An Individualized Exercise Prescription to Attenuate Symptoms Associated With Postural Orthostatic Tachycardia Syndrome

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BACKGROUND

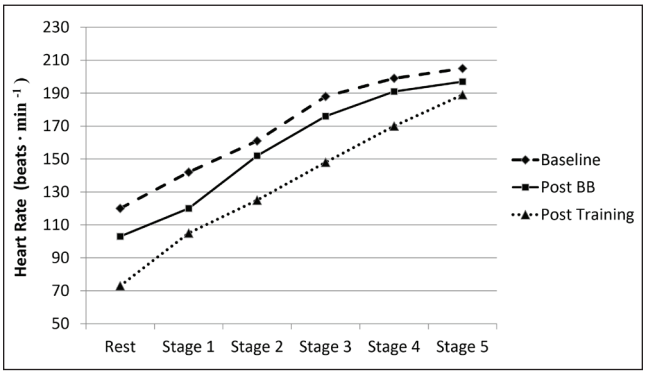
Ms. AB is a 20-year-old female who is training with a desire to become a professional ballerina. She is slender in appearance and has been her entire life, with a current body mass index (BMI) of 18 kg·m^{-2}. Since age 16 yr, she has experienced mild dyspnea with exertion. Initially thought to be exercise-induced asthma, her symptoms did not improve with bronchodilators. More recently, in addition to her exertional dyspnea, Ms. AB also experienced chest tightness, palpitations, and occasional lightheadedness and nausea when exercising or dancing. These symptoms were reproducible and excessive when compared to other dancers. Also of note was her complaint of profuse sweating.

In April 2012, her primary care physician referred her to a pulmonologist, who performed a pulmonary functional test (PFT) and a cardiopulmonary stress test on a cycle ergometer. While her PFT score and functional capacity were within normal limits, she was noted to have a marked and persistent rise in heart rate when assuming an upright position (120 beats·min^{-1}) prior to the exercise test, which did not normalize after three minutes of sitting on the cycle ergometer. However, despite the unusual heart rate response, the only conclusive finding was that she did not have asthma. Thus, her bronchodilators were discontinued.

Over the ensuing months Ms. AB enrolled in a professional ballet school, but her symptoms did not resolve. Despite being a trained athlete, she became symptomatic with everyday activities. On one occasion, her mother noticed she was visibly short of breath while carrying luggage up a flight of stairs. When she exercised at the gym, she was unable to increase the treadmill speed beyond 6.4 km/h (4 mph), as it exacerbated her symptoms.

Eventually, she returned to her physician. Concerned there may be some underlying cardiac abnormalities, her primary care physician referred Ms. AB for a cardiac evaluation. During the visit with the cardiologist, she again exhibited marked changes in heart rate (i.e., a heart rate rise of greater than 30 beats·min^{-1}), but despite the change from a supine to an upright position, there was no change in her blood pressure. No other abnormalities were noted. In view of the complaints of chest discomfort and palpitations during exercise, a stress echocardiogram was ordered. There were no structural cardiac abnormalities or findings of exercise-induced myocardial ischemia. However, fluctuations in heart rate at rest with body position changes and during exercise were striking. Upon standing, her heart rate rose to from 91 to 120 beats·min^{-1}. Furthermore, the heart rate rise during each stage was sudden and excessive (Figure 1). Typically, such an exaggerated heart rate response indicates deconditioning. However, this was not the case, as she completed

FIGURE 1. The heart rate response during a graded exercise test (GXT) is depicted before and after beta-blocker (BB) therapy. The heart rate response following exercise training is also shown.



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13.5 min of the Bruce protocol, achieving 13.9 METS (above-average exercise capacity).

Based on the heart rate changes that were observed with positional change and exercise, it was suspected that she may have postural orthostatic tachycardia syndrome (POTS). As part of treatment for POTS, it was recommended she increase her dietary sodium and fluid intake. She was also started on fludrocortisone (Florinef), an agent that reduces the amount of sodium lost from the body, therefore helping to maintain a proper balance of fluids. After starting fludrocortisone. she was prescribed an escalating dose of metoprolol. Fludrocortisone was started prior to the beta-blocker to increase her blood pressure (which was typically low), allowing her to better tolerate the metoprolol. To test the effectiveness of these changes, a second stress test was ordered to monitor her heart rate and symptoms while on these medications.

