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The impact of non-invasive vagus nerve stimulation on recovery following aerobic exercise in individuals with post-COVID syndrome: A randomized controlled clinical trial

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Abstract:

BACKGROUND AND AIM: Transcutaneous auricular vagus nerve stimulation (taVNS) has gained popularity recently and has been used to enhance recovery in various diseases, showing beneficial physiological and neurological effects. This study aimed to evaluate the efficacy of taVNS in post-exercise recovery for individuals experiencing Post-COVID Syndrome (PCS).

METHODS: Individuals aged 18-45 years with PCS were assigned to either taVNS group (n=22 patients) or placebo VNS group (n=22 patients) and engaged in an aerobic exercise regimen. This included a 5-minute treadmill warm-up, followed by 15 minutes of brisk walking and 15 minutes of jogging. Evaluations were conducted before and after the exercise using the H10 Polar autonomic device and a lactate meter. Participants in Group 1 received real taVNS, while those in Group 2 received placebo VNS, with a subsequent third evaluation.

RESULTS: There were statistically significant differences in the post-exercise evaluation parameters between taVNS and placebo VNS groups. . Parasympathetic nervous system (PNS) activity (p=0.009) and blood lactate levels (p=0.006) increased significantly in both groups, while the Root Mean Square of the Successive Differences (RMSSD) index (p=0.028) decreased. Both sympathetic nervous system (SNS) activity (p=0.01) and blood pressure (p=0.01) decreased similarly across the groups.

CONCLUSIONS: The study found that taVNS increased cardiac vagal control but did not significantly affect blood lactate levels or blood pressure. Further randomized controlled trials are required to investigate the effects of taVNS on recovery in different treatment groups.

Keywords:

Aerobic exercise, lactates, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), vagus nerve, vagus nerve stimulation

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Introduction

Coronavirus disease 2019 (COVID-19), caused by the novel coronavirus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has resulted in significant morbidity and mortality worldwide since the initial cases were identified in Wuhan, China, in December 2019.[1] Post-COVID syndrome (PCS) is defined by persistent symptoms and/or delayed or long-term complications from SARS-CoV-2 infection that last more than four weeks from the onset of symptoms.[2] An estimated 45% of COVID-19 survivors exhibit at least one persistent symptom at a median follow-up of four months, with a higher incidence of 53% among those who were hospitalized. The most commonly reported symptoms include fatigue, shortness of breath, muscle pain, disrupted sleep, impaired daily activities, and loss of smell and taste.[3] Additionally, exercise-related issues are commonly observed in post-COVID-19 patients, who often report fatigue and show diminished performance on the 6-minute walk test, even without impaired lung function.[4]

Evidence from respiratory diseases suggests that recovery after aerobic exercise can be hampered by diminished parasympathetic activity. Previous studies have demonstrated that vagus nerve activity increases post-exercise to help return the heart rate to pre-exercise levels.[5,6]

The literature suggests that transcutaneous auricular vagus nerve stimulation (taVNS) may be an effective approach for managing symptoms related to post-COVID conditions.[7,8] Enhanced vagus nerve activation has been shown to help regulate key biomarkers such as heart rate and blood pressure.[9,10] We hypothesized that taVNS could positively contribute to the regulation of the body's autonomic activity during recovery. In this study, we aimed to understand how the cardiovascular system, which is often affected in post-COVID individuals, responds to vagus nerve stimulation during recovery. We investigated the effects of taVNS on the recovery process following moderate and high-intensity aerobic exercise.

Materials and Methods

Participants in the study were randomly divided into two groups using the random.org website for the randomization process. A single-blinded assessment structure was implemented, where different physiotherapists managed the evaluations and interventions to maintain blinding throughout the study. The study was prospectively structured and adhered strictly to the principles outlined in the Helsinki Declaration. Ethics committee approval was obtained from Istanbul Medipol University Non-Interventional Clinical Trials Ethics Committee on 07/03/2023, under reference number E-10840098-772.02-1719. Additionally, the study protocol was registered under the Clinical Trials Number NCT 0x764x70, and informed consent forms were obtained from all participants.

Participants

The sample size was determined retrospectively using G*Power V.3.1.7 software from Kiel University, Germany. The analysis aimed for a study power of 95% and a 95% confidence level, assuming an effect size (f value) of 0.5 and a correlation of 0.8 among three repeated measures. With a margin of error set at 0.05, the software calculated a requirement of 20 patients. To accommodate potential dropouts, the final sample size was adjusted to 44 patients, with 22 participants in each group.[11]

During the study, a single session was conducted, followed by a recovery phase after aerobic exercise. Both groups participated in 30 minutes of treadmill exercise divided into moderate and high intensity, targeting 50–70% and 60–90% of maximal heart rate, respectively. The exercise session included a 5-minute warm-up phase on the treadmill, 15 minutes of fast walking, and 15 minutes of jogging. After the exercise, real taVNS was administered to Group 1, while Group 2 received placebo VNS.

