Cardiovascular exercise as a treatment of postural orthostatic tachycardia syndrome: A pragmatic treatment trial

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BACKGROUND Postural orthostatic tachycardia syndrome (POTS) is a heterogeneous disorder of orthostatic intolerance with few proven treatments.

OBJECTIVE The purpose of this study was to determine the efficacy of an unsupervised at-home training regimen for the treatment of POTS.

METHODS We reviewed the medical records including autonomic function testing, symptom scores, and activities of daily living in individuals with POTS who were invited to participate in a 6-month outpatient cardiovascular exercise program.

RESULTS Seventy-seven individuals were invited (invited group), 48 of 77 (62%) participated (treated group) and 43 of 77 (56%) of those completed. Twenty-nine of 77 (38%) did not participate (control group). After 6 months, 11 of 48 (23%) individuals in the treated group met heart rate criteria for POTS compared with 27 of 29 (93%) in the control group ($\chi^2$ test, $P < .0001$). Supine heart rate ($68 \pm 8$ beats/min vs $77 \pm 10$ beats/min; $P < .001$) and standing heart rate ($95 \pm 11$ beats/min vs $115 \pm 10$ beats/min; $P < .001$) decreased in the treated group compared with the control group. The frequency of syncope decreased in the treated group ($P < .001$). An improvement in the EuroQol perceived quality of life scale score was detected in the treated group (64 ± 9 vs 66 ± 8 after 6 months; $P = .52$).

CONCLUSION In this study, we report a successful pragmatic clinical trial of an outpatient exercise protocol in a tertiary care referral population that significantly improved cardiovascular function and quality of life in patients with POTS.

KEYWORDS Autonomic; Exercise; Neuropathy; Postural tachycardia syndrome; Syncope

Introduction

Postural orthostatic tachycardia syndrome (POTS) is an excessive increase in heart rate in the upright position associated with symptoms of orthostatic intolerance. Typical symptoms induced by the upright posture include lightheadedness, palpitations, visual blurring, weakness, presyncope, or syncope. Although the exact prevalence of POTS is unknown, some estimates suggest that up to 500,000 individuals in the United States may be affected. The chronic nature of the disease and the severity of symptoms result in diminished quality of life across multiple domains.

A number of pharmacological treatment options for POTS exist including $\beta$-blockade, blood volume expansion, and induced hypertension, but there are no studies of pharmacotherapeutic interventions above level B evidence. Furthermore, the off-label use of many medications has not afforded the majority of patients with POTS a successful outcome.

Recently, the positive effects of intense cardiovascular exercise in patients with POTS were reported in carefully monitored and supervised tertiary care studies and in a community-based registry study of patients with POTS. The results were remarkable for their improvement in both autonomic and cardiovascular parameters and quality of life. The primary objective of this quality improvement intervention was to assess whether these results could be replicated using an unsupervised intervention in a pragmatic clinical trial conducted in a tertiary care referral outpatient practice. To make the results more generalizable, all patients with idiopathic POTS were included irrespective of perceived POTS subtype and simple measurements of disability, quality of life, outcomes, and vital signs were the study outcomes.

Methods

Study design

This exercise protocol was developed as a program improvement project at the Autonomic and Peripheral Nerve Laboratory.
Laboratory Beth Israel Deaconess Medical Center. The study is a retrospective review of the patients treated as part of the program improvement project that was conducted in the neurology practice of a tertiary care teaching hospital. This retrospective review included all individuals with a clinical diagnosis of POTS. Subjects were seen as part of routine clinical care. All individuals with POTS seen in the outpatient autonomic disorders clinic from June 2009 to June 2018 were offered the opportunity to participate in an outpatient cardiovascular exercise program as part of their routine treatment of POTS. Individuals who agreed to participate in the exercise program were considered the “exercise treated” group of the study, while those who declined to participate were considered part of the “control” group of the study. The combination of these 2 groups is considered the “invited” group.

