Advance Publication

Circulation Reports
doi:10.1253/circrep.CR-24-0136

ORIGINAL ARTICLE
Cardiac Rehabilitation

Effects of Transcutaneous Auricular Vagus Nerve Stimulation on Hemodynamics and Autonomic Function During Exercise Stress Tests in Healthy Volunteers

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Background: Transcutaneous auricular vagus nerve stimulation (taVNS) is a potential treatment for cardiovascular disease, but data on its effects on physiological function during exercise are lacking. We investigated the effects of taVNS on hemodynamics and autonomic nervous system function during exercise stress tests.

Methods and Results: Sixteen healthy volunteers underwent exercise stress tests with and without taVNS in this study, with a randomized crossover design and with a washout period of at least 7 days. taVNS was set to a frequency of 100 Hz and maximum current intensity without causing discomfort. Hemodynamics and autonomic nervous system function were evaluated using plethysmography and heart rate (HR) variability, respectively. After exclusion of an outlier, data of 15 participants were analyzed. In tests with taVNS, HR was significantly reduced at maximum exercise (136.0±9.7 vs. 132.0±9.2; P<0.001) and 1 min after exercise (115.0±11.4 vs. 104.0±15.0; P<0.001), with minimal changes in blood pressure. The stroke volume and total peripheral resistance at maximum exercise significantly increased and decreased, respectively. Furthermore, low/high frequency ratio reflecting sympathetic dominance decreased at rest (3.7±2.5 vs. 1.6±1.3; P<0.001) and at maximum exercise (4.5±4.5 vs. 1.2±0.9; P<0.001).

Conclusions: taVNS can reduce HR with minimal effect on blood pressure by inducing parasympathetic dominance during exercise stress tests.

Key Words: Heart rate variability; Neuromodulation; Parasympathetic nervous system; Sympathetic nervous system

The autonomic nervous system sensitively reacts and adjusts acute responses to external or internal threats and dangers and dynamically regulates visceral and humoral functions to maintain body homeostasis. It consists of the sympathetic, parasympathetic, and enteric nervous systems. Imbalances between sympathetic and parasympathetic nervous function have been shown to be associated with the onset, progression, and recurrence of many cardiovascular diseases. In hypertension, heart failure, atrial fibrillation, and ventricular arrhythmia, this imbalance is caused by inappropriate sympathetic activation and parasympathetic inactivation. Thus, the treatment strategy is to suppress sympathetic activity and enhance parasympathetic activity, a process known as neuromodulation.[1] Transcutaneous auricular vagus nerve stimulation (taVNS) is one such method.

An increasing number of clinical studies have demonstrated that taVNS is effective in treating cardiovascular diseases. A double-blind randomized trial, the TREAT AF (Transcutaneous Electrical Vagus Nerve Stimulation to Suppress Atrial Fibrillation), showed that taVNS suppressed the frequency of paroxysmal atrial fibrillation.[2] Furthermore, taVNS was shown to improve global longitudinal strain on echocardiography, systemic inflammation, and quality of life in patients with heart failure with preserved ejection fraction,[3] and to be effective in treating postural

Received October 31, 2024; revised manuscript received January 24, 2025; accepted January 31, 2025; J-STAGE Advance Publication released online April 11, 2025 Time for primary review: 63 days

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ISSN-2434-0790

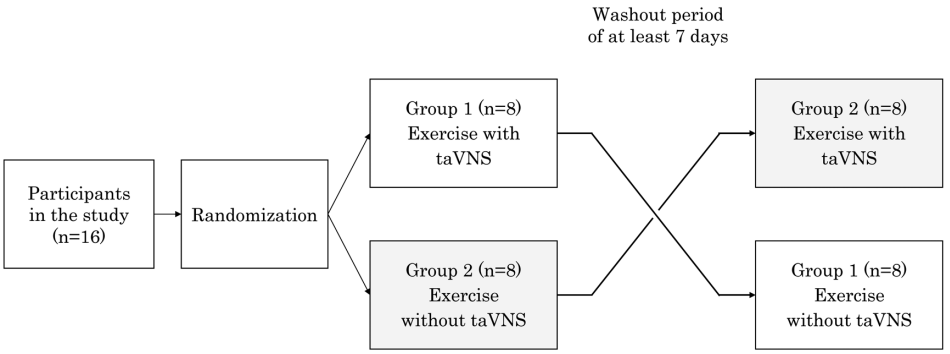

Figure 1. Study flow chart.

