JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 10, NO. 2, 2024

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

CLINICAL ELECTROPHYSIOLOGY - NEUROMODULATION

Noninvasive Vagus Nerve Stimulation in Postural Tachycardia Syndrome

A Randomized Clinical Trial

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ABSTRACT

BACKGROUND Low-level transcutaneous stimulation of the auricular branch of the vagus nerve at the tragus is antiarrhythmic and anti-inflammatory in animals and humans. Preliminary studies show that transcutaneous vagus nerve stimulation (tVNS) is beneficial in animal models of postural tachycardia syndrome (POTS).

OBJECTIVES In this study the authors conducted a sham-controlled, double-blind, randomized clinical trial to examine the effect of tVNS on POTS over a 2-month period relative to sham stimulation.

METHODS tVNS (20 Hz, 1 mA below discomfort threshold) was delivered using an ear clip attached to either the tragus (active; n = 12) or the ear lobe (sham; n = 14) for 1 hour daily over a 2-month period. Postural tachycardia was assessed during the baseline and 2-month visit. Heart rate variability based on 5-minute electrocardiogram, serum cytokines, and antiautonomic autoantibodies were measured at the respective time points.

RESULTS Mean age was 34 ± 11 years (100% female; 81% Caucasian). Adherence to daily stimulation was 83% in the active arm and 86% in the sham arm ($P > 0.05$). Postural tachycardia was significantly less in the active arm compared with the sham arm at 2 months (mean postural increase in heart rate 17.6 ± 9.9 beats/min vs 31.7 ± 14.4 beats/min; $P = 0.01$). Antiadrenergic autoantibodies and inflammatory cytokines were lower in the active arm compared with the sham arm at 2 months ($P < 0.05$). Heart rate variability was better in the active arm. No device-related side effects were observed.

CONCLUSIONS Our results support the emerging paradigm of noninvasive neuromodulation to treat POTS. Mechanistically, this effect appears to be related to reduction of antiautonomic autoantibodies and inflammatory cytokines, and improvement in autonomic tone. Further studies are warranted. (Autoimmune Basis for Postural Tachycardia Syndrome; NCT05043051). (J Am Coll Cardiol EP 2024;10:346-355) © 2024 by the American College of Cardiology Foundation.

Postural tachycardia syndrome (POTS) is a syndrome of orthostatic intolerance, with a constellation of symptoms, including palpitations, dyspnea, mental clouding, and fatigue.[1,2] Importantly, POTS is associated with significant reduction in quality of life and unemployment.[3] The majority of patients are young females and the prevalence is at least 0.2% of the adult population.[1,2]

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 4, 2023; revised manuscript received September 18, 2023, accepted October 17, 2023.

ISSN 2405-500X/$36.00 https://doi.org/10.1016/j.jacep.2023.10.015

The pathophysiology of POTS remains poorly understood, although a number of intermediary mechanisms have been proposed, including hypovolemia, inadequate vasoconstriction, peripheral denervation, and abnormalities in central sympathetic tone.[1,2,4] Another potential mechanism involves the presence of activating autoantibodies to the α1-adrenergic receptor (α1AR) and β1/2-adrenergic receptor (β1/2AR).[5,6] Importantly, POTS is characterized by enhanced sympathetic tone,[7] which in turn is associated with increased inflammatory cytokines.[8] Although a variety of pharmacological and nonpharmacological therapies have been utilized in the treatment of patients with POTS, management of such patients is often challenging,[1,4] highlighting the need for alternative therapies.

Noninvasive, transcutaneous vagus nerve stimulation (tVNS), delivered at the tragus of the ear is an emerging therapy in a variety of cardiovascular conditions, including atrial fibrillation and heart failure with preserved ejection fraction.[9,10] Importantly, tVNS has been shown to exert antiadrenergic and anti-inflammatory effects in humans.[9,10] The rationale for using tVNS in POTS included improvement of orthostatic symptoms through its central effects, attenuation of orthostatic tachycardia through its antiadrenergic effects, and mitigation of inflammation.[11] Recently, we have shown that tVNS improved autonomic imbalance and decreased inflammation in a rabbit model of autoantibody-induced hyperadrenergic POTS.[12] However, the effects of tVNS in patients with POTS remain to be determined. In this proof-of-concept, translational study, we evaluated the effect of chronic tVNS on orthostatic tachycardia in patients with POTS over a 2-month period relative to sham stimulation.