Subjects
All potential subjects who met the clinical definition of POTS were invited to participate. POTS was defined as an increase in heart rate of >30 beats/min from the supine to standing position with associated symptoms of orthostatic intolerance of at least 6 months’ duration (>40 beats/min increase in heart rate for individuals younger than 20 years). Individuals could not have any known medical condition or medication causing the tachycardia. Screening included, but was not limited to, diabetes, impaired glucose tolerance, vitamin deficiencies, heavy metal toxicity, thyroid disorders, pheochromocytoma, hypoadrenalism, anxiety, cardiac disease, volume depletion, drug abuse, and medication side effect. All individuals required confirmation of the diagnosis of POTS by orthostatic vital signs and symptoms consistent with a diagnosis of POTS within the prior 6 months and again at the time of study entry.

Protocol approvals, registrations, and patient consents
The study was designed as a quality improvement project in the autonomic disorders center at Beth Israel Deaconess Medical Center. Procedures were approved by the Beth Israel Deaconess Medical Center Institutional Review Board.

Intervention: Exercise protocol group
Participants in the exercise protocol were provided with a 20-minute description of the type of exercise on the initial visit along with a handout. The exercise protocol is demonstrated in Figure 1. Briefly, subjects began exercising on a recumbent bicycle for 10 min/d, 6 d/wk and each week added 3 minutes of exercise until they reached 45 minutes. After 12 weeks, participants were exercising for a total of 45 min/d, 6 d/wk on a recumbent bicycle. If subjects did not have access to a recumbent bicycle, a rowing machine or swimming was offered as an alternative option. Starting on week 13, subjects added 10 minutes of upright exercise on a treadmill or elliptical machine per day (or brisk walking/running outdoors if no equipment was available), 6 d/wk and reduced the time on the recumbent bicycle by an equal amount.

Intervention: Control group
Individuals who opted out of exercise were given routine clinical care recommendations regarding fluid and salt intake. Nonpharmacological therapies including compression stockings, abdominal binders, and physical countermaneuvers were discussed. Typical pharmacological therapies were considered on a case-by-case basis and included (but not limited to) fludrocortisone, midodrine, α-blockers, and pyridostigmine.

Orthostatic vital signs and autonomic testing
As part of routine medical care, all subjects completed orthostatic vital sign measurements at every visit. All subjects...
completed autonomic function testing within the 6 months before initiating the exercise protocol as part of routine clinical care, and many subjects completed autonomic testing within 2 months of exercise completion (ie, 6–8 months after study initiation). Thus, some patients may have been 2 months past the study completion date at the time of repeat testing.

Autonomic testing included a 45-minute tilt table test, 5 minutes of active standing, heart rate variability to paced breathing, and a Valsalva maneuver. The highest recorded heart rate during the first 10 minutes of tilt and the 5 minutes of active standing is reported. Complete details of autonomic testing are provided in the Online Supplement.

**Questionnaires**
Participants completed the following questionnaires at the time of autonomic testing or during clinical care visits: the Krupp Fatigue Severity Scale,\(^{19}\) the EuroQol Visual Analogue Scale (score of 100 = best imaginable health state; 0 = worst imaginable health state),\(^{20}\) and the Boston Autonomic Symptom Questionnaire.\(^{21}\) Individual symptoms are rated on a 0–10 scale (0 = no symptoms; 10 = maximal symptoms). Participants also recorded the number of syncopal or near-syncopal events that occurred over the preceding month at each clinical visit.

**Statistical analysis**
Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL). Data in the intervention and control groups are reported as mean ± SD or median and interquartile range. Analysis for the retrospective review is reported on an invited group basis, with last observation carried forward for incomplete data. The primary outcome for the study was the change in the number of individuals who met the criteria for POTS after intervention compared with preintervention. Other outcome measures included the changes in supine and standing heart rates after intervention and the change in symptom scores after intervention between the 2 groups. Baseline demographic data are analyzed using the unpaired \(t\) test if normally distributed, with Bonferroni corrections for multiple comparisons. Autonomic testing data are analyzed using the unpaired \(t\) test or \(\chi^2\) test for binary outcomes. Gender distribution and EuroQol questionnaire responses are analyzed using the Fisher exact test. Other ordinal questionnaire data are analyzed using the Kruskal-Wallis test and using the Mann-Whitney pairwise test with Bonferroni correction. Bonferroni corrections were made for multiple comparisons within questionnaire data. Significance for all studies is set at \(P < .05\).

