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Exercise in the Postural Orthostatic Tachycardia Syndrome

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Abstract

Patients with the Postural Orthostatic Tachycardia Syndrome (POTS) have orthostatic intolerance, as well as exercise intolerance. Peak oxygen uptake (VO_{2peak}) is generally lower in these patients compared with healthy sedentary individuals, suggesting a lower physical fitness level. During acute exercise, POTS patients have an excessive increase in heart rate and reduced stroke volume for each level of absolute workload; however, when expressed at relative workload (%VO_{2peak}), there is no difference in the heart rate response between patients and healthy individuals. The relationship between cardiac output and VO_2 is similar between POTS patients and healthy individuals. Short-term (i.e., 3 months) exercise training increases cardiac size and mass, blood volume, and VO_{2peak} in POTS patients. Exercise performance is improved after training. Specifically, stroke volume is greater and heart rate is lower at any given VO_2 during exercise after training versus before training. Peak heart rate is the same but peak stroke volume and cardiac output are greater after training. Heart rate recovery from peak exercise is significantly faster after training, indicating an improvement in autonomic circulatory control. These results suggest that patients with POTS have no intrinsic abnormality of heart rate regulation during exercise. The tachycardia in POTS is due to a reduced stroke volume. Cardiac remodeling and blood volume expansion associated with exercise training increase physical fitness and improve exercise performance in these patients.

Keywords

chronic orthostatic intolerance; exercise intolerance; physical activity; cardiovascular response; non-drug therapy

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Conflict of Interest Statement
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

Introduction

Over 500,000 people in the United States, primarily young women, suffer from chronic orthostatic intolerance (Robertson, 1999). Severely affected patients are unable to work, attend school, or participate in recreational activities, resulting in substantial morbidity. The Postural Orthostatic Tachycardia Syndrome (POTS, in which patients are unable to stand or remain upright for prolonged periods of time due to intolerable palpitations, dizziness, or near-syncope) is a major form of chronic orthostatic intolerance in young people, with few definitive therapies (Schondorf & Low, 1993). The underlying pathophysiology is not well understood, but recent research has suggested that physical deconditioning and reduced standing stroke volume may be important to the pathogenesis of POTS and the severity of its disability (Masuki *et al.*, 2007b; Joyner & Masuki, 2008; Fu *et al.*, 2010; Fu *et al.*, 2011; Galbreath *et al.*, 2011; Parsaik *et al.*, 2012; Shibata *et al.*, 2012).

In addition to orthostatic intolerance, patients with POTS also have exercise intolerance or low physical work performance (Low *et al.*, 2009). Peak oxygen uptake (VO_{2peak}), an indicator of physical fitness, is generally lower in POTS patients when compared with healthy sedentary individuals (Parsaik *et al.*, 2012; Shibata *et al.*, 2012). Reduced VO_{2peak} is consistent with physical deconditioning, which provides a strong rationale for retraining in the treatment of POTS or chronic orthostatic intolerance. Indeed, we have found that endurance exercise training is an effective non-pharmacological therapy for POTS (Fu *et al.*, 2010; Fu *et al.*, 2011; Galbreath *et al.*, 2011; Shibata *et al.*, 2012). Many patients can be “cured” or at least palliated substantially after a period of exercise training or increased physical activity. Exercise performance is improved after training in POTS patients.

Acute exercise responses in POTS

During acute sub-maximal and maximal exercise, especially in the upright position, POTS patients have lower stroke volume and higher heart rate for each level of absolute workload compared with healthy sedentary individuals matched for sex and age (Figure 1A and 1B) (Shibata *et al.*, 2012). However, when expressed at the relative workload (percent of VO_{2peak}), the heart rate responses are not different between POTS patients and healthy individuals (Figure 2) (Shook *et al.*, 2007). These results suggest that POTS patients have no intrinsic abnormality of heart rate regulation during exercise.