The study included individuals aged 18–45 with pulmonary involvement, diagnosed with COVID-19 either through SARS-CoV-2 reverse transcription-polymerase chain reaction or a positive rapid antigen test from an oropharyngeal-nasopharyngeal swab. Participants had experienced chronic symptoms for more than 12 weeks without requiring acute hospitalization. As shown in Figure 1, participants were screened for symptoms like fever, loss of taste and smell, myalgia, runny nose, and cough. Exclusion criteria included professional athletes

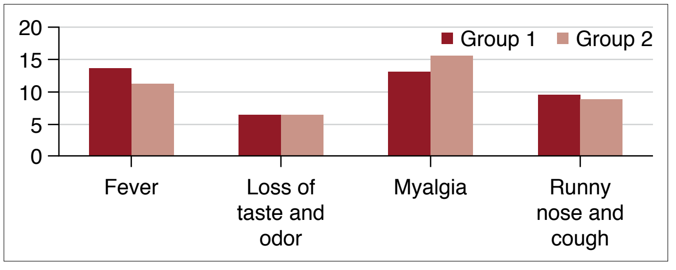

Figure 1: Additional outcomes

Table 1: Demographic information

	Group 1 Mean±SD	95% CI		Group 2 Mean±SD	95% CI		p
		Lower bound	Upper bound		Lower bound	Upper bound	
Age (years)	23.09±0.79	21.44	24.74	21.64±0.81	19.96	23.32	**0.062***
BMI (kg/m²)	22.94±4.01	21.16	24.72	23.61±5.90	21.00	26.23	**0.907***
Gender		11 Females 11 Males			10 Females 12 Males		0.763**

Values are presented as mean±SD (standard deviation). A p-value of <0.05 was considered statistically significant. *: Mann-Whitney U Test, **: Chi-Square Test. SD: Standard deviation, CI: Confidence interval, BMI: Body mass index (kg/m²)

and individuals with cardiopulmonary, orthopedic, neurological, or metabolic conditions.

Evaluation methods

Participants underwent initial assessments before the exercise intervention, with subsequent evaluations immediately following the exercise and after the administration of real taVNS or placebo VNS.

Autonomic system assessment

Autonomic evaluations were performed using a Polar H10 model chest strap for 5 minutes while seated during each measurement phase. Heart rate (HR) and the root mean square of successive differences between normal heartbeats (RMSSD) were evaluated, alongside the parasympathetic nervous system index (PNS 42 Index) and the sympathetic nervous system index (SNS Index), using the Kubios CADD program.[12]

Blood lactate level assessment

Blood lactate levels were assessed using a Lactate Scout 4 device. Measurements were taken after entering the code from the strip into the device.[13]

Blood pressure assessment

Blood pressure was measured using an Omron device, which recorded systolic and diastolic pressures along with heart rate.[7]

Treatment modalities

Aerobic exercise

The study involved treadmill exercises utilizing oxygen for sustained activity. Intensities were set at 50–85% of VO2max or 60–90% of maximum heart rate. Each session lasted 30 minutes, adhering to prescribed aerobic training protocols for optimal cardiovascular benefits and endurance improvements.

Vagus nerve stimulation

Stimulation was performed non-invasively through the auricular branch using the Vagustim® device for 25 minutes. The electrodes, custom-made to fit the size of the inner ear, were applied subcutaneously. The pulse parameters were set to modulated TENS mode with a frequency of 10 Hz and a pulse duration of less than 500 microseconds, utilizing a biphasic asymmetric waveform in both the right and left ears.[14]

Results

A total of 50 patients were initially included in our study. However, six were unable to participate for various reasons, leaving 44 patients who completed the study, with 22 in each group.

Demographic analysis, as shown in Table 1, revealed that the groups were similar in terms of age, body mass index (BMI), and gender. Participants had no comorbidities.

In-group post-exercise measurement outcomes are shown in Table 2. Analysis of the first and second measurements indicated that HR, PNS activity, and blood lactate levels significantly increased in both groups following exercise, while the RMSSD index significantly decreased. After administering real taVNS and placebo VNS, and analyzing the second and third measurements, taVNS was found to enhance cardiac vagal control. Both groups exhibited similar decreases in HR, SNS activity, blood lactate levels, and blood pressure parameters. Although there was a significant increase in the PNS index in both groups, the rate of increase was higher in Group 1. Furthermore, the RMSSD index showed a statistically significant increase in Group 1, while the increase in Group 2 was not significant.