**Data availability statement**
Data will be made available upon written request of investigators.

**Results**

**Demographic characteristics**
A total of 230 patients with postural tachycardia were screened. Of those screened, 153 were excluded for the following reasons: 141 were taking medications that caused postural tachycardia and 12 because of a known medical illness that caused tachycardia. Full details of exclusions are provided in the Online Supplement. The 77 remaining subjects with POTS were invited to participate in the exercise program—these were considered the invited cohort. A total of 48 subjects agreed to participate in the exercise protocol (the treated group), of whom 43 completed the protocol. A total of 19 subjects declined to participate and 10 subjects did not follow up after the initial visit (providing a total of 29 individuals as the control group). Those who declined to participate were unwilling to attempt the exercise protocol. A CONSORT diagram of patient allocation is shown in Figure 2. General demographic information of the invited cohort is provided in Table 1. Eight patients with the hypermobile form of Ehlers-Danlos syndrome and POTS were included, 5 in the exercise arm (5 completed) and 3 in the control arm of the study. No patients with known or suspected mast cell activation syndrome were included in this study.

**Orthostatic vital signs, autonomic testing, and POTS diagnosis**
In the primary invited group analysis at the study conclusion (after 6 months), the number of individuals who met heart rate criteria for POTS was 38 of 77 (49%; \(\chi^2\) test, \(P < .001\) vs baseline). The number of individuals who met the criteria in the exercise treated group was 11 of 48 (23%; 95% confidence interval 12%–37%), while the number of individuals who met heart rate criteria for POTS in the control...
The salutary effects of the implementation of an exercise program on cardiovascular autonomic control and symptoms of orthostatic intolerance are secondary to deconditioning, decreased left ventricular mass, and decreased cardiac output. The present study confirms and extends the findings of these studies. In this study, we report the successful pragmatic clinical treatment of POTS. Using an analysis of all invited subjects with last observation carried forward, we demonstrate that a standardized outpatient exercise regimen can diminish both the supine and standing heart rates in individuals with postural orthostatic tachycardia syndrome. The decrease in standing heart rate is greater than the decrease in supine heart rate, thereby reducing the number of individuals in the study group was 27 of 29 (93%; 95% confidence interval 77%-99%) ($\chi^2$ test, $P < .0001$).

The results before intervention and after 6 months of exercise for the intention to treat group are reported in Table 1. Forty-eight individuals in the treated group completed autonomic testing before study intervention, and 38 completed testing 6–8 months later. Twenty-nine individuals in the control group completed autonomic testing at baseline, but there was a significant decrease in supine heart rate ($P < .001$), standing heart rate ($P < .001$), and postural change in heart rate ($P < .001$) in the treated group compared with the control group (Table 1 and Figure 3). Nearly identical heart rate and blood pressure results were noted during tilt table testing, but because of fewer 6-month completers on tilt table testing, only the standing data are presented in Table 1.

### Symptom scores

The frequency of reported syncope or near-syncope was similar between groups at baseline. There was a significant decrease in the frequency of syncope in the treated group (median [interquartile range] 0 [0–2] events/mo in the treated group vs 3 [2–4] events/mo in the control group; $P < .001$).

After 6 months the severity of orthostatic lightheadedness, as measured by the Boston Autonomic Questionnaire, was reduced in the exercise group (8 ± 2 vs 7 ± 2 after 6 months; $P < .01$) but not in the control group (8 ± 2 vs 8 ± 2 after 6 months; $P = .81$). Similarly, the severity of postural dizziness was diminished in the exercise group (8 ± 2 vs 5 ± 2 after 6 months; $P < .001$) but not in the control group (8 ± 2 vs 8 ± 2 after 6 months; $P = .86$). The differences between groups were significant. There was an improvement in the EuroQol perceived quality of life scale score in the exercise group (61 ± 15 vs 71 ± 12 after 6 months; $P < .001$) compared with the control group (64 ± 9 vs 66 ± 8 after 6 months; $P = .52$). There were no statistically significant differences in the Krupp Fatigue Severity Scale in the treatment or control group after 6 months. The symptom scores between groups are presented in Figure 4.