Previous studies have found that baroreflex control of heart rate during exercise is similar between POTS patients and healthy individuals (Masuki *et al.*, 2007a). The tachycardia in POTS patients during exercise appears to be attributed to the reduced stroke volume (Masuki *et al.*, 2007b; Fu *et al.*, 2010; Shibata *et al.*, 2012), which is associated with exercise intolerance. Recent research has shown that there are sex-specific differences in heart size and blood volume even in the healthy population (Best *et al.*, 2014), and such sex differences are exaggerated in POTS (Fu *et al.*, 2010). It is possible that women born with small hearts (even though within a normal range) are more susceptible to the development of POTS. Conversely, POTS patients have small hearts which are likely a secondary change due to a physiological adaptation to the reduced physical activity level (namely, decreased myocardial load and work). We previously found that physical deconditioning elicited by

chronic bed rest leads to ventricular remodeling, which is not seen with equivalent degrees of acute hypovolemia (Perhonen *et al.*, 2001; Dorfman *et al.*, 2007). The small heart (Raj & Levine, 2013) coupled with reduced blood volume contributes to the reduced stroke volume, ultimately resulting in reflex tachycardia during exercise in POTS patients. These results support the cardiac origin of exercise intolerance in this syndrome.

We found that POTS patients and healthy individuals have a similar linear correlation between cardiac output and VO_2 during sub-maximal and maximal exercise (Figure 1C) (Shibata *et al.*, 2012). This observation indicates that POTS patients have a normal ability to increase cardiac output for the oxygen demand during exercise, as well as to utilize oxygen in the periphery. Many studies have shown that the slope of this relationship varies little in healthy humans with advancing age, sex, mode of exercise, overall fitness, or degree of effort (Astrand *et al.*, 1964; Julius *et al.*, 1967; Lewis *et al.*, 1983; Proctor *et al.*, 1998; McGuire *et al.*, 2001; Fu & Levine, 2005). If oxygen utilization by working muscles is impaired, such as in patients with mitochondrial myopathy (Haller *et al.*, 1991; Taivassalo *et al.*, 2003) and well-compensated heart failure with preserved ejection fraction (Bhella *et al.*, 2011), the slope of the relationship between cardiac output and VO_2 is augmented so that more blood flow is required to meet the metabolic demand of exercise. In contrast, if the heart is impaired and cannot meet the metabolic demand, such as in patients with severe de-compensated heart failure, the slope is depressed (Chomsky *et al.*, 1996; Mancini *et al.*, 1996).

Exercise training in orthostatic intolerance and POTS

There are no effective pharmacologic therapies for POTS patients so far. Though a recent study suggested that acute (i.e., 1 hour) administration of low-dose, but not high-dose, propranolol (a non-selective β-blockade) may provide a modest beneficial effect to improve heart rate control and exercise capacity in POTS patients (Arnold *et al.*, 2013), the impact of long-term propranolol use on exercise performance in these patients is unclear. POTS patients have a lower VO_{2peak} compared with healthy sedentary individuals (Parsaik *et al.*, 2012; Shibata *et al.*, 2012). The low VO_{2peak} and the cardiovascular responses during exercise in POTS patients cannot be improved by acute volume loading with saline infusion (Figueroa *et al.*, 2014), similar to what we found in previous bed rest studies (Shibata *et al.*, 2010).

Increasing evidence suggests that physical deconditioning is one important contributing factor for POTS. This provides rationale for retraining in the treatment of POTS. Although the effect of exercise training on orthostatic tolerance in healthy individuals is controversial (Greenleaf *et al.*, 1981; Convertino, 1993; Raven & Pawelczyk, 1993; Carrick-Ranson *et al.*, 2012; Hastings *et al.*, 2012), training appears to be beneficial to people with average and below average orthostatic tolerance. Indeed, increased orthostatic tolerance following a mild to moderate exercise training has been observed in patient populations (Brilla *et al.*, 1998; Mtinangi & Hainsworth, 1998). Endurance training expands blood volume and plasma volume (Saltin *et al.*, 1968), increases cardiac size and mass (Dorfman *et al.*, 2007b), and improves orthostatic tolerance (Dorfman *et al.*, 2007). These results suggest that exercise

training may be used as rehabilitative treatment for patients with chronic orthostatic intolerance, especially POTS.

We applied, for the first time, exercise training as a non-drug treatment to POTS patients (Fu *et al.*, 2010; Fu *et al.*, 2011; Galbreath *et al.*, 2011; Shibata *et al.*, 2012). A personalized short-term (i.e., 3 months) exercise training program was developed for each patient enrolled in our studies, with the key feature that training began in the recumbent or semi-recumbent position. Initially, patients trained 3 sessions per week for 20–30 minutes per session with target heart rate equivalent to approximately 75% of maximal. As the patients became relatively fit, the duration of the training sessions was prolonged, and subsequently sessions of increased intensity were added. Upright exercise (i.e., upright bike, elliptic machine, etc.) was added gradually as tolerated, though usually not until the second or third month. Each patient also performed 5 minutes of light exercise before and after the main workout as a warm-up and a cool-down. Patients also performed strength training. Weight lifting with low weights started from once weekly, 15–20 minutes per session and gradually increased to twice weekly, approximately 30 minutes per session. All training sessions were supervised closely by experienced trainers.