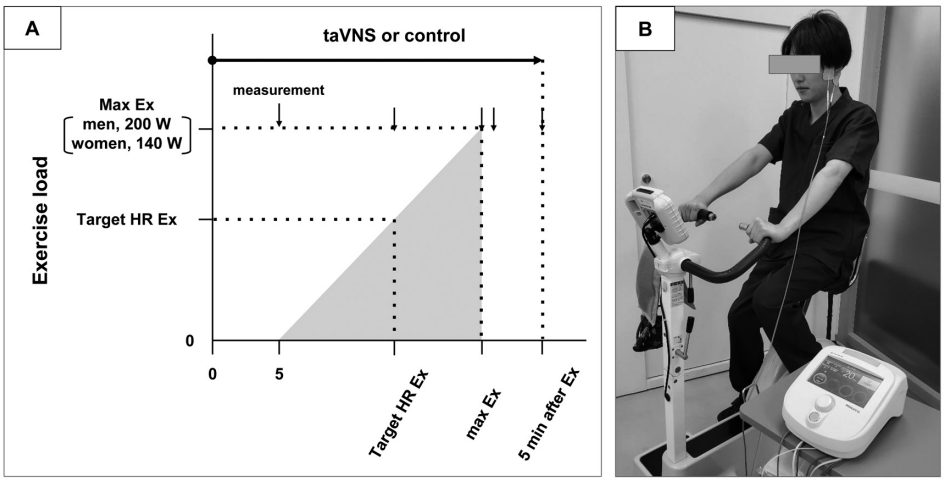

Figure 2. Exercise stress test design. (**A**) Experimental protocol. (**B**) Experimental scene. Ex, exercise; HR, heart rate; Max, maximum; taVNS, transcutaneous auricular vagus nerve stimulation.

tachycardia syndrome.[4] The main mechanism of taVNS was hypothesized to involve efferent vagus nerve stimulation, which increases parasympathetic function, as well as activation of central vagal projections in the brain via afferent nerve stimulation, leading to decreased sympathetic output, and consequently exerting anti-adrenergic and anti-inflammatory effects.

Despite previous research, the effects of taVNS on physiological functions during exercise remain unclear. If these effects are beneficial, then taVNS can be applied to cardiac rehabilitation. We previously reported the effects of taVNS on heart rate (HR), blood pressure (BP), and the autonomic nervous system during low-intensity exercise at 50 W in healthy volunteers.[5] taVNS was shown to safely suppress exercise-induced sympathetic activation with minimal effect on HR and BP. However, the effects of taVNS during higher intensity exercise remain unknown. Therefore, in this study, we aimed to clarify how taVNS affects hemodynamics and autonomic nervous function during an exercise stress test in healthy volunteers.

Methods

Participants

Sixteen healthy volunteers (11 men, 5 women) were recruited for this study. The patients were not diagnosed with hypertension, diabetes, heart disease, kidney disease, or lung disease during regular checkups conducted immediately before the study. None of the participants had a history of smoking. The aim of the study and its potential risks were explained to the participants before enrollment. All participants provided written informed consent. This study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of Nara Prefectural Seiwa Medical Center (approval no. 225).

Exercise Stress Tests and taVNS

All participants underwent exercise stress tests with and without taVNS following a 4-block randomized crossover design (**Figure 1**). This design was selected to minimize the

Table. Changes in Hemodynamics and Autonomic Function During Exercise Stress Tests

