

Short-term exercise training improves the cardiovascular response to exercise in the postural orthostatic tachycardia syndrome

Shigeki Shibata^{1,2}, Qi Fu^{1,2}, Tiffany B. Bivens¹, Jeffrey L. Hastings^{1,2}, Wade Wang¹ and Benjamin D. Levine^{1,2}

¹Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital, Dallas, TX, USA

²The University of Texas Southwestern Medical Center, Dallas, TX, USA

Key points

- Recent studies have suggested the presence of cardiac atrophy as a key component of the pathogenesis of the postural orthostatic tachycardia syndrome (POTS), similar to physical deconditioning; exercise intolerance is associated with a reduced stroke volume (SV) in POTS which may be the cause of the high heart rate (HR) at rest and during exercise.
- We determined whether physical 'reconditioning' with exercise training improves exercise performance in POTS.
- A lower SV resulted in a higher HR in POTS at any given oxygen uptake (\dot{V}_{O_2}) during exercise while the cardiac output (\dot{Q}_C)– \dot{V}_{O_2} relationship remained normal. $\dot{V}_{O_{2peak}}$ was lower in POTS than healthy sedentary controls.
- After 3 months of training in POTS, HR became lower at any given \dot{V}_{O_2} due to increased SV without changes in the \dot{Q}_C – \dot{V}_{O_2} relationship. $\dot{V}_{O_{2peak}}$ increased due to increased peak SV, and was proportional to total blood volume. HR recovery from exercise was faster after training than before training.
- Thus, exercise training improves physical fitness and cardiovascular responses during exercise in POTS.

Abstract Recent studies have suggested the presence of cardiac atrophy as a key component of the pathogenesis of the postural orthostatic tachycardia syndrome (POTS), similar to physical deconditioning. It has also been shown that exercise intolerance is associated with a reduced stroke volume (SV) in POTS, and that the high heart rate (HR) observed at rest and during exercise in these patients is due to this low SV. We tested the hypotheses that (a) circulatory control during exercise is normal in POTS; and (b) that physical 'reconditioning' with exercise training improves exercise performance in patients with POTS. Nineteen (18 women) POTS patients completed a 3 month training programme. Cardiovascular responses during maximal exercise testing were assessed in the upright position before and after training. Resting left ventricular diastolic function was evaluated by Doppler echocardiography. Results were compared with those of 10 well-matched healthy sedentary controls. A lower SV resulted in a higher HR in POTS at any given oxygen uptake (\dot{V}_{O_2}) during exercise while the cardiac output (\dot{Q}_C)– \dot{V}_{O_2} relationship was normal. $\dot{V}_{O_{2peak}}$ was lower in POTS than controls (26.1 ± 1.0 (SEM) vs. 36.3 ± 0.9 ml kg⁻¹ min⁻¹; $P < 0.001$) due to a lower peak SV (65 ± 3 vs. 80 ± 5 ml; $P = 0.009$). After training in POTS, HR became lower at any given \dot{V}_{O_2} due to increased SV without changes in the \dot{Q}_C – \dot{V}_{O_2} relationship. $\dot{V}_{O_{2peak}}$ increased by 11% ($P < 0.001$) due to increased peak SV ($P = 0.021$) and was proportional

to total blood volume. Peak HR was similar, but HR recovery from exercise was faster after training than before training ($P = 0.036$ for training and 0.009 for interaction). Resting diastolic function was mostly normal in POTS before training, though diastolic suction was impaired ($P = 0.023$). There were no changes in any Doppler index after training. These results suggest that short-term exercise training improves physical fitness and cardiovascular responses during exercise in patients with POTS.

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Corresponding author B. D. Levine: Institute for Exercise and Environmental Medicine, 7232 Greenville Avenue, Suite 435, Dallas, TX 75231, USA. Email: benjaminlevine@TexasHealth.org

Abbreviations HR, heart rate; IVRT, isovolumetric relaxation time; POTS, postural orthostatic tachycardia syndrome; SV, stroke volume; TPR, total peripheral resistance.

Introduction

The postural orthostatic tachycardia syndrome (POTS) is characterized by an excessive increase in heart rate (HR) during orthostasis, and the inability to stand or remain upright for prolonged periods of time due to intolerable light-headedness, weakness, and near-syncope (Low *et al.* 1995). This disorder affects over 500,000 Americans (Robertson, 1999), the vast majority of whom are premenopausal women. Although several mechanisms for this excessive orthostatic tachycardia have been postulated (Low *et al.* 2009), recent findings, including those from our laboratory suggest the presence of cardiac atrophy along with reduced blood volume as key components of the pathogenesis of this syndrome (Raj *et al.* 2005; Joyner & Masuki, 2008; Fu *et al.* 2010a), while autonomic regulation, including baroreflex regulation of HR is essentially intact (Fu *et al.* 2010a; Galbreath *et al.* 2011). Most of these patients also report high HR during exercise, as well as during quiet standing (Raj *et al.* 2005; Masuki *et al.* 2007; Raj & Robertson, 2007; Fu *et al.* 2010a,b, 2011).

