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Analysis of taVNS effects on baroreflex sensitivity and autonomic nervous system regulation during head-up tilt test

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Baroreflex dysfunction and autonomic imbalance are key pathophysiological features of hypertension, but current pharmacological approaches often fail to address these neural mechanisms. This study investigated whether transcutaneous auricular vagus nerve stimulation (taVNS) affects autonomic regulation during blood pressure perturbation. In a randomized, single-blind, sham-controlled, crossover design experiment, 32 normotensive adults received 90-min taVNS or sham exposure. Blood pressure perturbation was induced with the head-up tilt test (supine–tilt–supine). Baroreflex sensitivity (BRS) was analyzed only during the 10-minute tilt phase, whereas heart rate variability (HRV) was analyzed across four 5-minute segments (S-baseline, early-tilt, late-tilt, recovery). In the direct crossover analysis of the primary BRS outcome, pre-to-post changes did not differ significantly between taVNS and sham, and the baseline-adjusted sensitivity analysis yielded the same conclusion. Among the secondary HRV outcomes, differences averaged across analysis segments were significant only for SDNN and pNN30, whereas no analysis-segment-specific interaction was significant. Descriptive within-visit comparisons showed increases in BRS and several HRV measures during the taVNS visit. These findings provide preliminary evidence compatible with cardiovagal modulation during orthostatic stress, but do not establish a taVNS-specific improvement in BRS or blood pressure regulation. Further research involving patient cohorts and longitudinal study protocols is needed.

Keywords Transcutaneous auricular vagus nerve stimulation (taVNS), Head-up tilt test, Baroreflex sensitivity (BRS), Heart rate variability (HRV)

Article.

Introduction

Hypertension is one of the most prevalent risk factors for cardiovascular disease and affects more than 1.4 billion individuals worldwide[1]. Despite its high prevalence, only about 44% of hypertension patients receive a diagnosis and treatment, and among those undergoing therapy, only 23% achieve adequate blood pressure control[2]. The current standard of care relies primarily on pharmacological therapy; however, several limitations persist, including low medication adherence due to combination drugs, interindividual variability in drug responsiveness, and adverse side effects associated with antihypertensive agents[3]. Consequently, interest in developing alternative therapeutic strategies that are both effective and minimally invasive has been growing.

Hypertension is a multifactorial disorder, and autonomic nervous system (ANS) dysfunction has been recognized as a key pathophysiological contributor[4–6]. Among cardiovascular regulatory mechanisms, the arterial baroreflex contributes continuously to short-term blood pressure homeostasis[7–9]. Baroreceptor input from the carotid sinus and aortic arch reaches the nucleus tractus solitarius (NTS) through glossopharyngeal and vagal afferents, respectively[10,11]. The resulting reflex adjustments in heart rate, cardiac function, and vascular tone help stabilize arterial pressure[12]. In hypertensive patients, however, impaired baroreflex function leads to sympathetic overactivation and parasympathetic withdrawal, resulting in diminished reflex modulation capacity

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against blood pressure fluctuations[13–16]. Those abnormalities lead to sustained elevation of blood pressure and impaired blood pressure control[17,18]. Thus, approaches that modulate vagal function or baroreflex sensitivity may have relevance to autonomic dysfunction, although therapeutic efficacy requires direct clinical testing.

The VN is a mixed autonomic nerve with predominantly afferent fibers[10,19,20]. Vagal afferent input converges on the NTS, which participates in central integration of cardiovagal and sympathetic cardiovascular control[8,21]. This pathway provides biological plausibility that vagal modulation could influence BRS and HRV, while the present physiological measurements do not directly test a specific brainstem circuit[7,22]. Because of those physiological properties, modulation of vagal activity has therapeutic potential for restoring autonomic balance and mitigating cardiovascular risks such as hypertension.