	Rest	Target HR during exercise	Max exercise	1 min after exercise	5 min after exercise
Without taVNS					
HR (beats/min)	74.1±10.4	108.0±12.3[b,f]	136.0±9.7[a]	115.0±11.4[b]	82.4±12.6[a,d]
Systolic BP (mmHg)	120.7±16.9	130.1±24.9[f]	140.8±29.6[a]	136.3±21.2[b]	127.0±19.2[f]
Diastolic BP (mmHg)	73.7±15.6	75.3±15.8	78.9±16.7[c]	76.7±14.8	74.6±13.4
CO (L/min)	4.7±1.3	8.0±2.0[b]	11.0±3.0[a]	8.4±2.4[b]	5.7±1.9[d]
SV (mL)	64.3±14.9	74.0±18.8[c]	81.1±24.9[a]	73.2±19.2[c]	67.2±17.7[e]
TPR	1.4±0.3	1.3±0.3	1.2±0.3[b]	1.3±0.3[c]	1.4±0.3[f]
LF (ms^2)	985.1±1,048	417.2±333.3	679.0±1,673[c]	471.9±832.7	364.4±415.7
HF (ms^2)	390.2±303.6	291.5±355.7	374.5±755.3	486.4±714.9	667.8±933.4[f]
LF/HF	3.7±2.5	4.1±3.6	4.5±4.5	3.0±3.2	1.4±1.7[b,f]
With taVNS					
HR (beats/min)	71.9±10.0	106.0±11.3[c,f]	132.0±9.2[a]	104.0±15.0[b]	79.0±11.7[d]
Systolic BP (mmHg)	118.6±16.4	130.3±23.3[c,f]	141.7±27.1[a]	132.1±20.4[b]	123.5±16.9[e]
Diastolic BP (mmHg)	72.9±15.4	73.2±16.8	75.7±16.4[c]	75.7±15.0[c]	72.3±12.7
CO (L/min)	4.7±1.4	7.7±2.3[b]	11.0±2.9[a]	7.7±2.6[b]	5.4±1.5[d]
SV (mL)	65.7±16.2	72.0±20.1[f]	82.7±24.6[a]	72.7±19.7[c]	68.8±16.2[d]
TPR	1.4±0.3	1.3±0.3[e]	1.1±0.3[b]	1.2±0.2[c]	1.3±0.3[e]
LF (ms^2)	451.6±571.9	416.2±333.8	471.8±758.6	562.6±726.8	465.5±562.0
HF (ms^2)	398.5±449.9	721.7±868.5	1,036±1,967	1,233±1,583	941.4±1,134
LF/HF	1.6±1.3	1.9±1.8	1.2±0.9	1.3±1.6	1.0±1.1

Data are presented as mean±SD. [a]P<0.0001, [b]P<0.005, and [c]P<0.05 for comparison with rest. [d]P<0.0001, [e]P<0.005, and [f]P<0.05 for comparison with maximum exercise. BP, blood pressure; CO, cardiac output; HR, heart rate; HF, high-frequency; LF, low-frequency; Max, maximum; SV, stroke volume; TPR, total peripheral resistance; VNS, vagus nerve stimulation.

effects of participants' habituation to exercise stress testing on their autonomic nervous system and the possibility of sustained effects of taVNS on their autonomic nervous system. In particular, the participants were randomly assigned to 1 of 2 groups: Group 1, in which participants underwent an exercise stress test with taVNS followed by an exercise stress test without taVNS; or Group 2, in which participants underwent an exercise stress test without taVNS followed by an exercise stress test with taVNS. In both groups, the participants were allowed a washout period of at least 7 days between the 2 test styles. An exercise stress test protocol consisted of 5 min in a resting sitting position, a ramp load using an ergometer with an increment of 1 W/s with the maximum (max) load set at 200 W for males and 140 W for females, and 5 min in the resting sitting position after reaching the max exercise load (**Figure 2A**). The target HR was calculated using the following Karvonen's formula, according to Japanese cardiac rehabilitation guidelines: target HR = resting HR + 0.4×(max HR − resting HR).[6] The max HR was calculated by subtracting their age from 220. The tests were performed in an air-conditioned (20–25°C) room from 17:30 to 19:00.

taVNS, was performed using a SOL-M01 (Minato Medical Science), which was set to an alternating current, frequency of 100 Hz, pulse width of 600 μs, and a max current intensity that did not cause discomfort or muscle contraction and was applied to the area under the left auricular region where the auricular branch of the left vagus nerve runs (**Figure 2B**).

Measurements

We assessed hemodynamic and autonomic functions during the exercise stress tests. Hemodynamic parameters included HR, BP, cardiac output (CO), stroke volume (SV), and total peripheral resistance (TPR), which were non-invasively and continuously measured using a finger plethysmography tool, Finapres NOVA (Finapres Medical Systems, The Netherlands). Autonomic function was evaluated using variability in HR measured using a wearable HR sensor, my Beat WHS-1 (Union Tool). RR intervals were measured for each heartbeat, with a data sampling frequency of 1,000 Hz. The average values were calculated for 1 min before the following assessment points: 5 min at rest, when the target HR was reached, when the max exercise load was reached, and 1 and 5 min after exercise. We analyzed the RR interval data using frequency-domain methods. Autonomic function was evaluated using a low-frequency (LF) domain (0.04–0.15 Hz), a high-frequency (HF) domain (0.15–0.4 Hz), and the ratio of LF to HF (LF/HF).

Statistical Analyses

G*Power software (version 3.1.9.6) was used to determine the sample size required for comparing measurement values with and without taVNS. A sample size of 15 was calculated. T-test; Wilcoxon signed-rank test (matched pairs); and 2-tailed tests with parameters: effect size d=0.8, α err prob=0.05, power (1−β err prob)=0.8 were used.