Cardiac atrophy and reduced blood volume, resulting in a low stroke volume (SV) during exercise are clinically relevant physiological changes also observed after long-term bed rest (Saltin *et al.* 1968; Levine *et al.* 1997; Dorfman *et al.* 2008; Shibata *et al.* 2010). These adaptive responses are directly related to the critical symptoms observed commonly after bed rest as well as in patients with POTS, namely orthostatic intolerance and low physical work performance. A low SV during exercise is responsible for the reduced peak oxygen uptake ($\dot{V}_{O_{2peak}}$) after bed rest (Saltin *et al.* 1968; Shibata *et al.* 2010). Besides heart size and blood volume, cardiac diastolic relaxation also plays a role in maintaining left ventricular (LV) end diastolic volume and subsequently SV in the upright position and during exercise in humans. Whether cardiac atrophy in POTS would lead to impaired diastolic function, and therefore, low SV during exercise is unclear.

Results regarding cardiovascular response to exercise in POTS are limited. There is only one study published showing reduced SV during graded cycling exercise in

POTS patients (Masuki *et al.* 2007). Whether similar observations can be made during upright treadmill exercise is unknown. Physical exercise training has been shown to increase blood volume, cardiac size and mass in different patient populations (Saltin *et al.* 1968; Dorfman *et al.* 2007; Fu *et al.* 2010a). Whether exercise training would be beneficial in improving exercise performance and diastolic function in POTS is unclear. Thus, the purposes of this study were: (a) to evaluate cardiac diastolic function at rest and cardiovascular responses during exercise; and (b) to assess the effects of short-term (i.e. 3 months) exercise training on diastolic function and exercise performance in POTS.

Methods

Participants

Details of the recruitment process were reported previously (Fu *et al.* 2010a, 2011); patients were consecutive patients referred to our tertiary Autonomic Function Clinic for the diagnosis and management of POTS. At the time of the study, all patients met the inclusion criteria for POTS, and had a HR rise ≥ 30 beats min^{-1} or a rate that exceeded 120 beats min^{-1} that occurred after 10 min of standing without any evidence of orthostatic hypotension (Raj *et al.* 2005). Patients had POTS-related symptoms for 6 months to 5 years prior to participation in the study. Twenty-five patients (24 women, 1 man) were enrolled in an 'optimized' exercise training programme for 3 months with 19 (18 women, 1 man) completing the programme (Fu *et al.* 2010a). There were no differences in resting cardiac diastolic function parameters between those who finished the protocol *versus* those who dropped out except that septal mitral annular early diastolic velocity was slightly but significantly greater in the drop-out group. All patients were non-smokers. Although the exercise history in these patients was variable, and many of them reported a previously active life-style, all reported at least a brief period of change in physical activity or bedrest (Gaffney *et al.* 1985). All were screened with a careful

medical history, physical examination, 12-lead electrocardiogram (ECG), and a 10 min stand test. Patients had stopped taking medications that could affect the autonomic nervous system ≥ 2 weeks before screening and ≥ 4 weeks before testing. Ten age-matched healthy sedentary individuals (9 women, 1 man) served as controls. 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. This study followed guidelines set forth in the *Declaration of Helsinki*.

Protocol

All of the subjects were on an isocaloric constant diet consisting of 200 mEq of sodium, 100 mEq of potassium, and 1000 mg of calcium 3 days prior to testing. Foods were prepared by the Clinical and Translational Research Center at the University of Texas Southwestern Medical Center. All underwent an extensive set of autonomic and renal-adrenal measurements (previously published) (Fu *et al.* 2010*a,b*, 2011; Galbreath *et al.* 2011) before diastolic function assessment and maximal exercise testing. Female subjects were studied in the mid-luteal phase of the menstrual cycle (day 19 to 22 after the onset of menstruation, high oestrogen and progesterone). They took a pregnancy test and showed negative results on each study day.

Doppler echocardiography

Echocardiographic images (iE33, Philips Ultrasound) were obtained during supine rest and measurements were made during quiet guided expiration. A colour M-mode image of LV inflow was obtained with the sampling area positioned to extend from mid-atrium to the apex, directly through the mitral valve orifice. The resulting mitral inflow spatiotemporal velocity profile pattern was used to derive the early propagation velocity of mitral inflow (Rivas-Gotz *et al.* 2003; Prasad *et al.* 2007). Measurements of septal and lateral mitral annular early diastolic (E') velocities were obtained via standard tissue Doppler imaging techniques from the apical four-chamber view with a 4.0 mm sample volume (Sohn *et al.* 1997; Prasad *et al.* 2007). Mitral inflow velocities were assessed using pulsed wave Doppler with a sample volume of 2.0 mm positioned over the mitral valve leaflet tips. From these measurements were obtained of the peak inflow velocity during the early phase of LV relaxation (E) (Labovitz & Pearson, 1987; Hatle, 1993; Cohen *et al.* 1996) and during left atrial contraction (A) (Cohen *et al.* 1996). These values were subsequently used to calculate the E/A ratio (Labovitz & Pearson, 1987; Hatle, 1993; Prasad

et al. 2007). Isovolumetric relaxation time (IVRT) was considered as the time interval between the end of aortic outflow during systole and the opening of the mitral valve during diastole (Prasad *et al.* 2007). IVRT was determined using a five-chamber apical view with the sample volume set at 4.0 mm.