Three months of exercise training increased VO_{2peak} by 8% in POTS patients, 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”. Blood volume increased by 6% after training in POTS patients (Fu *et al.*, 2010; Fu *et al.*, 2011; Shibata *et al.*, 2012). Autonomic circulatory control and arterial-cardiac baroreflex function were improved after training (Galbreath *et al.*, 2011). Most importantly, 53% of the patients who completed the 3-month exercise training program no longer met the criteria for diagnosis of POTS, and thus, were “cured” (Fu *et al.*, 2010; Fu *et al.*, 2011). The severity of the POTS symptoms is one major factor that limits patients’ exercise tolerance and the effectiveness of training. For patients with moderate to severe POTS, three months may be too short to normalize their physical fitness levels and exercise capacity.

Exercise performance after physical training in POTS

After completion of the 3-month exercise training program, stroke volume and cardiac output during peak exercise were significantly increased (Figure 1A and 1C). Peak heart rate was similar after training versus before training (Figure 1B). Increases in heart size and mass and blood volume expansion associated with endurance exercise training seem to be responsible for the increases in peak stroke volume and cardiac output in these patients. Stroke volume became higher while heart rate was lower at any given VO_2 during exercise in POTS patients after training (Figure 1A and 1B) (Shibata *et al.*, 2012); however, both of these two variables were not normalized to the levels of healthy sedentary controls. These findings suggest that short-term (i.e., 3 months) exercise training may be insufficient for many POTS patients. A longer duration of training is needed to reverse functional capacity and effect a long-term “cure” of POTS in the majority of patients. We assume that patients must continue to train in order to preserve the improvements observed after the initial exercise intervention. Certainly from a public health standpoint, a life long habit of regular physical activity is a worthwhile goal and should be the target for all patients, not only those

with POTS. Life-long training at a "dose" of at least 4–5 times per week has profound effects on cardiovascular structure and function and should be encouraged (Bhella *et al.*, 2014). The relationship between cardiac output and VO_2 remained the same after training (Figure 1C). Heart rate recovery from peak exercise was faster after training in POTS patients (Shibata *et al.*, 2012), indicating an improvement in autonomic circulatory control (i.e., an increase in vagal reactivation and a decrease in sympathetic tone). Training did not affect blood pressure and total peripheral resistance responses to exercise in POTS patients (Figure 1E and 1F).

In summary, during acute exercise POTS patients have excessive increases in heart rate and reduced stroke volume at absolute workload compared with healthy sedentary individuals, but there is no difference in the heart rate responses between groups at relative workload (%VO_{2peak}). The cardiac output-VO_2 relation is similar between patients and healthy individuals. Exercise training increases VO_{2peak} and peak stroke volume and cardiac output in POTS patients. Stroke volume is higher and heart rate is lower at any given VO_2 during exercise after training. However, the cardiac output-VO_2 relation remains the same. It is suggested that patients with POTS have no intrinsic abnormality of heart rate regulation during exercise. The tachycardia in POTS is due to a reduced stroke volume. Cardiac remodeling and blood volume expansion associated with endurance training increase physical fitness and improve exercise performance in these patients.

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Highlights

- Patients with the Postural Orthostatic Tachycardia Syndrome (POTS) have exercise intolerance.
- During acute exercise, POTS patients have an excessive increase in heart rate and reduced stroke volume for each level of absolute workload; however, when expressed at relative workload, there is no difference in the heart rate response between patients and healthy individuals.
- Exercise performance is improved after short-term (3 months) exercise training. Specifically, stroke volume is greater and heart rate is lower at any given VO_2 during exercise after training versus before training.