### Discussion

The salutary effects of the implementation of an exercise program on cardiovascular autonomic control and symptoms of orthostatic intolerance and quality of life have been documented in several reports. These studies, which were conducted in a carefully monitored research environment and as a community-based registry study, were based on the hypothesis that the tachycardia and symptoms of orthostatic intolerance are secondary to deconditioning, decreased left ventricular mass, and decreased cardiac output. In this study, we report the successful pragmatic clinical treatment of POTS. Using an analysis of all invited subjects with last observation carried forward, we demonstrate that a standardized outpatient exercise regimen can diminish both the supine and standing heart rates in individuals with postural orthostatic tachycardia syndrome. The decrease in standing heart rate is greater than the decrease in supine heart rate, thereby reducing the number of individuals in the study.
who meet the heart rate criteria for POTS in the treated group by >75%. Coinciding with the improvement in cardiovascular parameters, the intervention resulted in improvements in orthostatic intolerance, a decrease in the frequency of syncope or near-syncope, and an improvement in perceived quality of life.

The effect of an exercise intervention on the natural history of POTS is not known; that is, were patients to return to their normal level of physical activity, would the postural tachycardia and symptoms of orthostatic intolerance return? At the very least, at the conclusion of our protocol, all patients who completed the program were able to exercise continuously for 45 minutes (or more) in the upright position, a task most were convinced was impossible for them 6 months earlier. The present study, consistent with prior reports, stresses the need to begin any exercise program in a semi-recumbent or seated position. Symptoms and quality of life improved in parallel with this improvement in exercise capacity. However, despite evidence of improved hemodynamics, symptoms, and functional capacity, most individuals still reported severe fatigue, suggesting that some symptoms are resistant to this intervention, and participants rated their quality of life far below the levels seen in healthy subjects.

Most patients report high levels of physical activity at the onset of POTS symptoms\(^6\); thus, we do not hypothesize that cardiovascular deconditioning is present in the acute phase and it is not known whether this intervention would be quite as effective early in the course of the disease. However, cardiovascular deconditioning is present in the vast majority of patients with POTS in the chronic disease state.\(^23\) In our study, both groups had been diagnosed with POTS for over 4 years, suggesting that the symptoms had been both chronic and stable and that deconditioning was likely.

We observed an improvement in health-related quality of life in the exercise compared with the placebo group, suggesting that the effects of the exercise protocol had effects that extended beyond the improvements in cardiovascular physiology. However, our data do not explain whether the effect on quality of life is directly related to the improvement in cardiovascular physiology or whether it is a pleiotropic effect of exercise on the patient’s sense of well-being as has been seen in a number of diseases such as depression, cancer, spinal cord injury, fibromyalgia, and healthy elderly.\(^24,25\)

The prescribed exercise in this and most other studies has been an endurance aerobic program with or without the addition of resistance exercise.\(^15,17,18\) It would be of interest to see whether resistance exercise such as weight training alone or flexibility exercise such as yoga would confer similar benefits. Such interventions may help address the challenges of blinding and provide a possible sham exercise protocol.

An important consideration with respect to any exercise intervention (or any therapeutic intervention) is whether
patients are able to adhere to the protocol, particularly without research center supervision and monitoring. Prior studies have noted that adherence to interventions with major lifestyle changes result in up to 70% dropout rates over a period of time. Of note, in the present study the 6-month duration extends the positive benefits of exercise 3 months longer than the 3-month study duration reported in prior studies. However, it is not possible to determine the level of adherence to the present protocol, although it appears unlikely that such positive benefits were obtained from non-adherence. Closely connected to this, exercise studies in POTS have a low completion rate, particularly in the outpatient setting. While low completion rates are not unique to POTS - exercise studies in general have a high dropout rate, the extent of the dropout rate remains a methodological concern. For example, in the 3-month hospital-based study, the completion rate was 71%, and in the community-based study of George et al, the completion rate was somewhat lower. In that study, of 251 participants who enrolled in the study, 117 (46%) did not finish the program. Training difficulty was the most common reason for failing to finish the program (reported by 57% of the non-completers). In the present study, 77 met the criteria and were invited to participate in the study. Of these, 62% agreed to participate and 10% did not finish the program. Of those who declined to participate, unwillingness to attempt the exercise program was the most common reason. Taken together, these studies highlight the importance of motivation in any exercise program and the need to incorporate adherence retention strategies. We incorporated adherence retention strategies that included goal setting, self-monitoring, decision-making tools, cognitive modification, and social support expansion. At a practical level, these adherence strategies were relatively brief discussions that occurred during the clinical visit but stressed weekly goals of exercise (ie, an increase in 3 min/wk), recognition of the challenges to be faced (it was going to be one of the most difficult challenges they would face), reorienting of preconceived negative outcomes, and enrollment of family members and friends into the social support structure to succeed at the exercise program.