Maximal exercise testing

Cardiac output (\dot{Q}_C) was measured with a modified acetylene rebreathing method (Jarvis *et al.* 2007). SV was calculated with coincident HR measured with 12-lead ECG. Blood pressure (BP) was measured by electro-sphygmomanometry (SunTech, Raleigh, NC, USA) with a microphone placed over the brachial artery to detect Korotkoff sounds. Mean arterial pressure (MAP) was calculated as [(systolic BP – diastolic BP)/3 + diastolic BP]. Total peripheral resistance (TPR) was calculated as the quotient of MAP and \dot{Q}_C , multiplied by 80 (expressed as dyn s cm^{-5}). \dot{V}_{O_2} was measured with the Douglas bag technique with gas fractions analysed by mass spectrometry (Marquette MGA1100). Ventilatory volume was measured using a Tissot spirometer.

Quiet standing \dot{Q}_C , HR, BP and \dot{V}_{O_2} were collected. After that, two submaximal steady-state workloads were determined based on individual fitness level so that $\sim 30\%$ and 60% of $\dot{V}_{O_{2\text{peak}}}$ could be achieved at each level. Each work load lasted 5 min, and steady-state \dot{Q}_C , HR, BP and \dot{V}_{O_2} were collected during the last 1 min. Following a brief break, a maximal exercise test was performed by using a modified Astrand-Saltin incremental treadmill protocol (Balke *et al.* 1965). Subjects walked or jogged at a constant speed, which was determined based on individual fitness level and submaximal steady-state data to achieve a peak work rate at 10–12 min; the grade was subsequently increased by 2% every 2 min until exhaustion. Douglas bags were collected in the second minute of each stage, with consecutive 45 s collections when the subject was nearing maximal effort. \dot{Q}_C , BP and HR were measured during the final 20 s of maximal exercise. HR recovery from exercise was calculated from peak exercise to minute 2 of recovery (Cole *et al.* 1999; Cole *et al.* 2000; Nishime *et al.* 2000; Rosenwinkel *et al.* 2001) in the sitting position.

Maximal exercise was defined as the inability to continue exercise despite vigorous encouragement. $\dot{V}_{O_{2\text{peak}}}$ was defined as the highest \dot{V}_{O_2} measured from at least a 40 s Douglas bag. \dot{V}_{O_2} was divided by \dot{Q}_C to calculate arterio-venous oxygen content difference ($a-v D_{O_2}$) according to the Fick equation.

Exercise training

Details of the exercise intervention have been previously reported (Fu *et al.* 2010*a*). The majority of the training

sessions were prescribed as 'base training' with target HR equivalent to ~75% of maximal. Initially, patients trained 2–4 times per week for 30–45 min per session by using a recumbent bike, rowing, or swimming. 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. Upright exercise was added gradually as tolerated, though usually not until the second or third month. By the end of the 3 month training, patients were exercising 5–6 h per week. HR was monitored during every session using a Polar monitor in all the patients and their physical activity level was quantified every 2 weeks. In addition to the endurance training, resistance training using weight lifting was also undertaken from once a week, 15–20 min per session to twice a week, 30–40 min per session. Additionally, patients were encouraged to increase their dietary salt and water intake, and elevate the head of the bed during sleeping at night.

Doppler echocardiography and the maximal exercise testing were repeated after 3 months of exercise training in all POTS patients. Patients were studied at the same time of the day during the mid-luteal phase of the menstrual cycle. Blood volume was measured by a modified carbon monoxide rebreathing technique (Gore *et al.* 2006) in POTS patients before and after training and in healthy controls, and these results were previously reported (Fu *et al.* 2010a).

Statistical analysis

Data are presented as means \pm SEM. Statistical probability was assessed with Student's paired *t* test to compare the differences before and after exercise training in POTS patients, and with an unpaired *t*-test to compare the differences between patients and controls. HR recovery from exercise in POTS patients before and after training was compared using two-way repeated measures analysis of variance. The Holm–Sidak method was used *post hoc* for multiple comparisons. The relationship between blood/plasma volume and $\dot{V}_{O_{2peak}}$ in POTS patients before and after training was determined by least-squares linear regression. All of the statistical analyses were performed with a personal computer based analysis program (SigmaStat; Systat Software Inc., San Jose, CA, USA). A *P* value of <0.05 was considered statistically significant.

Results

Subject characteristics

There were no significant differences in age, height, weight, body mass index, body surface area, and lean body mass

Table 1. Subject characteristics

Variables	POTS		
	Pre-training	Post-training	Controls
Age (years)	27 \pm 2	27 \pm 2	30 \pm 2
Height (cm)	167 \pm 1	167 \pm 1	171 \pm 3
Weight (kg)	69 \pm 4	68 \pm 4	65 \pm 5
Body mass index (kg m ⁻²)	25 \pm 1	24 \pm 1	22 \pm 1
Body fat (%)	34 \pm 2†	32 \pm 2†	24 \pm 3
Body surface area (m ²)	1.78 \pm 0.06	1.77 \pm 0.05	1.75 \pm 0.08
Lean body mass (kg)	45 \pm 2	45 \pm 2	50 \pm 4
Duration of illness (years)	2.4 \pm 0.4		

Values are means \pm SEM; †*P* < 0.05 compared with controls.

between POTS patients and healthy sedentary controls, while percentage body fat was higher in patients than in controls (Table 1). Anthropometric characteristics did not change in POTS patients after 3 months of exercise training, but physical activity level significantly increased in all the patients by design.

