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Is exercise as effective as pharmacologic management of heart rate reduction in patients with symptomatic postural tachycardia

IMPROVING SYMPTOMATIC POSTURAL TACHYCARDIA WITH PHARMACOTHERAPY VERSUS PHYSICAL CONDITIONING

By

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Capstone Project
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BACKGROUND

An estimated one to three million Americans are affected by orthostatic intolerance, with females under age 35 the most common. Postural orthostatic tachycardia syndrome (POTS) is a disorder marked by symptoms of orthostatic intolerance within the first ten minutes of a patient moving from supine to an upright standing position.\(^1\) Patients must experience a sustained heart rate increase of at least 30 bpm (40 for pediatric patients) or greater than 120 bpm in the absence of orthostatic hypotension (OH). A thorough clinical evaluation should be performed prior to head-up tilt (HUT) testing to exclude other causes of tachycardia.

Although the exact etiology of POTS is unclear, the onset is believed to follow major life stress such as sepsis, pregnancy, trauma, recent history of mononucleosis or viral infection, major surgery or a prolonged period of immobilization.\(^4\)\(^-\)\(^5\) When a patient achieves orthostasis under usual circumstances, 500 mL of blood descends into the abdomen and limbs as the autonomic nervous system (ANS) responds with immediate peripheral vasoconstriction. With four times the number of women to men diagnosed, the peripheral vasodilatory effects of female sex hormones and vasoconstrictive nature of testosterone are thought to be a contributing factor.\(^1\)

In POTS the exact pathophysiology is poorly understood but is thought to result from inadequate vasoconstriction leading to blood pooling in the splanchnic and peripheral vasculature.\(^1\)\(^,\)\(^4\) To compensate, a further increase in heart rate and catecholamine occurs following orthostasis. Cerebral hypoperfusion is responsible for the wide range of symptoms POTS patients may experience.\(^1\)\(^-\)\(^3\)\(^,\)\(^5\) In addition to tachycardia, patients often complain of extreme
fatigability, exercise intolerance, shortness of breath, palpitations, blurred vision and dizziness. Pre-syncope is the most common symptom with 30% resulting in an episode of syncope.4-5

The neuropathic subtype occurs when sympathetic denervation in the lower extremities results in impaired venoconstriction and venous pooling as a result. To compensate for the expected drop in mean arterial pressure (MAP), an extreme cardiac rate response occurs. Conversely, the hyperadrenergic subgroup is characterized by increased sympathetic tone (palpitations, tremors, hypertension, generalized anxiety) in the presence of standing plasma from elevated norepinephrine levels.1-3 The majority of POTS patients have been found to have low blood volume with varying degrees of hypovolemia in addition to low renin and aldosterone levels responsible for maintaining satisfactory plasma levels.1-3

Additional commonalities among patients diagnosed with POTS have been found and scientists have suggested there may be an autoimmune component. Positive antinuclear antibodies (ANA) were present in a quarter of POTS patients with Hashimoto thyroiditis, rheumatoid arthritis and lupus being the most common concurrent diagnoses.1-4 Cardiovascular deconditioning is often evident, although it is poorly understood whether this is a cause or a complication. The overall functional impairment may give way to prolonged inactivity further exacerbating the fatigue, dizziness, palpitations and unfavorable symptoms experienced by POTS patients.6-7

Despite the large prevalence of orthostatic intolerance, numerous barriers prevent patients from receiving effective medical treatment. Research has found the disability severity from POTS is equivalent to patients diagnosed with congestive heart failure and chronic obstructive pulmonary disease with as many as a quarter leaving their schooling or employment
without proper treatment.\textsuperscript{2,4,7} Without proper education and awareness, patients are often misdiagnosed with psychiatric disorders leading to a faulty patient-provider relationship. In one study when anxiety questionnaires that focused on cognitive symptoms rather than somatic, POTS patients were found to have a lower incidence of anxiety when compared to the control group.\textsuperscript{1,5} Adequate management of postural orthostatic tachycardia syndrome is contingent with accurate diagnosis and improved referral pathways.

**EFFICACY OF TREATMENT MODALITIES**

**Beta adrenergic blocking agents:**

Propranolol is a non-selective beta blocker that inhibits all β-receptors resulting in decreased heart rate and vasoconstriction. Blood pooling and tachycardia may be reduced through use of beta-adrenergic blocking agents as many studies support. One study compared groups of patients with POTS treated with bisoprolol compared to propranolol. Both groups demonstrated marked improvement of orthostatic intolerance after the first month of pharmacologic treatment, with further symptom reduction after three months.\textsuperscript{7-9} Pyridostigmine was added to both beta-blockers but did not demonstrate significant improvement compared to treatment with either propranolol or bisoprolol alone.\textsuperscript{8,10-12}

