Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 55, No. 25, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.02.043

Cardiac Origins of the Postural Orthostatic Tachycardia Syndrome

Qi Fu, MD, PhD,*† Tiffany B. VanGundy, MS,* M. Melyn Galbreath, PhD,*† Shigeki Shibata, MD, PhD,*† Manish Jain, MD,*† Jeffrey L. Hastings, MD,*† Paul S. Bhella, MD,*† Benjamin D. Levine, MD*†

Dallas, Texas

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

From the *Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas, Dallas, Texas; and †The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas. Supported by the National Institutes of Health (K23 grant HL075283); the National Space Biomedical Research Institute (grant CA00701); and the Clinical and Translational Research Center (formerly the General Clinical Research Center; grant RR00633).

Manuscript received November 3, 2009; revised manuscript received January 6, 2010, accepted February 1, 2010.

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