Cardiovascular responses during exercise

In the resting standing condition, a lower SV led to a lower \dot{Q}_C in POTS patients compared with healthy controls, although HR was higher in POTS patients (Table 2). Peak \dot{Q}_C was lower in POTS patients due to a lower peak SV with a similar peak HR compared with healthy controls during peak exercise while peak *a-vD*_{O₂} was comparable between groups, resulting in a lower $\dot{V}_{O_{2peak}}$ in POTS patients (Table 2).

Plots of \dot{V}_{O_2} versus SV showed that at any given \dot{V}_{O_2} , SV was lower in patients (downward shift) compared with controls (Fig. 1A), while plots of \dot{V}_{O_2} versus HR showed that at any given \dot{V}_{O_2} , HR was higher in POTS patients (upward shift) (Fig. 1B). After 3 months of exercise training, an upward shift in the relationship of \dot{V}_{O_2} versus SV and a downward shift in plots of \dot{V}_{O_2} versus HR were observed in POTS patients; however, these relationships were not completely normalized (Fig. 1A and B). Plots of \dot{V}_{O_2} versus \dot{Q}_C , as well as of \dot{V}_{O_2} versus *a-vD*_{O₂} from patients were not different from those of controls; these relationships did not change in POTS patients after 3 months of exercise training (Fig. 1C and D). Training did not alter MAP and TPR responses to exercise in POTS patients (Fig. 1E and F). $\dot{V}_{O_{2peak}}$ was correlated directly with blood/plasma volume in healthy controls and POTS patients (Fig. 2). This relationship was intact in POTS.

Table 2. Cardiovascular response during exercise

Variables	POTS		Controls
	Pre-training	Post-training	
Standing resting			
\dot{V}_{O_2} (l min ⁻¹)	0.24 ± 0.01	0.24 ± 0.01	0.26 ± 0.02
\dot{V}_{O_2} (ml kg ⁻¹ min ⁻¹)	3.5 ± 0.1†	3.5 ± 0.1†	3.9 ± 0.1
a-v D_{O_2} (ml dl ⁻¹)	7.2 ± 0.3††	7.0 ± 0.3††	5.6 ± 0.2
HR (beats min ⁻¹)	116 ± 4††	107 ± 4*††	91 ± 4
\dot{Q}_C (l min ⁻¹)	3.38 ± 0.14††	3.51 ± 0.17††	4.70 ± 0.33
SV (ml)	29 ± 1††	33 ± 2*††	52 ± 5
Peak exercise			
$\dot{V}_{O_{2peak}}$ (l min ⁻¹)	1.78 ± 0.08††	1.93 ± 0.08*††	2.40 ± 0.22
$\dot{V}_{O_{2peak}}$ (ml kg ⁻¹ min ⁻¹)	26.1 ± 1.0††	28.9 ± 1.1**††	36.3 ± 0.9
Peak a-v D_{O_2} (ml dl ⁻¹)	14.2 ± 0.5	14.4 ± 0.3	15.2 ± 0.7
Peak HR (beats min ⁻¹)	195 ± 3	194 ± 3	196 ± 4
Peak \dot{Q}_C (l min ⁻¹)	12.62 ± 0.58†	13.57 ± 0.64**†	15.79 ± 1.02
Peak SV (ml)	65 ± 3††	70 ± 3*††	80 ± 5
Peak lactate (mmol)	7.91 ± 0.45	7.87 ± 0.33	9.55 ± 1.36

Values are means ± SEM. * $P < 0.05$ and ** $P < 0.01$ compared with pre-training in POTS. † $P < 0.05$ and †† $P < 0.01$ compared with controls.

Both $\dot{V}_{O_{2peak}}$ and blood volume increased after training, but the relationship remained unchanged.

HR recovery from maximal exercise testing was significantly faster after training compared with before training in POTS patients (Fig. 3).

Left ventricular diastolic function from Doppler echocardiography

Table 3 depicts cardiac diastolic function at rest in healthy sedentary controls and POTS patients before and after exercise training. There was no difference in the E/A ratio, IVRT, and tissue Doppler imaging of early diastole between patients and controls, while propagation velocity of early mitral inflow was lower in patients than in controls ($P = 0.023$). There were no changes in any Doppler index after training in POTS patients. Consequently, propagation velocity of early mitral inflow remained significantly lower in POTS patients even after training compared with healthy sedentary controls ($P = 0.017$).

Discussion

The major new findings of this study are as follows: (a) Despite a marked functional limitation, cardiovascular control and oxygen delivery were normal and appropriate for the increase in oxygen uptake in patients with POTS; during maximal exercise, the lower peak SV in POTS patients led to a lower peak \dot{Q}_C with a similar peak HR compared with healthy sedentary controls. This led to a lower $\dot{V}_{O_{2peak}}$ with a similar peak a-v D_{O_2} . (b) SV at rest and during exercise increased after 3 months of exercise

training, leading to a lower HR at a given \dot{V}_{O_2} compared with before training, although they did not reach the level of healthy sedentary controls. (c) HR recovery from exercise was faster after training than before training in POTS patients. (d) The relationship between $\dot{V}_{O_{2peak}}$ and blood volume was intact in these patients and similar to healthy controls. (e) Resting cardiac diastolic function was mostly normal in POTS patients, though diastolic suction was impaired and not normalized by 3 months of training. These results suggest that short-term exercise training improves physical fitness and exercise performance in POTS.