METHODS

This was a prospective double-blind, sham-controlled, randomized clinical trial. Patients with POTS, defined as heart rate increase >30 beats/min from supine within 10 minute of standing, in the absence of orthostatic hypotension (>20/10 mm Hg fall in blood pressure), with chronic symptoms (>6 months), and in the absence of other acute cause of orthostatic tachycardia, were eligible for enrollment in the study. Patients were excluded if they had any of the following: significant hypertension, either supine or standing (>150 mm Hg systolic and >100 mm Hg diastolic), orthostatic hypotension (consistent drop in blood pressure >20/10 mm Hg with 10 min of standing), recent (<6 months) stroke or myocardial infarction, history or presence of significant immunological or hematological disorders, severe anemia (hematocrit <28%), history of vagotomy, and pregnancy or nursing. Patients were recruited from the arrhythmia clinic of the University of Oklahoma Health Sciences Center. The study was approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center and informed consent was obtained from all patients prior to enrollment in the study. The study was registered at ClinicalTrials.gov (NCT05043051).

Patients were randomly assigned (1:1) to active or sham tVNS using a Web-based randomization table, stratified by sex. Block randomization was used to decrease imbalances in the 2 groups over time. Active tVNS was performed using a tVNS device (Parasym device; Parasym Health) with an ear clip attached to the tragus (**Figure 1**), which is innervated by the auricular branch of the vagus nerve.[13] The ear lobe, which is devoid of vagal innervation,[13] was chosen as the site of stimulation in the sham group. Patients were unaware which site provides active stimulation to achieve blinding of treatment allocation. The investigators determining the clinical outcomes were also blinded to treatment allocation. tVNS was delivered at a frequency of 20 Hz and pulse width of 200 μs, as previously described in atrial fibrillation and heart failure studies.[9,10] The stimulation amplitude was individually titrated to 1 mA below the discomfort threshold. On average, this level corresponds to approximately half the bradycardia threshold.[14] Stimulation was delivered for 1 hour daily over a 2-month period, by the patients themselves after individual training. To ensure consistency, patients were instructed to use the right tragus (or earlobe) for all tVNS treatments. Patients were instructed to place the stimulation electrode in a similar fashion (at the respective sites for each group), without stating which is the active site to prevent unblinding, and were also provided written instructions pertaining to their group. Cathode and anode were color coded to ensure placement of cathode in the inside. Placement was confirmed by the coordinator during the initial training session. Patients were instructed to keep a daily log with the time and duration of tVNS application, amplitude settings, and any comments related to each daily session.

At baseline and 2 months, patients underwent a tilt test to determine postural tachycardia. Patients remained supine for 25 minutes, followed by 10 minutes of standing, as tolerated. To minimize the

ABBREVIATIONS AND ACRONYMS

α1AR = α1-adrenergic receptor

β1/2AR = β1/2-adrenergic receptors

COMPASS-31 = Composite Autonomic Symptom Scale 31

HF = high frequency

HRV = heart rate variability

IL = interleukin

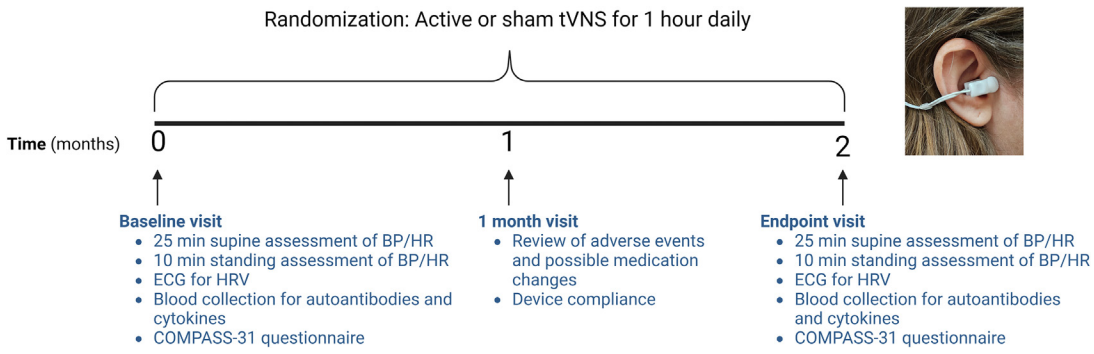
LF = low frequency

POTS = postural tachycardia syndrome

TNF = tumor necrosis factor

tVNS = transcutaneous vagus nerve stimulation

FIGURE 1 Schematic Representation of the Study Design and Timeline of Events



A representative example of active stimulation, with the ear clip attached to the tragus is shown in the inset. BP = blood pressure; COMPASS-31 = Composite Autonomic Symptom Scale 31; ECG = electrocardiogram; HR = heart rate; HRV = heart rate variability; VNS = vagal nerve stimulation.

effect of the diurnal variation of postural tachycardia on the results,[15] the tilt test was undertaken between 8 AM and 11 AM. The test was performed in the fasting state and no medications were withdrawn prior to the test. A 12-lead electrocardiogram was continuously recorded during both the supine and the upright positions. Blood pressure was recorded every 2.5 minutes using an oscillometric cuff. A blood sample (20 mL) was collected at 2.5 minutes prior to standing. Autonomic symptoms were assessed at the respective timepoints using the validated Composite Autonomic Symptom Scale 31 (COMPASS-31) questionnaire, which provides a global autonomic severity score (0-100; higher scores indicate worse symptoms) in 6 different domains (orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor).[16] A schematic representation of the study design and endpoints is shown in Figure 1.