Graphpad Prism (version 10.2.3) was used for statistical analysis. Outliers of the LF/HF ratio were determined based on a previous report by Shiraishi et al.[7] and excluded from the final analyses. Friedman's test with Dunn's post hoc test was used for evaluating changes in hemodynamics and autonomic function. We compared the HR at rest to target HR, HR at max exercise, HR at 5 min after exercise, and compared HR at max exercise to HR at 1 and 5 min after exercise. The Pearson correlation coefficient was used to determine the relationship between LF/HF at rest and its change during exercise. Wilcoxon matched-pairs

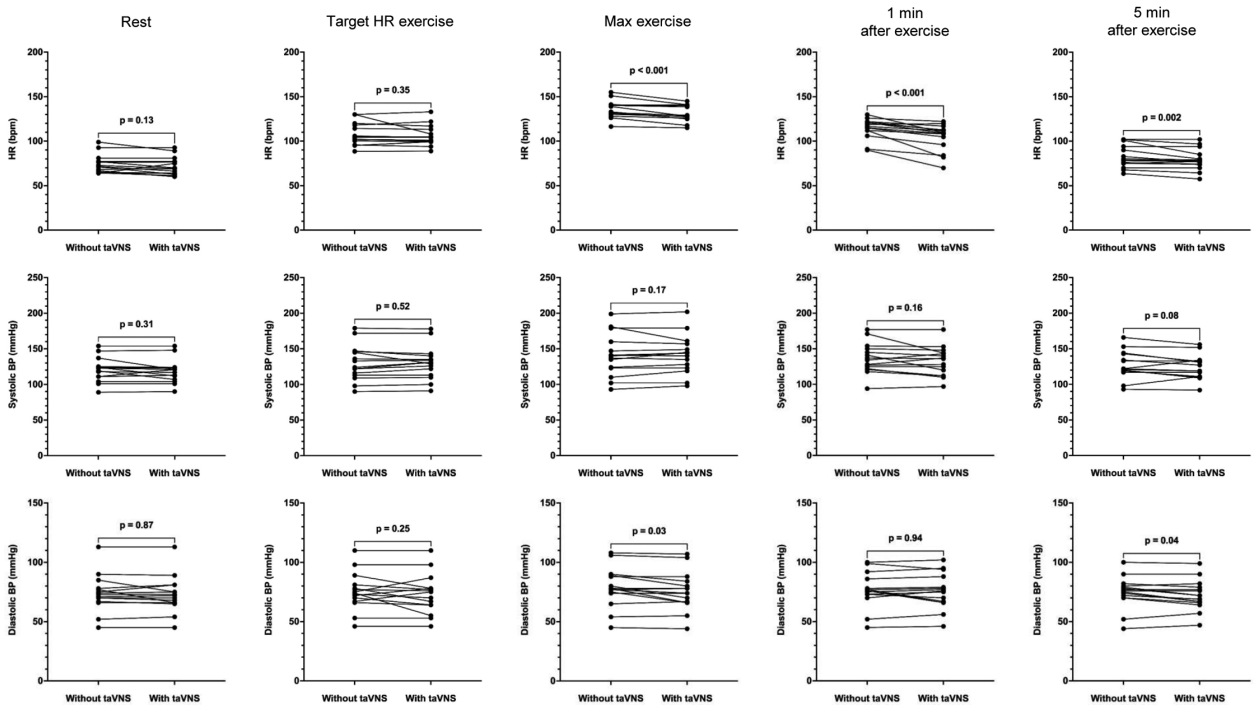

Figure 3. Comparison of heart rate (HR) and blood pressure (BP) between tests without and with transcutaneous auricular vagus nerve stimulation (taVNS).

signed-rank test was used for comparison between tests with and without taVNS, regardless of the normality of the data. Data are expressed as mean±standard deviation (SD). A statistically significant difference was defined as P≤0.05.

Results

All 16 participants completed the exercise stress tests without any complaints or abnormalities in vital signs and electrocardiography. After excluding the data of a participant with an LF/HF of 48.8 at max exercise load, which was an outlier, the data of the remaining 15 participants were analyzed. The mean age of the participants was 32.3±8.8 years. The mean height, weight, and body mass index of the participants were 165±8 cm, 63.5±13.1 kg, and 23.0±3.4, respectively. Subsequently, the participants were followed up for 3 months to ascertain continued good health. The mean max taVNS current intensity was 6.1±1.1 mA. The mean target HR was 115.5±4.7 beats/min. The exercise load required to reach the target HR was similar between with and without taVNS (106±24 vs. 100±27 W; P=0.057) conditions.

