical fitness. Left ventricular mass and end-diastolic volume increased by 12% and 8% after training, resulting in significant cardiac remodeling. The heart became much larger and probably more distensible after exercise training. Blood and plasma volumes also increased markedly after training. Ten (53%) of 19 patients no longer met criteria for POTS after completion of the 3-month exercise training program and thus were cured. More importantly, patient quality of life, as assessed by 36-item Short-Form Health Survey, improved significantly after short-term exercise training in virtually all of these patients, including those with persistence of orthostatic tachycardia. We speculate that more prolonged or intense training, or both, may be necessary to reduce upright tachycardia further in those patients.

Study limitations. First, it may be difficult to attribute the improvements in POTS symptoms after exercise training only to the training program because patients were encouraged to increase their daily salt and water intake and to elevate the head of the bed during sleeping at night. The latter 2 activities can also expand blood volume and increase orthostatic tolerance. However, these suggestions are often given by clinicians to their patients, whereas the therapeutic effects seem to be limited in most patients. Second, the size of the control group was relatively small, and the control-to-case ratio was 16:27, namely, 1:1.7. However, adding more healthy subjects would not likely change our results and conclusions, because the power for detecting the difference between POTS patients and healthy controls was 0.80 or more for all major outcome variables in the present study. Third, 6 patients exited the 3-month training program, and therefore, our retention and treatment completion rate was 76%. Retention in the exercise training program is one of the important measures of treatment effectiveness. Previous and recent studies have shown that the adherence to exercise training (57), to antihypertensive drug treatment (58), or to cardiac rehabilitation (59) ranges from approximately 35% to approximately 68%. Our reten-

tion rate is actually higher than the findings of these studies, suggesting that compliance with this approach is within the range of other drug or nondrug interventions in common diseases.

Conclusions

Patients with POTS had a smaller heart coupled with reduced blood volume compared with healthy controls. We therefore propose the name the Grinch syndrome to focus on this pathophysiologic state. The marked orthostatic tachycardia in these patients seemed to be a physiologic compensatory response to a smaller stroke volume that was attributable to cardiac atrophy and hypovolemia. The function of the autonomic nervous system was intact in POTS patients. Short-term exercise training increased cardiac size and mass and expanded blood and plasma volume, and thus improved or even cured POTS. These results suggest that POTS per se is indeed a consequence of deconditioning and that carefully prescribed exercise training can be used as an effective nondrug therapy for POTS patients.

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Key Words: arterial pressure ■ autonomic control ■ endurance training ■ orthostatic tolerance ■ vasomotor sympathetic activity.