As expected, the beta-blocker attenuated the orthostatic tachycardia changes. Additionally, her heart rate response was 10 to 20 beats·min^{-1} lower during each submaximal stage of exercise (Figure 1), but no difference in total treadmill time or peak heart rate was noted when compared to the previous test.

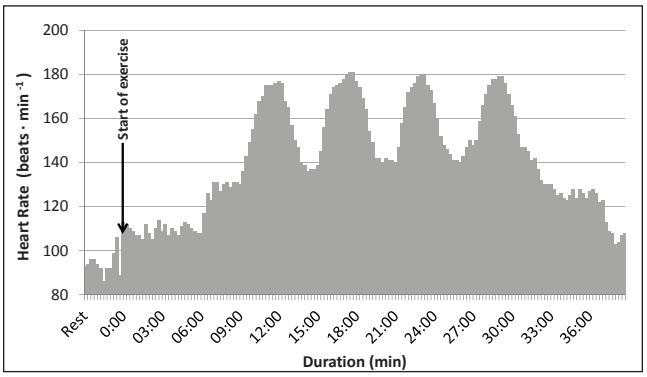
Once Ms. AB returned to the cardiologist, these results confirmed the original suspicion of POTS. However, except for her excessive sweating, which had markedly improved, other symptoms were only slightly improved. It was believed that given Ms. AB's continued intolerance to vigorous exercise, any additional symptomatic improvement would only be achieved by designing an exercise program that closely resembles her exercise routine (ballet dance). Subsequently, she was referred to work with a clinical exercise physiologist in the Preventive Cardiology unit at the Henry Ford Hospital in Detroit.

Given her intolerance to vigorous exercise, a program of high-intensity interval training (HIIT) was utilized to improve her functional capacity while simulating the intensity of her dance routine. Based on a European model (6), Ms. AB's HIIT protocol consisted of four intervals of high intensity (i.e., 90% of heart rate reserve [HRR]) interspersed between five intervals of "recovery" at a moderate intensity (i.e., 60% of HRR) (Figure 2). The training heart rates were based on a recent stress test while on beta-blockade therapy and the goal times for each exercise and recovery intensity interval were 4 and 3 min, respectively.

When Ms. AB arrived for her baseline visit, she appeared anxious, but other than a slightly elevated resting heart rate (90 beats·min^{-1}), she did not display any signs of orthostatic intolerance. Her heart rate increased only five beats from sitting to standing and her blood pressure was stable (102/70 mm Hg seated to 110/80 mm Hg standing) for more than 5 min of standing. Because of her slender size, the heart rate monitor chest lead strap (Polar) was modified with adhesive tape, as it was too large in circumference to fit.

During her first session, it was apparent that the high-intensity target rate of 170 to 177 beats·min^{-1} would be unattainable. Running at an initial speed of 12.1 km/h (7.5 mph) and 0% grade, she reported a rating of perceived exertion of 17 (Borg 6-20) and had to slow down to a moderate-intensity interval after 1.5 min and with her heart rate reaching only 162 beats·min^{-1} (70% of HRR). Subsequent heart rates during high-intensity intervals were also near 160 beats·min^{-1}, as intensity was titrated down to 6.5 mph. Her main reason for not being able to complete the intervals was dyspnea of a similar intensity to what she experienced during dancing.

FIGURE 2. This is the heart rate response during a typical training session using high-intensity interval training (HIIT). Note the gradual rise in heart rate following the initiation of exercise during warm-up, followed by peaks and valleys of heart rate response during and between high- and moderate-intensity exercise intervals.