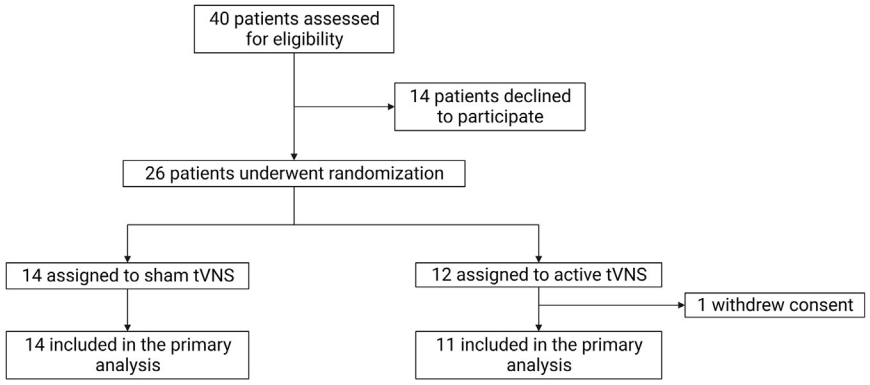
SERUM AUTOANTIBODY ACTIVITY ANALYSIS. Serum activation of α1AR or β1AR in α1AR- or β1AR-NFAT-β-lactamase CHO-K1 cells was assessed using the GeneBLAzer FRET (fluorescence resonance energy transfer)-based β-lactamase reporter assay (Invitrogen/Thermo Fisher Scientific). Briefly, cells were plated in 96-well plates and incubated overnight. Cells were then treated with sera (1:50) for 5 hours, followed by addition and incubation of the β-lactamase substrate CCF4-AM (LiveBLAzer-FRET B/G Loading Kit; Invitrogen/Thermo Fisher Scientific) for 2 hours. The plates were read using a BioTek multimode microplate reader. All samples were assayed in triplicate. Negative (buffer) and positive (phenylephrine or isoproterenol) controls were included in each assay. Outputs were calculated as the ratio of the emissions 460/530 nm (blue/green) after subtraction of the background values and expressed as fold increase over buffer baseline. To ensure rigor, the investigators performing these assays were blinded to group assignment.

SERUM CYTOKINE ANALYSIS. Serum samples were stored in aliquots at −80°C until assayed in batches of 12 to 16. Inflammatory cytokines, including tumor necrosis factor α (TNF-α), interleukin (IL)-6, IL-8, and interferon γ, were measured using the Bio-Plex pro human cytokine multiplex assay (Bio-Rad Laboratories) analyzed on a Bio-Rad Bio-Plex 200 system. The investigators performing the cytokine assays were blinded to group assignment.

HEART RATE VARIABILITY ANALYSIS. For calculation of heart rate variability (HRV), a 5-min electrocardiogram recorded in the supine and upright position was used. Patients were asked to abstain from alcohol, smoking, and exercise for 12 hours and caffeine for 4 hours and prior to the visit to avoid any interference with the results. Analysis and interpretation of the HRV data was performed in a blinded fashion, using the Kubios HRV software (Kubios Inc), as previously described.[10,17] Given the relatively short duration of the recordings, only the frequency domain data were analyzed.[17]

STATISTICAL ANALYSIS. The primary outcome of the study was a comparison of orthostatic tachycardia (standing - supine) at the 2-month time point between the 2 arms. Secondary outcomes included postural changes of HRV parameters (Δ standing - supine), as surrogates of the changes in cardiac autonomic tone,[18] antiadrenergic antibody activity,

FIGURE 2 Flow Diagram of Participant Recruitment and Follow-Up



tVNS = transcutaneous vagus nerve stimulation.

inflammatory cytokines, and autonomic symptoms, based on the COMPASS-31 questionnaire.[16] Continuous variables are presented as mean ± SD and categorical variables are presented as percentages. Baseline characteristics were compared between groups using *t* test for continuous variables and Fisher exact test for categorical variables. Outcomes were compared between the 2 arms using a mixed linear regression model, after adjusting for baseline values. The linear regression model allows for testing for time-by-group interactions, indicating a differential effect of treatment over time. Time-by-group interactions were included in the model, and if significant were followed by time trend analyses stratified by intervention group. For all pairwise testing, we adjusted for multiple comparisons using Tukey's method. For each model, the assumptions of normality and constant variance were checked using QQ plots and residual plots, respectively. Analysis was performed according to the intention-to-treat principle. Statistical significance was declared at $P < 0.05$. All statistical analyses were performed using SAS 9.4 software (SAS Institute).