Changes in Hemodynamics and Autonomic Function

Table shows the changes in the hemodynamic and autonomic functions. HR significantly increased from at rest to the target HR during exercise and max exercise, and significantly decreased from that at max exercise to 5 min after exercise in both tests, with and without taVNS. Systolic BP, CO, and SV significantly increased from rest to max exercise and significantly decreased from max exercise to 5 min after exercise in both tests. In contrast, TPR significantly decreased from rest to max exercise and significantly increased from max exercise to 5 min after exercise in both tests. In the tests without taVNS, the LF/HF ratio significantly decreased from that at max exercise to 5 min after exercise, whereas with taVNS, no statistically significant changes were observed throughout the exercise stress test.

In addition, in tests with taVNS, a significant negative correlation was observed between LF/HF at rest and the change in LF/HF (ΔLF/HF) between rest and max exercise (R^2=0.55; P=0.0015), whereas in the test without taVNS, no correlation was observed (R^2=0.06; P=0.36).

Comparison Between Tests With and Without taVNS

As shown in **Figure 3**, taVNS significantly reduced HR at max exercise and at 1 and 5 min after exercise, whereas it had no effect on systolic BP. As shown in **Figure 4**, taVNS had little effect on CO throughout the exercise stress test, but significantly increased SV at max exercise and decreased TPR at max exercise, and 1 and 5 min after exercise. As shown in **Figure 5**, taVNS significantly decreased LF/HF at rest, target HR during exercise, and at max exercise.

Discussion

Main Findings

To the best of our knowledge, this is the first study to demonstrate the effects of taVNS on the hemodynamics and autonomic nervous system function during exercise stress tests in healthy volunteers. The study demonstrated that (1) taVNS can be safely performed during exercise stress tests, (2) taVNS reduces HR at max exercise and

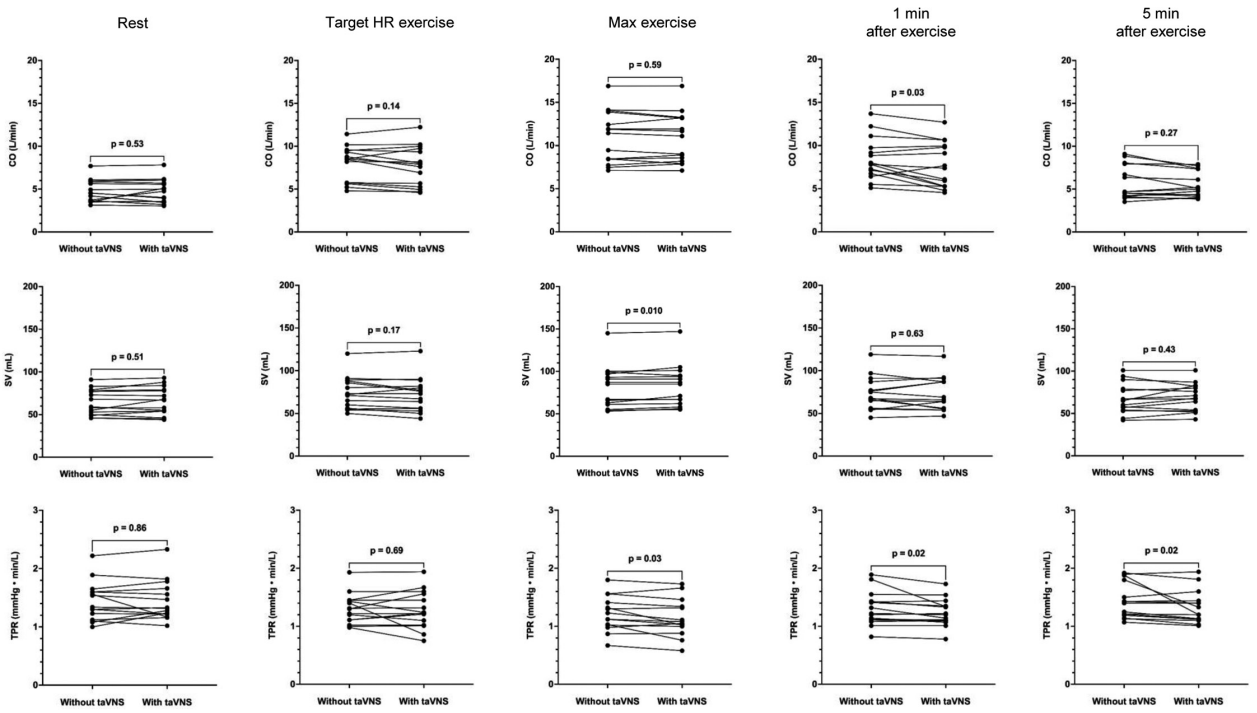

Figure 4. Comparison of cardiac output (CO), stroke volume (SV), and total peripheral resistance (TPR) between tests without and with transcutaneous auricular vagus nerve stimulation (taVNS).