Over the next two weeks, Ms. AB continued to perform her interval training program under the guidance of a clinical exercise physiologist. Her symptoms improved and she was able to increase the duration and number of the high-intensity intervals (i.e., increasing from three to four intervals). Interestingly, her heart rate during high-intensity intervals was >170 beats·min^{-1}, as originally anticipated. Part of the inability to increase her exercise heart rate was related to the timing of her metoprolol and fludrocortisone, as she had varied the time of day these were taken. Following the initial two weeks of supervised exercise, Ms. AB transitioned to performing her exercise at home.

Ms. AB continued her prescribed exercise program and returned three months later for a follow-up stress test. Despite no change in her functional capacity (13.9 METS), there were marked improvements in her submaximal heart rate (Figure 1). While her metoprolol remained unchanged, she was taken off fludrocortisone by her dermatologist because of pruritic rash. Upon her return to the cardiologist, she remained free of orthostatic tachycardia and subjectively reported significant improvements for exertional dyspnea, which, in her words, resulted in "better performances on stage." With this result, her physician continued to prescribe metoprolol and exercise training and did not re-prescribe fludrocortisone.

Epidemiology

Postural orthostatic tachycardia syndrome is a condition that is common in the age group of 15 to 50 yr, primarily effecting females more than males by an approximate ratio of 5:1 (1,7). The prevalence of POTS is unknown but has been

estimated at 170 cases per 100,000 individuals (8). Reluctance of diagnosis and spontaneous resolution of symptoms contribute to the elusiveness of the diagnosis and likely low estimate of the true prevalence of POTS.

Etiology

POTS is classified as a syndrome because of its consistent symptoms. Its etiology is considered either primary/idiopathic (not associated with another disease or syndrome), or secondary, occurring in association with a particular disease or disorder (7,10).

There are several physiological abnormalities that are thought to be potential causes of POTS, including hypovolemia, elevated plasma norepinephrine, and a small heart size (3,4,10). Many patients with POTS are hypovolemic, and have an average of 13% lower plasma volume (10). Decreased plasma volume can impair venous return and result in tachycardia, especially in response to moving from a supine to a standing posture and the resultant fluid volume shifts. In many patients with POTS, the renin-angiotensin-aldosterone system is not regulated properly in response to hypovolemia and can result in an absence of blood volume expansion, as would occur in most individuals. This explains why fluids, sodium, and fludrocortisone are often effective treatment options.

In addition to hypovolemia, Fu et al. found left ventricular mass to be significantly reduced, by 16%, in patients with POTS compared to normal patients (3). They termed this observation the "Grinch syndrome," akin to the main character of Dr. Seuss's famous children's book because his heart was "two sizes too small." Thus, orthostatic tachycardia can be a response to cardiac atrophy and hypovolemia. Raj et al. provided an in-depth discussion of other common POTS phenotypes, such as neuropathic, central hyperadrenergic, norepinephrine transporter deficiency, and mast cell activation (10).

Diagnosis and Clinical Manifestations

POTS is characterized by having chronic, consistent symptoms of orthostatic intolerance for 6 mo or longer. See Table 1 for common symptoms associated with POTS. In addition, other criteria for diagnosing POTS include (11):

- Heart rate increase >30 beats·min^{-1} from supine to standing (within 10 min of standing) in the absence of blood pressure dropping (>20/10 mm Hg decrease)
- Standing plasma norepinephrine >600 pg·mL^{-1}
- Symptoms worsen upon standing and improve with recumbence

Before confirming the diagnosis of POTS, ruling out such reversible causes as hypovolemia, prolonged bed rest, or certain medications should be an initial step (10). Some common medications known to exacerbate or cause orthostatic intolerance are alpha receptor blockers, diuretics, beta-blockers, nitrates, monoaminoxidase inhibitors, and angiotensin converting enzyme-inhibitors (5). Hematology should also be assessed for potential blood count, electrolyte, and hormonal imbalances that may contribute to such symptoms as anemia, hyponatremia, and hypothyroidism (14), respectively.

TABLE 1. The most common symptoms that occur in those with untreated postural orthostatic tachycardia syndrome.