Sample size and power calculations. Assuming a mean heart rate increase upon standing in the control group of 43 ± 17 beats/min[19] and a 40% reduction in the active group, a sample size of 26 patients would provide at least 80% power to detect the specified effect sizes at a 2-sided significance α level of 0.05.

RESULTS

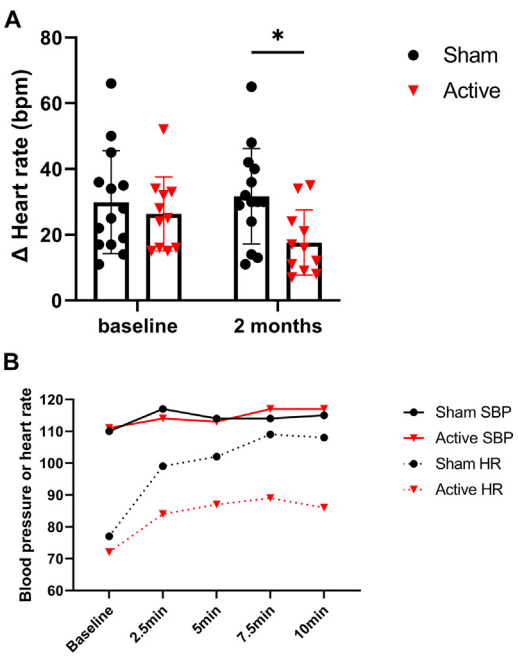
STUDY POPULATION. From July 2022 through February 2023, 40 patients were screened for eligibility and 26 patients were enrolled in the study (Figure 1). Among the 26 patients, 12 (46%) were randomized to the active stimulation group and 14 (54%) were randomized to the sham group. During follow-up, 1 patient in the active group withdrew consent due to personal reasons not related to the intervention (Figure 2). Thus, of the 26 randomized patients, 25 patients completed the study and were

TABLE 1 Baseline Characteristics of the Patients

Characteristic	Sham (n = 14)	Active (n = 12)	*P* Value
Age, y	30.8 ± 5.6	31.2 ± 5.5	0.86
Female	14 (100)	12 (100)	1.0
Caucasian	11 (79)	10 (83)	0.60
Body mass index, kg/m^2	28.5 ± 7.9	27.3 ± 7.4	0.69
History of COVID-19 infection	7 (50)	5 (42)	0.71
Duration of symptoms ≥1 y	9 (64)	7 (58)	1.0
Comorbid conditions			
Fibromyalgia	2 (14)	2 (17)	1.0
Migraines	9 (64)	8 (67)	1.0
Ehlers-Danlos 3	7 (50)	5 (42)	0.71
Gastroparesis	4 (29)	3 (25)	1.0
Hypothyroidism	4 (29)	3 (25)	1.0
Medical therapy			
Midodrine	8 (57)	7 (58)	1.0
Fludrocortisone	4 (29)	3 (25)	1.0
Propranolol	7 (50)	6 (50)	1.0
Ivabradine	1 (8)	1 (7)	1.0
Supine systolic BP, mm Hg	109.5 ± 6.7	108.9 ± 9.5	0.85
Supine diastolic BP, mm Hg	72.4 ± 6.7	69.4 ± 6.9	0.27
Supine heart rate, beats/min	68.2 ± 9.9	64.2 ± 6.9	0.25
COMPASS-31 score	48.4 ± 11.8	47.8 ± 10.8	0.90

Values are mean ± SD or n (%).
BP = blood pressure; COMPASS-31 = Composite Autonomic Symptom Scale 31.

FIGURE 3 Effect of Transcutaneous Vagus Nerve Stimulation on Orthostatic Tachycardia



(A) Comparison of orthostatic tachycardia between the 2 groups. (B) Representative examples of systolic blood pressure (SBP) and heart rate (HR) changes during tilt test in patients from each group. *$P < 0.05$.

included in the final data analysis. The baseline characteristics of the patients were roughly balanced between the 2 groups (Table 1). Notably, all participants were female (mean age 34 ± 11 years; 81% Caucasian) and were already taking at least 1 medication for POTS (Table 1). No medication changes occurred during the follow-up period. In addition, 12 patients had a history of COVID-19 infection within the prior year. Patients had significant functional impairment at baseline, as evidenced by a COMPASS-31 score of >40 in both arms (48.4 ± 11.8 vs 47.8 ± 10.8 in sham and active groups, respectively; $P = 0.90$).