Vagus nerve stimulation (VNS) is a neuromodulation approach involving the application of electrical impulses to the VN to modulate ANS function[19,20,23,24]. Invasive VNS is performed by surgically implanting electrodes around the VN and connecting them to a pulse generator. This approach is approved by the US Food and Drug Administration for the treatment of epilepsy and depression[25]. In animal studies, invasive VNS has been shown to reduce blood pressure and improve autonomic regulation[26]. However, the surgical procedure is associated with risks of complications such as infection, coughing, and voice alteration[27]. To prevent those risks, transcutaneous auricular vagus nerve stimulation (taVNS) has been proposed as a noninvasive, low-cost alternative[28,29]. taVNS stimulates the auricular branch of the vagus nerve (ABVN), which is located in the cymba concha and tragus of the ear[30]. Recent studies have reported that taVNS increases parasympathetic activity and improves HRV, and it has gained attention as a safe and effective method for autonomic modulation. Clancy et al. (2014) demonstrated that taVNS increased HRV and decreased muscle sympathetic nerve activity in healthy adults, promoting a shift toward parasympathetic predominance[31]. De Couck et al. (2017) reported that short (10 min) and long (1 h) taVNS sessions produced moderate increases in HRV parameters, such as the standard deviation of normal-to-normal intervals (SDNN), with more pronounced effects in females than males[32]. Moreover, Antonino et al. (2017) showed that taVNS significantly enhanced cardiac baroreflex sensitivity (BRS) and reduced the low frequency/high frequency (LF/HF) ratio within a short period, confirming its parasympathetic activation effect[33].

Most previous taVNS studies have compared pre- and post-stimulation changes in resting conditions. Although this approach is useful for evaluating autonomic modulation at rest, resting measurements alone may not fully characterize baroreflex responsiveness when the cardiovascular system is challenged. The arterial baroreflex continuously contributes to short-term blood pressure regulation at rest; however, assessment during orthostatic stress can provide additional information on reflex responsiveness under changing hemodynamic demand. Therefore, evaluating the effects of taVNS during controlled blood pressure perturbation may provide a more physiologically informative assessment of its influence on baroreflex-mediated autonomic control.

The head-up tilt test (HUTT) is a standard method used to induce blood pressure perturbation. During the HUTT, the transition from the supine to the tilt position causes blood to pool in the lower extremities under the influence of gravity, leading to reductions in central venous return and stroke volume and eliciting compensatory autonomic cardiovascular responses that help maintain arterial pressure. During this process, the heart rate increases and vascular tone is adjusted, allowing the ANS to compensate for the instability caused by postural change[34,35]. Therefore, the HUTT is a useful method for eliciting the autonomic responses associated with postural transitions and evaluating baroreflex-mediated autonomic regulation and the dynamic adaptability of the cardiovascular system, making it suitable for investigating how taVNS influences autonomic responsiveness during orthostatic stress.

In this study, we used the HUTT protocol to identify the effects of taVNS on baroreflex-mediated autonomic responses during induced blood pressure perturbation. This approach allowed us to examine the physiological influence of taVNS in healthy subjects, thereby establishing a foundation for future applications in clinical populations with autonomic dysfunctions such as hypertension. BRS during tilt was the primary physiological outcome, and phase-specific HRV measures were secondary outcomes. Within-visit pre- and post-stimulation comparisons described observed changes, whereas direct crossover Condition × Time contrasts evaluated whether the magnitude of change differed between taVNS and sham.

Methods

Participants

This study enrolled healthy participants with normal blood pressure. None of the participants had a history of cardiovascular disease, epilepsy, or recurrent syncope. Participants were instructed to abstain from caffeine, alcohol, and nicotine for at least 12 h before the experiment. This study was approved by the Institutional Review Board of Hanyang University, and all experimental processes were conducted in accordance with the guidelines of the Declaration of Helsinki (HYUIRB-202501-005-2). Data were collected from March 18 to November 14, 2025. Prospective registration was not completed before enrollment; the trial was retrospectively registered on March 20, 2026 at https://cris.nih.go.kr/cris/index/index.do (KCT0011752) to improve transparency. The experiment was conducted in Room 204 of College of Medicine Ⅱ at Hanyang University. Written informed consent was obtained from all participants before their enrollment. Sample size was estimated using G*Power based on the effect size reported in a previous study[36]. Specifically, the effect-size estimate was derived from the RMSSD Time × Condition interaction reported in that study (partial $\eta^2 = 0.082$), corresponding to an effect size of $f = 0.299$. Using $\alpha = 0.05$, power = 0.95, two groups, three measurements, a correlation among repeated measures of 0.5, and a nonsphericity correction of 1, the required sample size was calculated to be 32 participants. Because a suitable crossover BRS effect estimate during orthostatic stress was unavailable, the study was not prospectively powered for the direct BRS Condition × Time effect.