Lightheadedness	Fatigue
Dizziness	Sweating
Palpitations	Tremors
Exercise intolerance	Near syncope

Treatment

Because POTS is a syndrome that manifests from various causes, the treatment and management of POTS will vary. Nonpharmacologic treatments include fluid replacement of 2 L·d^{-1}, along with sodium ingestion (2 to 4 g·d^{-1}). However, caution must be taken, as these measures may be contraindicated for individuals with chronic kidney disease, hypertension, and heart failure (12).

While the FDA has not approved any pharmacological agents for the treatment of POTS, there are many "off label" drugs that have been used to improve symptoms. Fludrocortisone, as prescribed in the case of Ms. AB, is a synthetic adrenocortical steroid that mimics the actions of endogenous aldosterone (13). This leads to greater sodium and water retention, which elevates blood volume and pressure. Beta-blockers are another common drug prescribed to treat POTS. However, if orthostatic tachycardia is a compensatory response to a low stroke volume, introducing a beta-blocker can lead to increased symptoms. Severe hypovolemia notwithstanding, the use of a low-dose beta-blocker is known to improve symptoms and possibly improve exercise performance (2).

Other medications used to improve symptoms of POTS are those that increase sympathetic output centrally (clonidine) or peripherally (alpha-one agonists, such as midodrine) or acetylcholinesterase inhibitors, such as pyridostigmine. Each of these work through different mechanisms to increase vascular resistance. Note that the Clinical Exercise Physiology Association makes no endorsement of off-label drug treatment.

CLINICAL EXERCISE IMPLICATIONS

Exercise Testing

Parsaik et al. (9) reported in a cohort of 184 patients with POTS that the prevalence of deconditioning (<80% of predicted peak $\dot{V}O_2$) was 93%. What is not known is whether deconditioning is antecedent to or a result of POTS. Regardless, the use of exercise testing in this population can be helpful. Aside from determining deconditioning, performing a GXT can assist in ruling out other potential causes (e.g., supraventricular tachycardia or myocardial ischemia) as well as establishing an exercise prescription. Depending on the severity of symptoms, selecting a treadmill or cycle protocol with small workload (METs) increments may decelerate the onset of symptoms. However, in the case of Ms. AB, because she was already a trained athlete, the use of a lower MET increase protocol was not necessary.

Exercise Prescription and Training

Exercise, along with increased fluid and sodium intake, is a common nonpharmaceutical treatment of POTS (5,9). In general, the effects of aerobic training and resistance training counteract the symptoms of POTS through various mechanisms. An example is increased leg muscle tone following resistance training, which may improve venous return via the skeletal muscle pump. Similarly, aerobic exercise may result in increased plasma volume as well as an improved autonomic balance between the parasympathetic and sympathetic arms of the autonomic nervous system.

When compared to a common pharmacological treatment (i.e., low-dose propranolol), exercise training is shown to have greater efficacy (4). Fu et al. reported that combined aerobic and resistance training in patients with POTS improved baroreflex sensitivity, preserved stroke volume, and normalized renal-adrenal response during an upright hemodynamic challenge (4). An important finding was the overall improvement in self-reported quality of life in an exercise trained group as compared to no change in a group treated with a beta-blocker.

While the American College of Sports Medicine guidelines do not have a current recommendation for training the individual with POTS, the current literature suggests slow and progressive aerobic and resistance training, beginning with non-upright modalities (e.g., recumbent bike, swimming, etc.) and gradually incorporating upright exercises (e.g., walking, elliptical, etc.). Suggested exercise intensity and duration is 75 to 85% of peak heart rate and for 30 min (4), respectively. As with any exercise prescription, many factors will dictate the initial intensity and duration. In the case of Ms. AB, she was more tolerant to exercise compared to many individuals diagnosed with POTS. In retrospect, the fact that she was a dancer and exercise-trained regularly may have masked symptoms at rest, thus making the diagnosis more difficult. Regardless, the use of exercise training in this unique patient population has good physiological rationale, leading to enhanced patient outcomes.

Keywords: exertional dyspnea, hypovolemia, sympathetic response

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