Cardiovascular response to exercise in POTS

The lower $\dot{V}_{O_{2peak}}$ in POTS patients (28%) was primarily attributable to a lower peak \dot{Q}_C (20%), since peak a-v D_{O_2} was comparable between patients and controls. Moreover, given the comparable peak HR between groups, the lower peak \dot{Q}_C in POTS patients was primarily attributable to a lower SV (19%). Thus, exercise intolerance in POTS patients is most easily explained by a low SV during exercise. A similar observation was made by Masuki and Joyner (Masuki *et al.* 2007) in their elegant study in which POTS patients showed smaller SV, higher HR, and comparable \dot{Q}_C during cycle ergometer with fixed workloads of 25, 50 and 75 watts compared with healthy individuals. This finding coupled with the present study strongly supports the cardiac origin of exercise intolerance in this syndrome. These physiological characteristics are quite similar to those observed after bed rest deconditioning. For instance, previous work

including from our laboratory has shown that $\dot{V}_{O_{2peak}}$, \dot{Q}_C and SV decreased by approximately 26%, 27% and 29%, respectively, after 3 weeks of bed rest (Saltin *et al.* 1968; Shibata *et al.* 2010).

An important observation in this study is that POTS patients and healthy sedentary controls had a similar linear relationship between \dot{V}_{O_2} and \dot{Q}_C . The slope of this linear

relationship has been reported to vary little in healthy adults with ageing, 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). Conversely, the slope is augmented, such that more blood flow is required to meet the metabolic demand of exercise, in patients with mitochondrial