Measurement systems

Electrocardiogram (ECG) and blood pressure data were collected using a Task Force® Monitor 3040i (CNSystems, Graz, Austria). Continuous and noninvasive blood pressure monitoring was performed by placing finger cuffs on the right index and middle fingers. The right arm was supported with a sling to ensure that the finger cuffs were maintained at heart level. RR interval (RRI) values were extracted from the ECG signals, and simultaneously recorded systolic blood pressure (SBP) values were obtained. The blood pressure data were calibrated to oscillometric blood pressure values obtained in the left arm. In addition, respiratory activity was recorded using a physiological recording system (MP160, Biopac Inc., USA) to monitor potential drowsiness during the experiment.

Study protocol

This study was conducted using a randomized, single-blind, sham-controlled, crossover design. Participants were assigned to one of two intervention sequences (taVNS → rest → sham or sham → rest → taVNS) using a pre-specified allocation list designed to achieve an approximately equal (1:1) distribution; 15 participants received taVNS first and 17 received sham first. The allocation sequence was generated using a computer-based randomization procedure by a researcher who was not involved in conducting the experiments. Participants were assigned sequentially according to enrollment order. However, investigators conducting the experiments had access to the allocation list, and formal allocation concealment was therefore not implemented. All participants completed two laboratory visits. In each visit, they experienced one of the two conditions: taVNS or sham condition. For the first visit, participants underwent anthropometric measurements (height and weight), followed by a sufficient resting period. After resting, heart rate (HR), SBP, and diastolic blood pressure (DBP) were measured using an oscillometric method with the participant in a seated position. Participants then received either taVNS or sham according to the assigned sequence. A washout period of at least two days was implemented before the second visit to minimize any potential carryover effects from the previous stimulation. The alternate stimulation condition was applied during the second visit. Throughout the entire experiment, all participants were positioned supine on a tilt table. The HUTT procedure was performed twice in each condition, encompassing two distinct phases: pre-stimulation and post-stimulation.

taVNS

The taVNS system consisted of a medical stimulator (ELEXIR, NuEyne, Korea) and ear electrodes (tVNS Technologies, Germany) specifically designed for attachment to the cymba concha—an area exclusively innervated by the ABVN. Electrodes were positioned on the left ear, and taVNS was administered with a pulse width of 250 μs and a frequency of 25 Hz[37,38]. The stimulation intensity was gradually increased from 0 mA in 0.1 mA increments up to each participant's individual sensory threshold. In the sham condition, the same electrodes were attached, and participants were informed that stimulation would be applied at a very weak intensity; however, no electrical current was actually delivered. After the first HUTT, taVNS or sham was applied for 60-min and continued during the subsequent 30-min HUTT, resulting in a total exposure of 90-min. This protocol was intended to assess the acute physiological response during continued stimulation, rather than to compare stimulation durations.

HUTT

Before the HUTT, participants rested in the supine position for at least 10 min. The HUTT was conducted for a total duration of 30 min and consisted of three phases. The first phase was a 10-minute supine period to assess baseline autonomic activity. The second phase involved a 10-minute tilt period at 60° to evaluate autonomic responses during orthostatic stress. The motorized table reached 60° in approximately 10 s. The transition interval was excluded when the synchronized analysis files were constructed, so the analyzed 10-minute tilt period began after the table reached 60°. The third phase consisted of a 10-minute supine recovery period to observe autonomic restoration after tilting. Harms included dizziness, nausea, headache, and burn-related skin irritation. If any harm occurred, the experiment was immediately terminated. An overview of the HUTT protocol is summarized in Fig. 1.

Feature extraction

We used MATLAB R2025a software (The MathWorks, Inc., Natick, MA, USA) to extract the BRS and HRV parameters from the RRI and SBP values acquired by the Task Force® Monitor. BRS was calculated using only the 10 min of data obtained from the tilt phase, when blood pressure perturbations were most pronounced. The

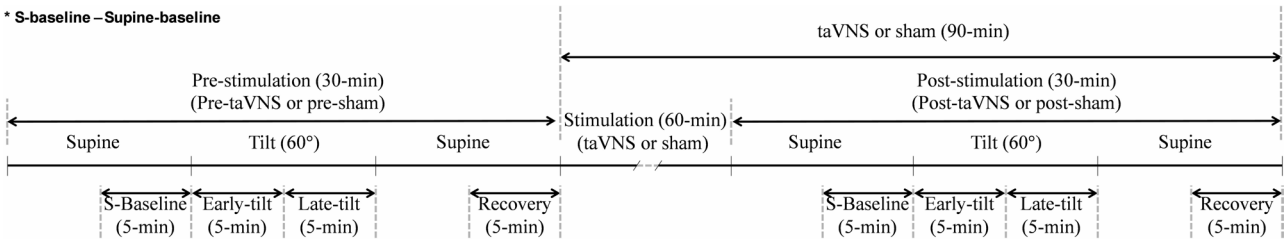


Fig. 1. Experimental protocol used in this study.