Adherence to the protocol of daily stimulation, defined as ≤4 sessions missed on average per month, was 83% in the active group and 86% in the sham group at 2 months ($P = 0.99$). There were no crossovers. The average stimulation amplitude was 15.4 ± 8.6 mA and 16.3 ± 9.1 mA in the active and sham groups, respectively ($P = 0.79$). There were no device-related adverse events during follow-up.

ORTHOSTATIC TACHYCARDIA. Baseline postural tachycardia was 26.4 ± 11.3 beats/min in the active group and 29.9 ± 15.6 beats/min in the sham group ($P = 0.51$). The increase in heart rate during the postural test was significantly attenuated at 2 months in the active group compared with the sham group (17.6 ± 9.9 beats/min vs 31.7 ± 14.4 beats/min; $P = 0.01$) (Figure 3). No patient had a drop in their blood pressure >20 mm Hg during the postural test.

ANTIAUTONOMIC AUTOANTIBODIES. β1AR autoantibody activity was significantly decreased at 2 months in the active group compared with the sham group ($P = 0.01$) (Figure 4A). Likewise, α1AR autoantibody activity was significantly lower in the active group compared with the sham group ($P = 0.04$) (Figure 4B).

CYTOKINES. Serum TNF-α levels were significantly decreased at 2 months in the active group relative to the sham group (8.3 ± 4.6 pg/mL vs 13.9 ± 5.1 pg/mL; $P = 0.01$) (Table 2). As expected in the absence of acute infection or inflammatory or autoimmune condition in our patients,[20,21] the levels of the rest of the cytokines examined were low, and were not significantly different between the 2 groups (Table 2).

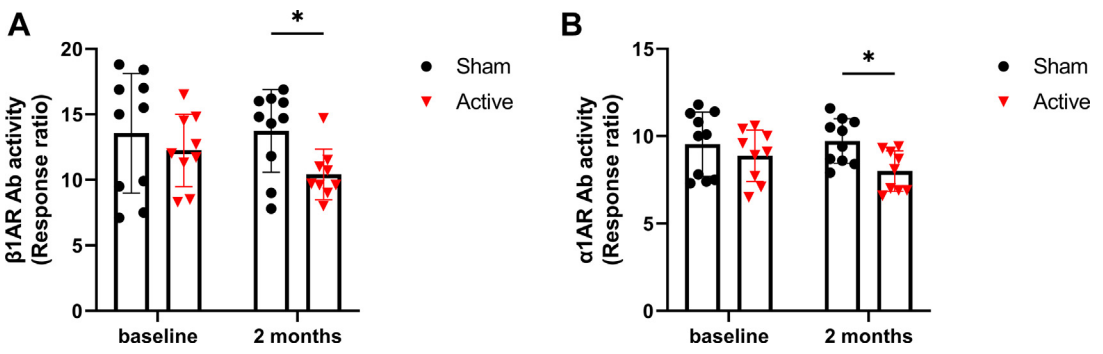
HEART RATE VARIABILITY. Considering that frequency domain measures perform better than time domain measures when short duration (5-minute) recordings are examined,[17] we focused only on frequency domain parameter analysis. The change in low frequency (LF) and high frequency (HF) from supine to standing was significantly attenuated in the active group compared with the sham group (Figure 5). Similarly, the postural change in LF/HF ratio, which reflects sympathovagal balance,[18] was significantly lower in the active group compared with the sham group (Figure 5).

AUTONOMIC SYMPTOMS. Autonomic symptoms were assessed using the COMPASS-31 questionnaire[16] and are summarized in Table 3. There was a numerical, albeit not statistically significant, difference between the 2 groups (47.3 ± 8.2 vs 42.6 ± 6.3 in the active vs sham groups; $P = 0.07$) (Table 3). This effect was mainly driven by a significant improvement in secretomotor function in the active group compared with the sham group (6.1 ± 3.7 vs 2.9 ± 3.3; $P = 0.001$) (Table 3).