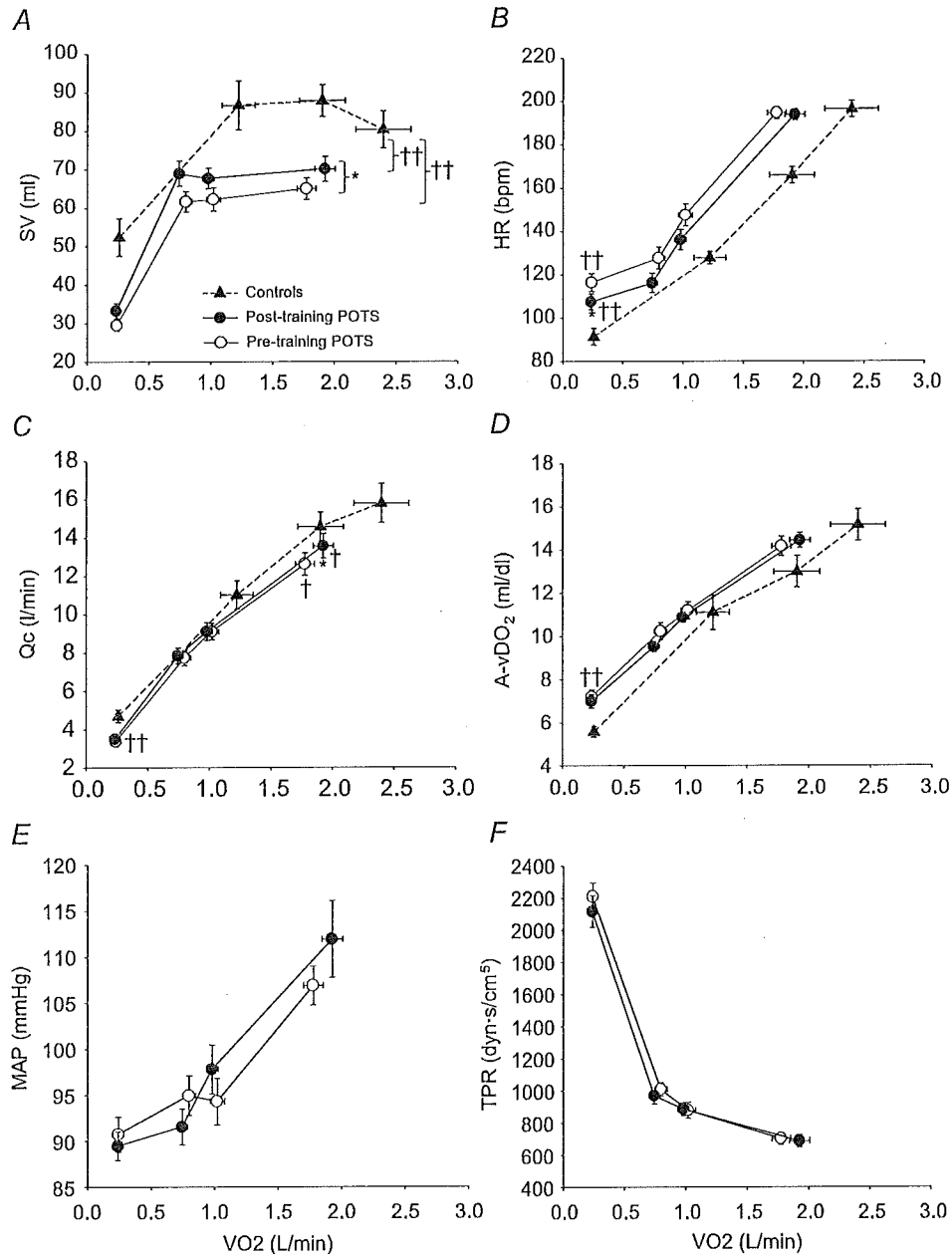


Figure 1. Changes in stroke volume (SV, A), heart rate (HR, B), cardiac output (\dot{Q}_C , C), arterio-venous oxygen content difference (a-v $\dot{D}O_2$, D), mean arterial pressure (MAP, E), and total peripheral resistance (TPR, F) in relation to changes in oxygen uptake (\dot{V}_{O_2}) during upright treadmill exercise before and after 3 months of exercise training in patients with POTS ($n = 19$) and healthy sedentary controls ($n = 7$). Values are means \pm SEM. * $P < 0.05$, pre-training compared with post-training in POTS. †† $P < 0.01$, patients compared with controls.

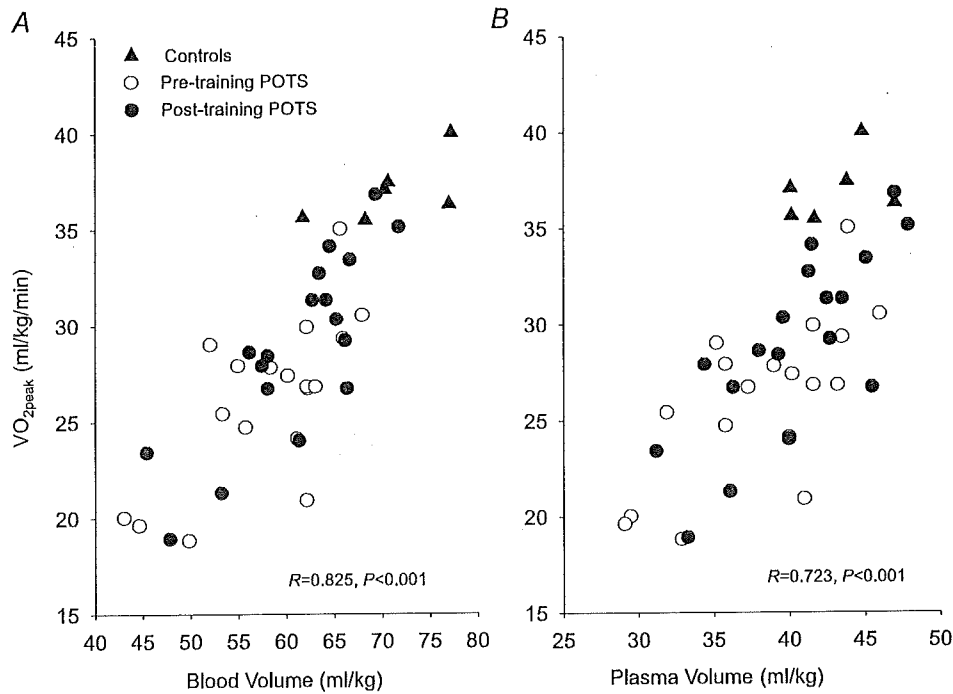


Figure 2. Peak oxygen uptake ($\dot{V}_{O_{2peak}}$) as a function of blood volume (A) and plasma volume (B) in healthy controls and patients with POTS before and after 3 months of exercise training

myopathy (Haller *et al.* 1991; Taivassalo *et al.* 2003) presumably due to impaired oxygen utilization by working muscles. In contrast, the slope is depressed in patients with severe heart failure (Chomsky *et al.* 1996; Mancini *et al.* 1996; Bhella *et al.* 2011), reflecting impaired ability of the heart to meet the metabolic demand. Thus, our results indicate that POTS patients have a normal ability to increase \dot{Q}_C for the oxygen demand during exercise, as well as to utilize oxygen in the periphery, consistent with the finding that a-v D_{O_2} in these patients was comparable with that of healthy controls at any given \dot{V}_{O_2} . Therefore, the higher HR in POTS patients at any given \dot{V}_{O_2} is most likely explained by a normal autonomically mediated compensatory response of the heart to the lower SV in order to maintain the required \dot{Q}_C and O_2 delivery.

Effects of training on exercise performance in POTS

Numerous studies have shown that $\dot{V}_{O_{2peak}}$ increases after several months of endurance exercise training in both men and women with a wide range of age (Ekblom *et al.* 1968; Hartley *et al.* 1969; Saltin *et al.* 1969; Seals *et al.* 1984; Ehsani *et al.* 1991; Stratton *et al.* 1994; Beere *et al.* 1999; McGuire *et al.* 2001; Fujimoto *et al.* 2010). We also found that $\dot{V}_{O_{2peak}}$ increased by 8% in POTS patients after 3 months of training. The increase in $\dot{V}_{O_{2peak}}$ was primarily caused by an increase in peak \dot{Q}_C with no changes in peak a-v D_{O_2} , in contrast with several previous investigations that showed an improvement of peripheral

oxygen extraction after training (Ekblom *et al.* 1968; Seals *et al.* 1984; Beere *et al.* 1999; McGuire *et al.* 2001). The duration of training in those investigations was equal to (Beere *et al.* 1999) or longer than (Ekblom *et al.* 1968; Seals *et al.* 1984; McGuire *et al.* 2001) that of the present study. One previous report, which similarly demonstrated