Table 2: Results of in-group post-exercise measurements

	Group 1					Group 2				
	1st OM	2nd OM	3rd OM	OM 1-2	OM 2-3	1st OM	2nd OM	3rd OM	OM 1-2	OM 2-3
HR (bpm)*	85.68±13.95	93.10±17.31	84.60±12.30	**0.021**	**≤0.00**	80.91±10.69	97.77±15.03	86.73±11.88	**≤0.00**	**≤0.00**
RMSSD (ms)*	31.40±20.27	22.77±13.42	31.82±20.02	**0.023**	**0.028**	43.00±26.20	16.45±10.46	21.14±44.98	**0.001**	0.22
PNS (ms^2)*	-1.05±1.09	-1.32±1.55	0.09±1.57	0.299	0.009	-0.05±1.25	-0.60±2.32	0.01±1.80	0.125	0.018
SNS (ms^2)*	2.05±1.40	3.14±2.47	1.91±1.31	**0.027**	**0.010**	1.23±1.90	4.23±2.71	2.09±2.47	**≤0.00**	**≤0.00**
Blood lactate level (mmol/L)**	3.45±3.17	7.41±4.55	4.05±3.26	**0.002**	**0.006**	2.00±2.18	7.68±5.22	3.41±2.32	**≤0.00**	**0.002**
Blood pressure (mm/hg)*	118.64±10.53	118.27±15.83	111.23±11.85	0.878	**0.010**	117.50±12.65	122.00±14.45	110.59±15.82	0.071	**≤0.00**

A p-value of <0.05 was considered statistically significant. *: Paired Sample t-test (HR, RMSSD, PNS, SNS, and blood pressure were parametric), **: Mann-Whitney U Test (Blood lactate levels were nonparametric).
OM: Observation moment, HR: Heart rate, RMSSD: The Root mean square of successive differences between normal heartbeats, PNS: Parasympathetic nervous system, SNS: Sympathetic nervous system

Discussion

Our study focused on young adults experiencing post-COVID symptoms. Globally, it is estimated that at least 65 million people exhibit symptoms of post-COVID syndrome, a figure that is likely significantly higher due to many unreported cases. The incidence of post-COVID ranges from 10% to 30% among non-hospitalized cases, 50% to 70% among hospitalized cases, and 10% to 12% among vaccinated individuals. Symptoms of post-COVID can range from mild impairment to severe systemic disease.[15,16]

Our findings indicate significant increases in heart rate recovery (HRR), PNS activity, and blood lactate levels, along with a statistically significant decrease in the RMSSD index in both groups during initial and subsequent measurements before and immediately after exercise. Following the administration of taVNS and placebo VNS, taVNS was shown to enhance cardiac vagal control, as evidenced by the second and third assessments. Both groups exhibited similar decreases in HRR, SNS activity, blood lactate levels, and blood pressure. Although there was a notable increase in PNS activity in both groups, Group 1 showed a more substantial increase. Furthermore, while the RMSSD index showed a statistically significant increase in Group 1, the increase in Group 2 was not significant. Chronotropic variables were similarly affected across both groups.

Yu and Kong[16] demonstrated that neuromodulation methods like vagus nerve stimulation have a neuroimmunotherapeutic effect on COVID-19. Additionally, other studies suggest the use of VNS as a potential therapeutic strategy to alleviate prolonged symptoms associated with COVID.

Research assessing the effectiveness of taVNS on COVID-19 found that it improved symptoms.[17] In another study, it was reported that both the left and right branches of the vagus nerve act as the natural pacemakers of the heart, and therefore, taVNS can affect heart rate and Heart Rate Variability (HRV) through vagal efferents.[18,19] Additionally, existing data indicate that the HRR component represents parasympathetic activity, i.e., vagal tone.[20] In Mulder's study,[21] it was found that wearing the taVNS device during exercise led to a decrease in HRR both during rest and exercise. Similarly, in our study, HRR exhibited a comparable decrease in both groups during the recovery process after a single session of exercise.

Previous studies have emphasized that post-exercise HRR is crucial for recovery speed, given that heart rate peaks during exercise and decreases steeply with the cessation of exercise, demonstrating the recovery effect.[22,23] In a study examining heart rate variability using the Polar H10 device, the acute effects of yoga exercises were evaluated at baseline and after the intervention. The results indicated that median HR values were higher in yoga practitioners than in the control group.[24] Similarly, in our study, an increase in HRR values was observed in both groups after exercise compared to initial values. The resting heart rate is largely regulated by the vagus nerve.