DISCUSSION

In this translational study, we showed for the first time that intermittent, transcutaneous electrical stimulation of the auricular branch of the vagus

FIGURE 4 Comparison of Antiautonomic Autoantibody Activity Between the 2 Groups



(A) β1-adrenergic receptor (β1AR) autoantibody activity. (B) α1-adrenergic receptor (α1AR) autoantibody activity. *$P < 0.05$. Ab = antibody.

nerve at the tragus, over a 2-month period, attenuated the orthostatic tachycardia in patients with POTS. This favorable effect was associated with a decrease in β1AR and α1AR autoantibodies, improvement in cardiac autonomic function, and decrease in serum inflammatory cytokines (**Central Illustration**). Collectively, these data suggest that tVNS, a low-cost, low-risk intervention, applied for a short period of time in selected patients with POTS, may result in a significant amelioration of their disease. The importance of this finding is highlighted by the paucity of evidence-based interventions that have been shown to consistently benefit this patient population.[1] Importantly, given that the treatment of POTS typically requires a personalized approach to each patient,[4] autonomic modulation may offer another option in these patients. Notably, compliance with tVNS therapy was comparable to other pharmacological[22] or nonpharmacological[23] interventions in a similar patient population. Our results corroborate recent experimental evidence from our group, that tVNS is able to improve orthostatic tachycardia in a rabbit model of autoimmune POTS.[12,24] These results are certainly promising and provide the basis for the design of further randomized clinical trials to evaluate the long-term efficacy of autonomic neuromodulation therapy for patients with POTS.

An overall enhancement of sympathetic tone at rest and an increase in sympathovagal balance with tilt are characteristics of POTS, and these changes of autonomic function are major contributors of postural tachycardia.[7,25] Improvement in cardiac autonomic function by tVNS, highlighted by a decrease in LF and increase in HF, resulting an overall decrease in LF/HF ratio (a surrogate for sympathovagal balance), may be responsible to the attenuation of postural tachycardia in our study. Importantly, it has been previously shown that tVNS activates central vagal projections in the brain in humans, leading to decreased sympathetic output.[26] These data are consistent with 2 recent experimental studies from our group, showing a similar improvement in HRV parameters during tilt with the use of tVNS, in a rabbit model of POTS.[12,24]

Recent animal and human data support the role of antiadrenergic autoantibodies in the pathogenesis of POTS, at least in a subset of patients.[4-6,27] In addition to the increased prevalence of these autoantibodies in POTS compared with control subjects, sera from POTS patients act as a partial α1AR antagonist, significantly shifting phenylephrine contractility curves to the right, while increasing β1AR activation, thus explaining the excessive orthostatic tachycardia observed in POTS patients.[5,6] A decrease in autoantibody activity in our study by tVNS may account at least in part for the observed attenuation of orthostatic tachycardia. Moreover, the improvement in the sudomotor function of these patients, a purely

TABLE 2 Effect of Treatment on Serum Inflammatory Cytokines

	Baseline			2 mo		
	Sham	Active	*P* Value	Sham	Active	*P* Value
Tumor necrosis factor α	12.9 ± 5.9	12.8 ± 4.7	0.92	13.9 ± 5.1	8.3 ± 4.6	0.01
Interleukin-6	1.5 ± 0.7	1.4 ± 0.5	0.78	1.5 ± 0.8	1.4 ± 0.7	0.80
Interleukin-8	8.8 ± 1.2	8.5 ± 1.4	0.64	8.6 ± 1.9	8.0 ± 2.1	0.15
Interferon γ	1.0 ± 0.3	0.9 ± 0.4	0.82	0.9 ± 0.4	0.7 ± 0.2	0.13

Values are mean ± SD.

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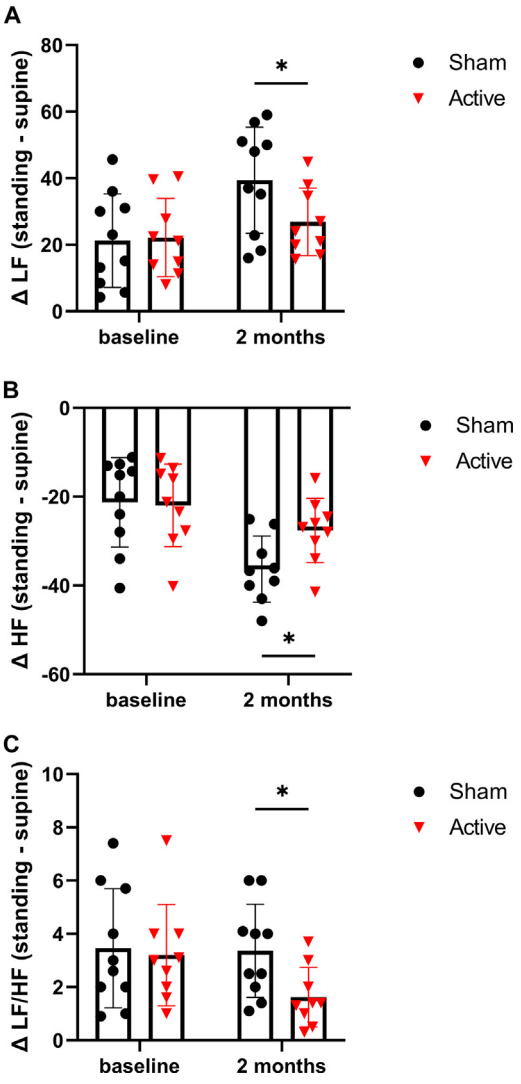
FIGURE 5 Comparison of Heart Rate Variability Measures Between the 2 Groups