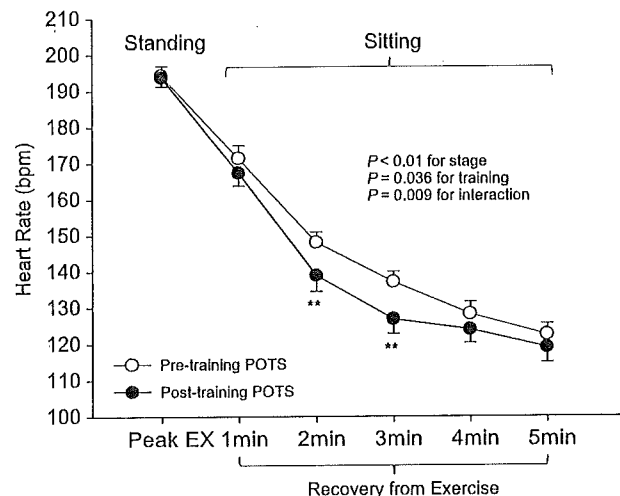


Figure 3. Heart rate (HR) recovery from exercise in POTS patients before and after exercise training. Peak EX, maximal exercise. Values are means \pm SEM. ** $P < 0.01$ compared with pre-training in POTS.

Table 3. Left ventricular diastolic function from Doppler echocardiography

Variables	POTS		Controls
	Pre-training	Post-training	
Mitral inflow			
E_{\max} (cm s ⁻¹)	84.4 ± 4.6	84.0 ± 3.8	90.0 ± 4.4
A_{\max} (cm s ⁻¹)	51.8 ± 2.5	53.9 ± 3.4	57.1 ± 6.3
E/A ratio	1.67 ± 0.10	1.68 ± 0.14	1.73 ± 0.20
IVRT (cm s ⁻¹)	90.4 ± 3.6	91.0 ± 5.0	90.8 ± 4.9
TDI-E			
Lateral (cm s ⁻¹)	15.3 ± 0.7	15.7 ± 0.6	15.7 ± 0.7
Septum (cm s ⁻¹)	12.0 ± 0.5	11.5 ± 0.5	12.0 ± 0.6
V_p (cm s ⁻¹)	60.1 ± 3.1†	60.3 ± 3.4†	74.1 ± 4.9

Values are means ± SEM. IVRT, isovolumetric relaxation time. TDI-E, tissue Doppler imaging of early (diastole). V_p , propagation velocity of early mitral inflow. †P < 0.05 compared with controls.

no changes in a-v D_{O_2} after exercise training in young adults, conducted a relatively short duration of training (~10 weeks) (Hartley *et al.* 1969). There are two possible explanations for our findings. One, POTS patients had much lower levels of physical fitness than healthy sedentary controls, and 3 months of training may not have been long enough to normalize their physical fitness levels. Two, patients started training in the semi-recumbent position to avoid the upright posture that elicits their symptoms, while upright exercise was not added until the second or third month of training. Thus, the intensity of training may not have been strong enough to cause changes in peripheral oxygen extraction in these patients within the time frame of this study.

The increase in peak \dot{Q}_C after training was caused by an increase in peak SV of 8% in the present study, consistent with the previous finding that POTS patients showed concentric hypertrophic remodelling in the left ventricle after training (Fu *et al.* 2010a). The similar increase in peak SV after exercise training was observed in many (Ekblom *et al.* 1968; Hartley *et al.* 1969; Seals *et al.* 1984; Ehsani *et al.* 1991; Stratton *et al.* 1994; McGuire *et al.* 2001; Fujimoto *et al.* 2010) but not all (Beere *et al.* 1999) prior studies in healthy individuals. This discrepancy is likely to be explained by different exercise regimens and/or subject backgrounds. In the present study, SV became larger at any given \dot{V}_{O_2} after training including the resting standing condition with the relationship between \dot{V}_{O_2} and \dot{Q}_C being constant, which consequently led to a lower HR at any given \dot{V}_{O_2} . This observation provides a strong physiological explanation for our previous finding as to why orthostatic tachycardia was substantially improved after training in most POTS patients (Fu *et al.* 2010a). Increases in cardiac size/mass and blood volume associated with exercise training were responsible for the increase in SV

in these patients. We found that $\dot{V}_{O_{2peak}}$ was correlated directly with blood volume in controls and patients before and after training, suggesting that expanded blood volume with training may contribute to the increased physical fitness level and cardiovascular performance in POTS (Hagberg *et al.* 1998). It is also possible that training might improve leg venous function and increase venous return during exercise in POTS.

However, neither $\dot{V}_{O_{2peak}}$ and \dot{Q}_C nor SV reached the level of healthy secondary controls after training although all of these physiological parameters were significantly improved. In contrast, it was reported that the decrease in $\dot{V}_{O_{2peak}}$, \dot{Q}_C and SV after 3 weeks of bed rest deconditioning was normalized above the level of pre-bed rest by 8 weeks of exercise training (Saltin *et al.* 1968). It is possible that chronic physical deconditioning may require a longer period of training to restore the deconditioned heart compared to the acute physical deconditioning of short-term bed rest.