HRV analysis was performed across all three phases of the HUTT. In each phase, consecutive 5-minute segments without overlap were used to calculate the HRV parameters. Four specific 5-minute segments were selected for HRV analysis: the last 5-minute segment before the tilt phase, while supine, was used to assess baseline autonomic activity (Supine-baseline, S-baseline), reflecting resting parasympathetic tone in the absence of orthostatic stress; the first 5-minute segment after reaching the 60° tilt position (early-tilt) was used to evaluate the initial autonomic response to orthostatic stress, marked by vagal withdrawal and sympathetic activation; the last 5 min before the end of the tilt phase (late-tilt) was selected to assess the adaptive response to sustained orthostatic load and capture the persistence or modulation of sympathetic predominance over time; and the last 5 min of the recovery phase (recovery), following the return to the supine position, was used to examine the reactivation of parasympathetic activity and overall autonomic recovery after stress exposure.

Baroreflex sensitivity

BRS was used as an index to evaluate baroreflex-mediated autonomic regulation of the cardiovascular system. BRS was estimated by quantifying beat-to-beat changes in inter-beat intervals (IBIs) in response to spontaneous fluctuations in SBP. Inter-beat intervals (IBIs) used for BRS analysis were derived from ECG R–R intervals and are therefore equivalent to the RR intervals used in HRV analysis. In this study, BRS was calculated using the sequence method[39,40], which is based on the beat-to-beat correlation between SBP and IBI. In the sequence method, sequences in which SBP and IBI simultaneously increased or decreased for three or more consecutive beats were identified as up sequences and down sequences, respectively. For each sequence, the linear regression slope between SBP and IBI was calculated. The mean slope of all up sequences was defined as the up-slope BRS, and the mean slope of all down sequences was defined as the down-slope BRS. The overall mean slope of all valid sequences was defined as the all-slope BRS. A sequence was considered valid only when the beat-to-beat changes in SBP and IBI exceeded threshold values of 1 mmHg and 4 ms, respectively[41,42]. In addition, only sequences with a correlation coefficient greater than 0.85 were included in the analysis.

Heart rate variability

The HRV parameters were extracted in both the time and frequency domains. The time-domain analysis provides information on how specific parameters vary over time, and the frequency-domain analysis indicates which frequency components contribute to those parameters[43]. In the time domain, mean HR, SDNN, the percentages of adjacent NN intervals differing by more than 30 ms and 50 ms (pNN30 and pNN50, respectively), and the root mean square of successive differences between adjacent NN intervals (RMSSD) were calculated. In the frequency domain, power spectral density was analyzed within the low-frequency (0.04–0.15 Hz) and high-frequency (0.15–0.40 Hz) bands, and the LF/HF ratio was computed as a descriptive spectral-power ratio. Definitions of the parameters included in the time- and frequency-domain parameter sets are summarized in Table 1.

Statistical analysis

All statistical analyses were performed using IBM SPSS version 27 (IBM Corp., Armonk, NY, USA). For paired comparisons, normality of the within-participant differences was assessed using the Shapiro–Wilk test. Paired t-tests or Wilcoxon signed-rank tests were then applied as appropriate. Descriptive values in the tables are expressed as mean ± SD. The trial protocol specified paired t-tests or Wilcoxon signed-rank tests with Benjamini–Hochberg false discovery rate (BH-FDR) correction. To directly compare pre-to-post changes between conditions while accounting for the crossover design, additional mixed-effects analyses were performed. Mixed-effects models included Condition (taVNS vs. sham), Time (pre- vs. post-stimulation), Condition × Time, Period (first vs. second intervention period), and Sequence (taVNS-first vs. sham-first), with participant as a random intercept. HRV, hemodynamic, and respiratory models additionally included Analysis segment and Condition × Time × Analysis segment. BRS models constituted the main treatment-specific analyses, and baseline-adjusted models were sensitivity analyses. Exploratory ordinary least-squares regressions were used to examine associations between pre-taVNS baseline values and the corresponding pre-to-post changes. For HRV, baseline values were obtained from the pre-taVNS S-baseline segment, whereas BRS baseline values were obtained from the pre-taVNS tilt period. The baseline-change regressions were exploratory, and complementary crossover models included Baseline × Condition, Period, and Sequence. BH-FDR correction was applied within each corresponding outcome family. Unless otherwise specified, all reported p-values are FDR-adjusted, and statistical significance was set at $p < 0.05$.