(A) Low frequency (LF). (B) High frequency (HF). (C) LF/HF ratio. *$P < 0.05$.

adrenergic function, may also be related to a decrease in autoantibodies. In contrast, in our recent animal studies there was no change in autoantibody levels after tVNS treatment, likely because of the short duration of the study.[12,24] It should be noted, however, that the exact mechanisms for this effect have not been clearly defined, and further studies are warranted to better characterize the link between POTS, antiautonomic autoantibodies, and autonomic modulation.

There is accumulating evidence supporting an inflammatory component in the pathogenesis of POTS.[8,28,29] Notably, unbiased proteomic analysis of plasma from POTS patients indicated that a proinflammatory and hyperadrenergic state exists compared with control subjects.[28] These data suggest that chronic autoimmune activation and inflammation may contribute to a hyperadrenergic state, leading to POTS.[8,28,29] Importantly, we have shown that TNF-α levels were significantly decreased by active compared with sham stimulation in the current study. This effect, similar in magnitude to our previous human studies,[9,10] is consistent with the well-characterized anti-inflammatory effects of VNS.[30,31] Specifically, the vagus nerve provides the efferent and possibly the afferent limb of the cholinergic anti-inflammatory pathway, by which the brain modulates inflammation.[30,32] Notably, short periods of VNS (only 4 minutes daily in one study) may be sufficient to induce a long-lasting anti-inflammatory response.[31,32] In addition, tVNS resulted in activation of central vagal projections in the brainstem in humans, which persisted well after cessation of stimulation.[26] Taken together, these observations lend credence to the notion that the effects of tVNS are characterized by "memory," thus allowing for brief periods of stimulation to result in long-lasting effects. Consistent with this notion, 1 hour of daily stimulation resulted in a decrease in TNF-α levels at 2 months in this current study. Importantly, the anti-inflammatory effect of tVNS may contribute to the alleviation of noncardiac symptoms of POTS.[11]

The severity of the autonomic symptoms in our patient population indicate a symptomatic population, consistent with other cohorts of POTS patients.[33] While the COMPASS-31 questionnaire is a simple and validated tool to assess autonomic symptoms, it was not developed specifically for POTS.[16] This may explain in part the absence of a clear improvement in autonomic symptoms in our study. It is also possible that COMPASS-31 is not sensitive enough for short-term changes in autonomic symptoms. A more POTS-specific assessment of symptom burden[34] might have resulted in better discrimination between the 2 groups. Nonetheless, the significant improvement in secretomotor function, which includes sweating, is consistent with the antiadrenergic effects of tVNS. Future studies should correlate the use of tVNS to improved patient reported outcomes.

STUDY LIMITATIONS. The small sample size of this study is a limitation. While these results cannot be considered definitive, they nonetheless provide a proof of concept of a beneficial effect of tVNS in this patient population and form the basis for further human studies. However, given the lack of improvement in the overall COMPASS-31 score, it cannot be concluded from this study that tVNS improved patient reported outcomes. Even though the patient population consisted of females exclusively, it is unlikely that sex differences in the effects of tVNS exist, based on our previous experience.[9,10] POTS is a heterogeneous disease, with multiple pathophysiologic mechanisms.[1,2] We did not attempt to phenotype our patients into one of the described POTS phenotypes.[1,2] However, in the absence of a gold standard for phenotyping of patients with POTS, such an approach would have increased the variability and would have limited the generalizability of our results. The optimal duration and the ideal timing of tVNS is yet to be determined. We used 1 hour of daily stimulation based on our recent results showing that this approach improved clinical outcomes in patients with atrial fibrillation and heart failure with preserved ejection fraction.[9,10] It is possible that longer stimulation would have resulted in a better outcome. However, this approach would have decreased patient adherence. Finally, our follow-up extended only up to 2 months. Therefore, future studies should include longer follow-up to establish the long-term efficacy of tVNS in this patient population.