The most similar study of exercise in POTS in the outpatient setting is the POTS registry study of George et al. In this multicenter outpatient registry study, 304 individuals were screened and 251 individuals were included. A major difference between the present study and that by George et al is the inclusion and exclusion criteria. In the present study, 67% of patients were excluded because they had potentially reversible causes of postural tachycardia. The registry study did not report on the exclusion of reversible causes of POTS. The completer rate in the study by George et al was 41% of the 251 enrolled patients, while it was 56% of the invited group in the present study. The completion rate of the invited cohort in the present study was 56%.

Figure 4  Symptom scores. The symptom scores for both groups are shown in a radial plot. The symptom scores are normalized to maximum and minimum values, with more severe symptoms/higher scores on the outside of the plot. The control group, shown in the blue plot, is largely unchanged from the baseline data. The exercise group, shown in the red plot, is significantly improved in all measures except the Krupp Fatigue Severity Scale. *P < .01 between groups.
Furthermore, the study by George et al was a community-based study whereas the present study took place in a tertiary care center where patients were less likely to be treatment naive and thus may be more refractory to treatment. Despite major differences between study design and inclusion criteria, cardiovascular outcomes were remarkably similar between the studies.

Most individuals with POTS have a history of physical activity before the onset of the illness, so the goal of exercise was appealing to most individuals despite concerns about an inability to succeed.\textsuperscript{10,15} It has been reported by patients was appealing to most individuals despite concerns about connective tissue disorders, such as Ehlers-Danlos syndrome, may create additional challenges to study retention. However, given the adaptability of the exercise program in this trial to include swimming as a therapy, the goal of exercise can still be incorporated across all POTS subtypes to improve the generalization of the results. In this study, only 8 individuals with Ehlers-Danlos syndrome were included, but all 5 who participated in the active treatment arm showed significant improvement without adverse effects. At the very least, it is reasonable to conclude on the basis of the existing evidence that in those patients willing to enter an exercise program, the intervention has a positive effect but also demonstrates that completion rates can be increased with greater physician involvement and adherence retention strategies.

This protocol was developed as a program improvement project that meets the criteria for a pragmatic clinical trial to optimize generalizability of the results. To limit the concerns that the interventions studied in explanatory trials are generalizable to clinical practice, we conducted the study in the outpatient clinical setting, with infrequent monitoring and supervision throughout the study with the aim to provide a real-world clinical practice setting.

Patients were provided with a clear description of the training program, with printed supplemental information and were provided opportunities for follow-up calls or visits as part of their routine medical care. While this design is a strength, there are several limitations to the present study. Subjects were allocated into treatment and control by their baseline characteristics did not differ between groups and the intention-to-treat analysis demonstrated a robust overall treatment effect. Some of the study subjects did not complete the study (although substantially fewer than in prior studies). Furthermore, the last observation carried forward analytical approach would have biased the study outcome to no effect and suggests that missing data do not compromise the study outcomes. Compliance with the treatment program is also self-reported; thus, an analysis of the invited group was used to determine the efficacy of the exercise program on outcome measures. Questionnaires were self-reported and were obtained only at the start and finish of the study.

Despite these limitations, we observed improvements in both supine and standing heart rates, and reductions in postural tachycardia, of patients with POTS after 6 months of exercise. More than 75% of patients in the treated group did not have POTS at the study conclusion. In addition, there was an associated improvement in symptoms and quality of life. The positive benefits of cardiovascular exercise in the treated group were robust, while the control group was largely unchanged after 6 months. This exercise protocol may be clinically beneficial across all subtypes of postural tachycardia syndrome, although additional study is needed for confirmation.

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2021.01.017.

References