We also found that HR recovery from exercise was significantly faster after training than before training in POTS patients. These results suggest that there are neural changes that occur after training that are relevant. It has been proposed that early recovery of the HR after acute exercise is dominated by vagal reactivation with sympathetic withdrawal becoming more important later in recovery (Imai *et al.* 1994; Pierpont *et al.* 2000). The rate of HR recovery from exercise has also been proposed to be associated with fitness level and global measures of health (Shetler *et al.* 2001). Thus, the faster HR recovery from exercise after training in our patients indicates an increase in vagal reactivation, a decrease in sympathetic tone, and an improvement in physical fitness level.

Cardiac diastolic function in POTS

Propagation velocity was lower in POTS patients compared with controls, while other Doppler indices were comparable between groups. Propagation velocity is primarily determined by passive filling and intra-ventricular pressure gradients within the ventricular cavity that actively draw blood from the base to the apex (Garcia *et al.* 2000). These intra-ventricular pressure gradients were previously shown to reflect the magnitude of diastolic suction during early diastole (Popovic *et al.* 2006). Filling pressure is usually high during supine exercise; however, Masuki *et al.* (2007) found that even while supine POTS patients tended to have low SVs. Because all other parameters of diastolic function were normal in our patients, the abnormality of diastolic function in POTS appeared limited to diastolic suction, rather than an intrinsic abnormality of relaxation.

Previous longitudinal studies have consistently shown that exercise training improves Doppler variables of LV diastolic function in young healthy individuals (Naylor

et al. 2005; Kivisto *et al.* 2006; Baggish *et al.* 2008; Weiner *et al.* 2010). It was also reported that short-term physical deconditioning due to bed rest led to impaired LV diastolic suction, which could be prevented by daily exercise training in young healthy subjects (Dorfman *et al.* 2008). However, there were no changes in any Doppler indices after training in POTS patients. Given the fact that this training paradigm increased, but did not entirely normalize, blood volume in these patients (Fu *et al.* 2010a), we suspect that the persistently abnormal resting propagation velocity was a function of a persistently low equilibrium volume. We speculate that more training, especially in the upright position would be required to completely normalize diastolic suction.

Perspectives

Results from this study confirm that in this referral population of patients with POTS, cardiovascular deconditioning plays an important role in the functional disability, and both orthostatic and exercise tachycardia observed in this condition. It is important to emphasize that even 20 h of bedrest induces substantial cardiovascular deconditioning in healthy individuals (Gaffney *et al.* 1985). This process may induce a downward spiral of hypovolaemia, cardiac atrophy (~1%/week in bed), worsening orthostatic intolerance and physical disability which can be quite profound. By demonstrating a normal cardiac output response to exercise, and a normal relationship between blood volume and $\dot{V}_{O_{2peak}}$, this study also demonstrates that the exertional tachycardia in POTS patients is appropriate for the metabolic demand. This tachycardia therefore appears 'appropriate' rather than 'inappropriate' and reflects the normal autonomic adjustments to the stimulus of exercise. Targeted therapy directed at the underlying pathophysiology improved, but did not completely normalize, the exercise responses in these patients and we speculate that perhaps longer durations of training may be necessary for a full functional recovery. What levels of physical activity must be maintained in patients with POTS to achieve and maintain normal functional capacity is uncertain; however we speculate that a lifetime adherence to an active life-style will be necessary.

Limitations

First, although the two groups were matched for age, sex and body mass index, percentage body fat was greater in POTS patients than in healthy controls presumably due to physical deconditioning. Second, the control group did not undergo a similar exercise training programme. However, previous studies from our laboratory showed that $\dot{V}_{O_{2peak}}$ increased similarly in

initially healthy sedentary individuals and POTS patients (13% *versus* 11%) after 3 months of training (Iwasaki *et al.* 2003).

Conclusion

In conclusion, the present findings emphasize that cardiovascular control during exercise is normal in patients with POTS. Moreover, they highlight the similarity between POTS and deconditioning by showing lower physical performance due to a low stroke volume during exercise in patients with POTS. Although physical fitness level and cardiovascular responses during exercise were improved after short-term (i.e. 3 months) exercise training, diastolic suction remained unchanged in these patients. Whether prolonged upright exercise training is needed to completely normalize exercise capacity and cardiac function in POTS patients remains to be determined.

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Author contributions

Shigeki Shibata contributed to 1) conception and design of the experiments; 2) collection, analysis and interpretation of data; and 3) drafting the article and revising it critically for important intellectual content.

Qi Fu contributed to 1) conception and design of the experiments; 2) collection, analysis and interpretation of data; and 3) drafting the article and revising it critically for important intellectual content.

Tiffany B. Bivens contributed to collection and analysis of data.

Jeffrey L. Hastings contributed to 1) collection, analysis and interpretation of data; and 2) revising it critically for important intellectual content.

Wade Wang contributed to collection and analysis of data.

Benjamin D. Levine contributed to 1) conception and design of the experiments; 2) collection, analysis and interpretation of data; and 3) revising the article for important intellectual content.

All authors approved the final version of the manuscript.

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