Another measure from the Polar H10 system, RMSSD, reflects the beat-to-beat variance in heart rate and is the primary time-domain measure used to estimate vagally mediated changes reflected in heart rate variability.[24] Studies have indicated that RMSSD values represent cardiac vagal control and that cardiac vagal activity increases with an increase in RMSSD.[25] According to our evaluation results, taVNS was found to enhance cardiac vagal control during the recovery process. The RMSSD value decreased in both groups due to increased parasympathetic activity after a single session of exercise. However, RMSSD values increased statistically significantly in Group 1 following vagus nerve stimulation, while the increase in RMSSD value was not significant in Group 2 after placebo application. This implies that vagus nerve stimulation enhances cardiac vagal activity, which is linked to increased autonomic control. The findings of the study demonstrate the efficacy of vagus nerve stimulation in boosting cardiac vagal activity, as evidenced by the significant rise in RMSSD values in Group 1 compared to the placebo group. This highlights the therapeutic potential of vagal modulation in promoting autonomic balance and underscores its importance in cardiovascular health interventions.

The data collected by the H10 Polar device include PNS and SNS values, which serve as markers of parasympathetic and sympathetic nervous system activity, respectively, and are analyzed using Kubios software. In assessments of the OSS activity, an increase in the PNS index suggests an enhanced parasympathetic activity, while a decrease in the SNS index indicates reduced sympathetic activity.[26] To our knowledge, no study has specifically explored the impact of taVNS on recovery using PNS and SNS indices as variables. The results of this study showed a notable increase in PNS values in Group 1, where actual taVNS was administered, and significant changes in SNS values were observed in both groups. We believe this is related to the enhanced autonomic regulation observed in the taVNS group during recovery following exercise.

Recovery after intense training is typically assessed through the measurement of lactate levels. Techniques such as cold water immersion, ice application, and neuromuscular electrical stimulation are employed to accelerate recovery.[27] Akinci et al.[28] analyzed the impact of three different recovery methods on blood lactate levels before and during recovery periods at 0.5 and 20 minutes post high-intensity training. They found no significant changes in lactate levels following treatment. Similarly, Miętkiewska-Szwacka et al.[29] determined that neuromuscular electrical stimulation did not effectively aid post-exercise recovery. Our research assessed the impact of both real and placebo vagus nerve application on lactate levels during post-exercise recovery. Similar to other studies, no significant differences were found in lactate measurements during recovery time between the groups.

Another study reported significantly higher blood pressure levels in individuals with a history of COVID-19, noting that exercise influenced HR and systolic blood pressure measurements during recovery.[30] When we assessed the effect of taVNS, applied acutely in our study after exercise, we observed that the systolic blood pressure did not exhibit any superiority compared to the placebo group. We believe this outcome may be linked to the acute application of taVNS.

In recent years, taVNS has been introduced as a novel method for treating COVID-19, with ongoing research into its effectiveness. Although the exact mechanisms of vagus nerve stimulation are not yet fully understood, it is known to be effective across multiple systems.[31]

Upon analyzing the treatment results of our study, we found that it facilitated reorganization of the autonomic nervous system, yielding effects similar to those documented in the literature. Consequently, we believe that it may serve as a viable treatment option for various diseases of the respiratory and cardiac systems, including COVID-19. Additionally, our results indicated an enhancement in cardiac function and recovery after exercise with VNS in individuals with post-COVID syndrome. However, we recommend further exploration of different stimulation parameters across diverse study groups engaged in intensive exercise training, as well as an assessment of the long-term effects.

Although post-COVID syndrome is multifactorial, one significant cause is autonomic nervous system dysfunction.[30,31] Research has established a strong link between parasympathetic activity and exercise capacity, indicating that vagal activity predominantly enhances physical fitness.[25] Studies have highlighted the necessity for comprehensive assessments of cardiac vagal activity measures.[29] While previous research has assessed the impact of taVNS on post-exercise recovery in post-COVID syndrome, our study is the first to specifically address autonomic dysfunction in this patient group. To our knowledge, no other studies have yet examined the effects of taVNS on the recovery process in this particular context.

Admittedly, our study has limitations that warrant acknowledgment. Firstly, a larger participant cohort could have enhanced the robustness of our findings. Additionally, we did not examine the long-term effects of the interventions, which could provide valuable insights into their sustained impacts. Moreover, assessing heart rate variability only at the study's conclusion, rather than continuously throughout its duration, represents a limitation. Despite these limitations, our study establishes a foundational framework for future investigations in this field.

Ethics Committee Approval

The study was approved by the Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (No: E-10840098-772.02-1719, Date: 07/03/2023).

Authorship Contributions

Concept – H.G., T.T., G.D.; Design – H.G., T.T., G.D.; Supervision – H.G., T.T., G.D.; Funding – H.G., G.D.; Materials – H.G., G.D.; Data collection &/or processing – T.T., H.G.; Analysis and/or interpretation – H.G., T.T., G.D.; Literature search – H.G.; Writing – H.G., T.T., G.D.; Critical review – H.G., T.T., G.D.

Conflicts of Interest

There are no conflicts of interest.

Use of AI for Writing Assistance

No AI technologies utilized.

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Peer-review

Externally peer-reviewed.

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