after exercise with minimal effect on BP, and (3) taVNS decreases LF/HF, suggesting induction of parasympathetic dominance.

Assessment of Autonomic Nervous Function

We analyzed HR variability, a non-invasive, repeatable, and inexpensive method, among others such as baroreflex sensitivity, microneurography, blood levels of catecholamines, and ^{123}I-MIBG imaging, for the objective quantitative assessment of the impact of taVNS on autonomic function during exercise therapy.

HR variability is caused by fluctuations in the autonomic nervous system because the sinoatrial node is under autonomic control and a decline in HR variability is thought to reflect an impaired autonomic nervous function. Frequency-domain analysis is a method of HR variability analysis that can detect and quantify 2 major spectral components, LF and HF, from the RR interval series derived from electrocardiography. A previous study[8] reported that the LF component amplitude during supine rest is almost unaffected by administration of propranolol with a sympathetic nerve blocking effect, but is almost eliminated by the administration of atropine with a vagus nerve blocking effect. Propranolol suppressed the LF component amplitude during standing. Therefore, LF is considered to be related to both sympathetic and parasympathetic nerve activity. In contrast, since the HF component amplitude decreases in proportion to the dose of atropine administered, HF is considered to be related to parasympathetic nerve activity.[9] Therefore, the LF/HF ratio reflects the balance between sympathetic and parasympathetic activity, and a high value suggests sympathetic dominance.[10,11] Normal values of LF, HF, and the LF/HF ratio in the sitting position have been reported to be 591±291 ms^2, 657±777 ms^2, and 2.8±2.6, respectively.[12]

HR variability analysis does not accurately evaluate autonomic nervous function, and therefore its use remains controversial.[13–15] Despite these problems, we emphasize the fact that there are numerous reports indicating that parameters derived from HR variability analysis are closely associated with the prognosis of patients with cardiovascular disease,[16–18] and that in previous studies, which stated that taVNS was effective in treating patients who had cardiovascular disease, HR variability parameters were improved by taVNS.[2–4]

Effects of taVNS on Hemodynamics

In this study, taVNS did not induce any adverse events. This finding is consistent with that of a systematic review and meta-analysis on the safety of taVNS.[19] Therefore, we consider that taVNS is a safe and feasible option for clinical intervention, even during exercise.

Similar to a review and meta-analysis on the cardiovascular effects of taVNS,[20] we found that taVNS had no effect on HR or BP at rest. In the meta-analysis, HR with taVNS was slightly reduced compared with that with the control procedure (mean difference=−1.23; 95% confidence interval (CI) −1.74, −0.72; P=0.0005), and this very small reduction in HR was not regarded as an adverse event in any of the studies included in the meta-analysis, whereas BP remained unchanged.

To the best of our knowledge, no studies have been conducted on high-intensity exercises. In the present study, taVNS significantly reduced the HR at max exercise.