A single blind crossover trial analyzed the efficacy of low dose propranolol compared to high dose propranolol. The first phase of the trial analyzed standing heart rate and blood pressure in addition to patient recorded symptom burden after 20 mg of propranolol was given. The second phase of the study repeated the same steps after initiating 80 mg of propranolol. A decrease in delta heart rate was seen after both doses of propranolol, and a greater standing systolic blood pressure was recorded after the higher dose was given.\textsuperscript{7} No significant difference
in symptom burden between the low dose and high dose group was recorded \((P = 0.527)\) with improvement in mental clouding, dyspnea and light headedness after the low dose only.\(^7\)

**Acetylcholinesterase inhibition:**

The second most common pharmacologic treatment modality for heart rate reduction and symptom improvement is through the inhibition of acetylcholinesterase. One retrospective study examined 203 patients that met inclusion criteria who were treated with pyridostigmine. Of the 203 patients, only 68 were able to tolerate the adverse reactions that resulted.\(^8,10\) Of the patients able to tolerate the medication, 51% recorded a marked improvement in fatigue, palpitations and pre syncope. Although pyridostigmine was able to reduce standing heart rate, another study found that patients reported decreased symptoms when compared to their baseline symptom profiles, but that not when compared to the placebo group.\(^8,10\)

**Adrenergic receptor agonist:**

Midodrine is an adrenergic receptor agonist commonly prescribed to patients with symptomatic orthostatic tachycardia. A retrospective single center study examined the treatment outcomes of 47 patients that were treated with either midodrine or a beta blocker. The study found that both groups experienced a reduction in standing blood pressure and heart rate, but the beta blocker group was more likely to credit the medication for their symptom improvement.\(^13\) A different study looked at the efficacy of midodrine hydrochloride when combined with conventional modalities and found that more patients reported short term
symptom improvement than with the beta blocker group alone, suggesting the importance of combination therapy.9,13

Exercise:

Several studies have suggested the importance of using exercise to treat symptomatic orthostatic tachycardia and correct possible cardiac deconditioning as a contributing cause.14-16 Unfortunately, treatment through exercise alone is associated with less patient compliance, as the patients are unable to tolerate most forms of exercise. Research has shown that when structured programs beginning with semi recumbent exercise that is gradually increased to upright conditioning, symptom remission can be reached within a few months. 14-16 After completing three months of supervised exercise conditioning, patients had faster heart rate recovery, decreased overall heart rate, and increased stroke volume. 15,16 Similarly, a randomized double-blind trial that gave propranolol or placebo treatment followed by three months of physical training resulted in significant reduction of standing heart rate following both phases of the study.16 Patients were issued a 36-item health survey questionnaire that found the patients who underwent the exercise training reported social function and quality of life improvement.16

LIMITATIONS

Overall heart rate reduction and the patient reported symptom improvement remains varied. Due to the subjective nature, this aspect of efficacy is difficult to quantify. Many studies were limited by the amount of participants despite promising study results. Access to specialized physical training for cardiac deconditioning management is a significant barrier keeping patients
from accessing the care and management. Clinically it may seem easier to prescribe medications to focus on lowering the blood pressure, however, many of the common medications given produces fatigue and weakness leading to decreased compliance. Cardiac conditioning is effective in giving patients better coping mechanisms in addition to developing a core regimen to prevent future episodes of deconditioning.

**CONCLUSION**

The exact etiology and pathophysiology responsible for the development of POTS remains poorly understood. Many general practitioners are not aware of the large prevalence of this disorder and the range of symptoms varies per individual. POTS patients are often misdiagnosed with anxiety, panic attacks, vasovagal syncope and chronic fatigue syndrome due to their young age. Vital signs are typically recorded in a seated position contributing further to their overall well appearance in clinic. Young female patients presenting with vague symptoms of dizziness, palpitations and fatigue can easily be screened by obtaining orthostatic vital signs. Proper diagnosis is essential to improving referral of these patients to an autonomic specialist, electrophysiologist or a syncope clinic where they can be better managed. With early diagnosis and treatment, 60% of POTS patients return to their prior level of function. When providers are adequately trained to recognize this disorder, they will have the capacity to better educate patients on the nature of their symptoms. These patients should be educated on aggravating factors to avoid such as extreme heat and dehydration. Sodium tablets have also proven to be beneficial in decreasing symptom burden and can be initiated by a general practitioner.

**FUTURE RESEARCH**
Several studies have shown long-term success following physical conditioning programs. Patient compliance is lacking for this form of treatment since exercise is poorly tolerated due to upright position triggering the symptoms that are already bothersome at baseline. Current research has identified POTS remission following conventional therapy utilizing exercise training, increased water intake, and increased dietary sodium. Future research is needed to further analyze whether each of these factors are independent treatment modalities.

Due to the multifaceted etiology behind these debilitating symptoms, further research should aim to effectively identify the physiologic cause for each patient so that individualized treatment can be initiated. Early research suggests a correlation between teenagers that develop POTS and having an excessively stimulated neurological system and high achieving personality. Furthermore, new treatment options can be further studied once the specific cause of orthostatic intolerance is more understood. It may be possible to prevent the development of these symptoms according to stratified risk factors.
References