TABLE 3 Effect of Treatment on Autonomic Symptoms

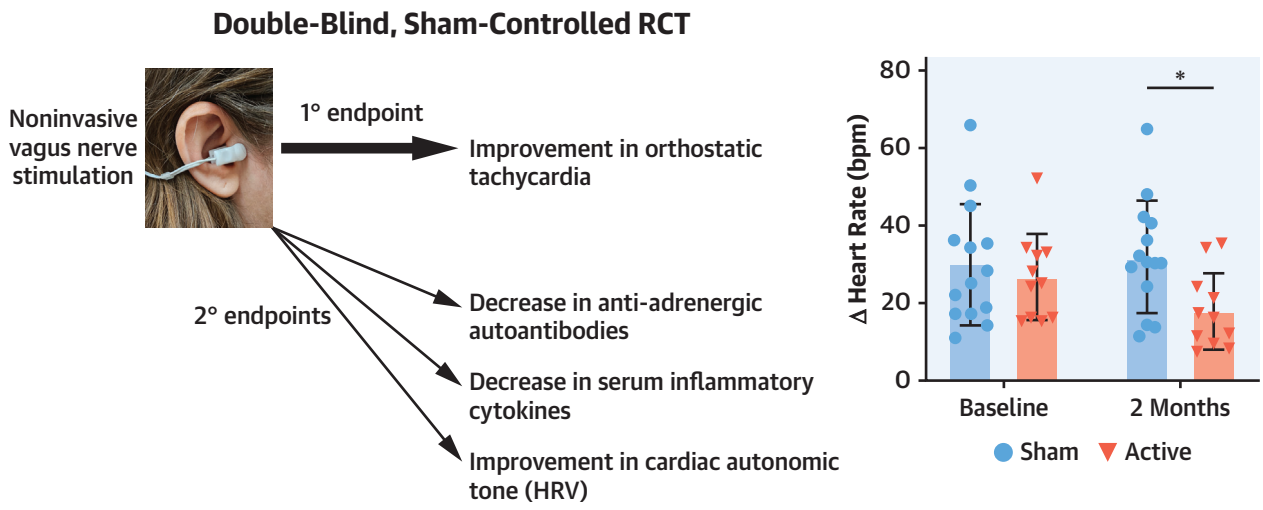
	Baseline			2 mo		
	Sham (n = 14)	Active (n = 12)	*P* Value	Sham (n = 14)	Active (n = 11)	*P* Value
Total	48.9 ± 9.5	48.8 ± 8.6	0.95	47.3 ± 8.2	42.6 ± 6.3	0.07
Orthostatic intolerance	25.9 ± 4.2	26.1 ± 4.5	0.92	23.9 ± 4.6	23.1 ± 5.0	0.60
Vasomotor function	2.7 ± 1.2	2.5 ± 1.4	0.97	2.8 ± 1.0	2.7 ± 0.7	0.50
Secretomotor function	5.8 ± 3.6	5.6 ± 3.5	0.82	6.1 ± 3.7	2.9 ± 3.3	0.001
Gastrointestinal function	10.3 ± 4.6	10.2 ± 3.5	0.94	10.3 ± 4.7	9.8 ± 3.9	0.59
Bladder function	1.6 ± 1.8	1.9 ± 1.4	0.84	1.6 ± 1.7	1.7 ± 1.4	0.69
Pupillomotor function	2.5 ± 1.1	2.5 ± 0.8	0.94	2.5 ± 1.2	2.5 ± 1.2	0.97

Values are mean ± SD.

CONCLUSIONS

Our results support the emerging paradigm of noninvasive neuromodulation to treat POTS. Mechanistically, this effect appears to be related to reduction of antiadrenergic autoantibodies and inflammatory cytokines and improvement in cardiac autonomic tone. Further studies to optimize patient

CENTRAL ILLUSTRATION Summary of Study Design and Primary and Secondary Endpoints



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In a double-blind, sham-controlled, RCT, noninvasive vagus nerve stimulation improved orthostatic tachycardia compared to sham stimulation at 2 months (inset). This effect appears to be related to decrease in anti-adrenergic autoantibodies and inflammatory cytokines, and improvement in cardiac autonomic tone (assessed by HRV). HRV = heart rate variability; RCT = randomized controlled trial.

selection and maximize the efficacy of this novel noninvasive therapy are warranted.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute R01HL161008 to Dr Stavrakis and R01HL128393 to Dr Yu, NIH/National Institute of General Medical Sciences 1U54GM10493, and individual donations from Francie Fitzgerald and family through the OU Foundation Fund. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Noninvasive autonomic modulation using low-level tragus stimulation attenuated the orthostatic tachycardia in patients with POTS. This favorable effect was associated with a decrease in antiadrenergic autoantibodies, improvement in cardiac autonomic function, and decrease in serum inflammatory cytokines.

TRANSLATIONAL OUTLOOK: Future studies should correlate the use of autonomic modulation to improved patient-reported outcomes. Further studies to optimize patient selection and maximize the efficacy of this novel noninvasive therapy are warranted.

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KEY WORDS **autoantibodies, autonomic modulation, inflammation, postural tachycardia syndrome**