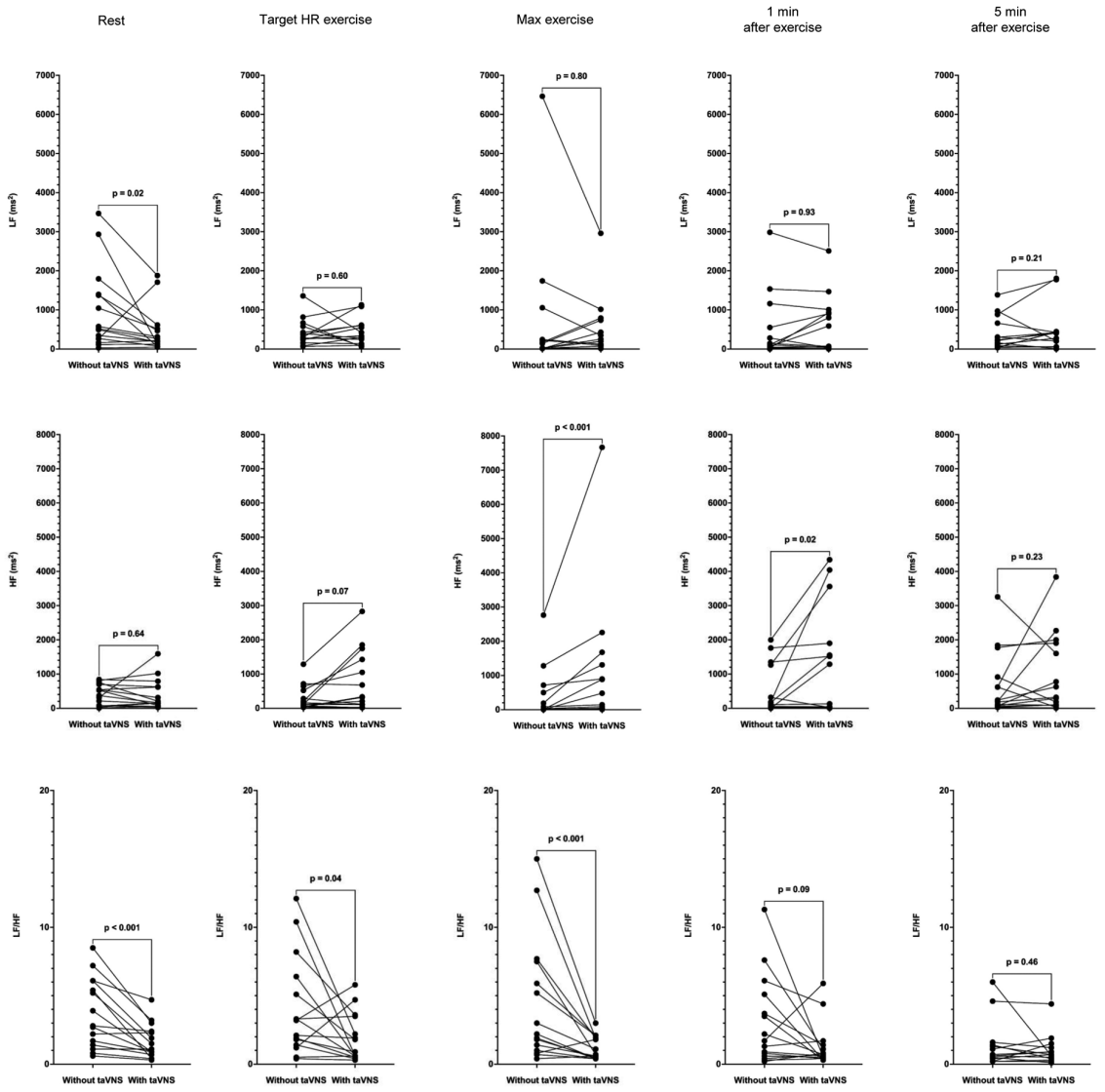

Figure 5. Comparison of low frequency (LF), high frequency (HF), and LF/HF in heart rate (HR) variability between tests without and with transcutaneous auricular vagus nerve stimulation (taVNS).

Moreover, taVNS had little effect on BP. In our previous study on low-intensity exercise, taVNS had no effect on either HR or BP.[5] Therefore, the HR suppression effect of taVNS was considered greater during high-intensity exercise than during low-intensity exercise. Furthermore, it is noteworthy that taVNS reduced the HR with little change in BP during exercise. This effect is quite different from that of β-blockers, which reduce both HR and BP.[21]

HR recovery is commonly defined as the change in HR at peak exercise to 1 min after exercise cessation and reflects the dynamic balance and interaction between sympathetic and parasympathetic nervous functions. Decreased HR recovery is closely associated with an increased risk of cardiovascular events and all-cause mortality.[22,23] In the present study, compared with the tests without taVNS, tests with taVNS showed a significant reduction in HR at 1 min after exercise, which suggests that taVNS can increase HR recovery, at least in healthy participants.

The effects of taVNS on CO, SV, and TPR have not yet been reported. In the present study, taVNS reduced TPR at max exercise and at 1 and 5 min after exercise and increased SV at max exercise. This suggests that taVNS has a systemic vasodilatory effect leading to afterload reduction, at least in healthy participants. Investigating whether these effects are observed during exercise in patients with cardiovascular disease is important.