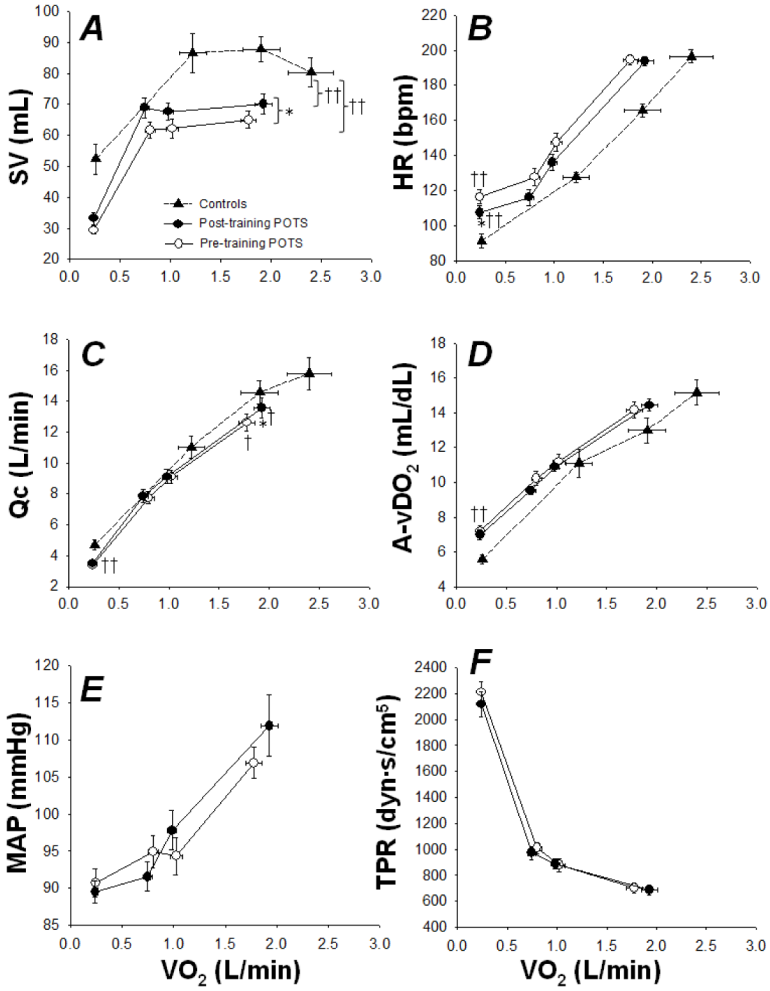

Figure 1.

Changes of stroke volume (SV, A), heart rate (HR, B), cardiac output (Qc, C), arterio-venous oxygen content difference (A-vDO_2, D), mean arterial pressure (MAP, E), and total peripheral resistance (TPR, F) in relation to changes of oxygen uptake (VO_2) during upright treadmill exercise in healthy sedentary individuals and patients with POTS before and after 3-month endurance training. Adapted with permission from Shibata et al (Shibata *et al.*, 2012).

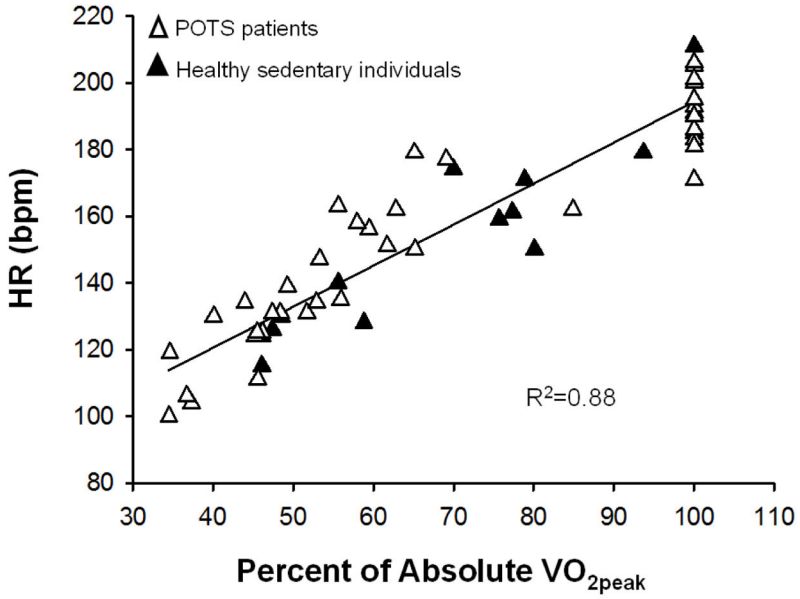

Figure 2.

Heart rate (HR) responses, when expressed at percent of peak oxygen uptake (VO_{2peak}), between POTS patients and healthy sedentary individuals. Data from our laboratory (Robin *et al*., 2007 abstract).