Effects of taVNS on Autonomic Nervous Function

Compared with tests without taVNS, tests with taVNS revealed significantly reduced LF/HF at rest, target HR during exercise, and max exercise. This result is consistent with that reported by Hua et al.,[20] who reported that taVNS significantly reduced the ratio compared with control procedures (mean difference=−0.14; 95% CI −0.23, −0.04;

P=0.007). However, no data were found during exercise. According to the study by Yokota et al.[24] on the effects of taVNS on hemodynamic and autonomic function at rest, participants with higher baseline sympathetic activity experienced higher parasympathetic response to taVNS. Similarly, in the present study with exercise stress tests, there was a significant negative correlation between LF/HF at rest and ΔLF/HF between rest and max exercise. When applying taVNS, we should be aware that the therapeutic response may vary depending on the baseline autonomic function status of patients.

Feasibility of taVNS for Cardiac Rehabilitation

Cardiac rehabilitation is an important component of the treatment for all patients with cardiovascular disease, improving their quality of life, preventing progression and recurrence, and reducing rehospitalization and mortality rates. To achieve these goals, sufficient exercise load should be provided to improve cardiopulmonary fitness and skeletal muscle strength while minimizing the risk of adverse events.[6,25] However, aerobic exercise and resistance training are less commonly performed for various reasons, especially in hospitalized patients in Japan.[26] A previous study reported a high incidence of hospitalization-related disorders at 37.1%.[27] One of the reasons for this may be that some patients experience tachycardia, elevated BP, and severe arrhythmias due to inappropriate sympathetic dominance, even when receiving optimal medical therapy.

Our results support the possibility that taVNS can make cardiac rehabilitation safer and more effective in patients with tachycardia caused by inappropriate sympathetic dominance.

However, it is unclear whether these results can be replicated in patients with cardiovascular disease as many of them have an imbalance between sympathetic and parasympathetic function, which is often modified with β blockers and renin–angiotensin inhibitors. Notably, taVNS can also cause bradycardia and hypotension. Chronotropic incompetence, defined as the inability to adequately increase HR during exercise, is commonly and closely associated with poor exercise capacity and prognosis in patients with cardiovascular disease.[28] Rather than making cardiac rehabilitation safer and more effective, taVNS may worsen chronotropic insufficiency and reduce exercise capacity. As with β-blockers in cardiac rehabilitation, it may be necessary to lower the target HR when using taVNS.[29] The application of taVNS to cardiac rehabilitation requires careful research while considering various possibilities.

Comparison With Previous Clinical Studies

In previous clinical studies that showed taVNS is effective in treating cardiovascular diseases, taVNS was set to a frequency of 20 Hz and a pulse width of 200 μs, and was performed for only 1 h daily for several months.[2–4] This suggests that taVNS has sustained effects on the autonomic nervous system function under certain conditions. However, the use of taVNS in the present study differed from that in previous studies in the following ways: in the present study, (1) taVNS was set to a frequency of 100 Hz and a pulse width of 600 μs, and (2) taVNS was performed continuously throughout the exercise stress test, only once and not repeatedly. Although this study does not allow us to comment on the duration of taVNS, when applying taVNS to cardiac rehabilitation it is necessary to be aware of the effects of its repetition.

Study Limitations

The present study had 5 limitations. (1) The autonomic nervous system was evaluated using HR variability only and not by using other methods, such as measurement of blood catecholamine concentrations. (2) Investigators and participants could not be blinded because sham stimulation with taVNS was not used as a control. (3) The ventilatory anaerobic threshold was not evaluated using a cardiopulmonary exercise test. (4) The effects of changing the parameters of taVNS on hemodynamics and autonomic nervous function were not examined. The parameters used in this study were determined based on Yokota et al.'s[24] study as a reference in order to have a stronger effect on the autonomic nervous system. (5) The chronic effects of repeated taVNS were not evaluated.

Conclusions

taVNS can reduce HR with minimal effect on BP by inducing parasympathetic dominance during exercise stress tests in healthy volunteers. These results help to determine whether taVNS can be used in clinical applications for cardiac rehabilitation.

Acknowledgments

We thank Kazuyuki Tabira, Department of Physical Therapy, Faculty of Health Sciences, Kio University, Koryo, Japan, for helpful suggestions and for providing measurement equipment. We thank Editage (www.editage.jp) for English language editing.

Sources of Funding

This research received no grant from any funding agency in the public, commercial or not-for-profit sectors.

Disclosures

The authors declare that there are no conflicts of interest.

IRB Information

The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of Nara Prefectural Seiwa Medical Center (approval no. 225).

Data Availability

The deidentified participant data will not be shared.

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