Domain	Parameter	Definition
Time domain	Mean HR	Mean heart rate
	SDNN	Standard deviation of NN intervals
	RMSSD	Root mean square of successive differences between adjacent NN intervals
	pNNx	Percentage of consecutive NN intervals that differ by more than x ms
Frequency domain	LF	Low frequency power calculated by Lomb–Scargle periodogram (0.04–0.15 Hz)
	HF	High frequency power calculated by Lomb–Scargle periodogram (0.15–0.4 Hz)
	LF/HF ratio	Ratio of LF to HF spectral power

Table 1. Definitions of the HRV Parameters.

Characteristic	Value
Participants	32 (male: 15)
Age, years	25.28 ± 3.28
Weight, kg	64.78 ± 14.84
Height, cm	167.43 ± 7.63
SBP, mmHg	109.43 ± 8.83
DBP, mmHg	70.53 ± 8.80
HR, bpm	79.53 ± 11.19

Table 2. Participant characteristics.

Parameters	Difference in pre-to-post change (taVNS – sham), ms/mmHg	95% CI	*p*-value
Up-slope	1.46	− 1.32 to 4.24	0.302
Down-slope	2.01	− 0.34 to 4.36	0.229
All-slope	1.74	− 0.64 to 4.12	0.229

Table 3. Direct crossover comparison of pre-to-post changes in BRS between the taVNS and sham sessions.

	Tilt (10 min)				
	Pre-taVNS		Post-taVNS		
Parameters	Mean	SD	Mean	SD	*p*-value
Up-slope	9.59	2.94	12.10	3.74	0.003
Down-slope	9.28	3.57	12.16	3.45	< 0.001
All-slope	9.43	3.11	12.13	3.34	< 0.001

Table 4. Comparison of BRS from Pre- to Post-taVNS Across Tilt Sessions.

Results

Data acquisition and participant exclusion

We initially enrolled 36 participants in this study. Four participants were excluded from the analysis due to poor signal quality or suspected drowsiness based on respiratory monitoring, resulting in a final dataset of 32 participants. The mean age was 25.28 ± 3.28 years, and the sample included 15 males and 17 females. No experimental sessions were stopped due to harms. The mean HR, SBP, and DBP values measured before the experiment are presented in Table 2.

Differences in baroreflex-mediated autonomic control from pre- to post-stimulation

Direct crossover and baseline-adjusted comparisons of BRS between taVNS and sham

Pre-stimulation BRS differed between the two conditions, with lower baseline values before taVNS than before sham (Table S1). The main treatment-specific analysis directly compared pre-to-post changes in BRS between the taVNS and sham conditions using the crossover mixed-effects model. No significant Condition × Time effect was observed after BH-FDR correction for up-slope (estimate 1.46 ms/mmHg, 95% CI − 1.32 to 4.24, $p = 0.302$), down-slope (2.01, − 0.34 to 4.36, $p = 0.229$), or all-slope BRS (1.74, − 0.64 to 4.12, $p = 0.229$; Table 3). Given the baseline imbalance, baseline-adjusted models were additionally examined as a sensitivity analysis. After adjustment for pre-stimulation BRS, no significant differences between taVNS and sham were observed for up-slope, down-slope, or all-slope BRS (Table S2). Thus, although BRS increased significantly from pre- to post-stimulation within the taVNS visit, neither the direct crossover nor the baseline-adjusted analysis demonstrated a significant taVNS-specific BRS effect.

Changes in BRS during taVNS stimulation

BRS was used to assess the effect of taVNS on baroreflex control during induced blood pressure perturbation (tilt). The up-slope BRS increased from 9.59 ± 2.94 to 12.10 ± 3.74 ms/mmHg ($p = 0.003$), and the down-slope BRS increased from 9.28 ± 3.57 to 12.16 ± 3.45 ms/mmHg ($p < 0.001$) (Table 4; Fig. 2).

Changes in BRS during sham stimulation

As in the taVNS analysis, BRS was evaluated pre- and post-sham during the tilt phase (Table 5; Fig. 3). No significant differences were observed for either the up-slope or down-slope values (up-slope: 12.18 ± 4.70 to 13.23 ± 7.70, $p = 0.881$; down-slope: 12.16 ± 4.13 to 13.03 ± 6.51, $p = 0.611$).

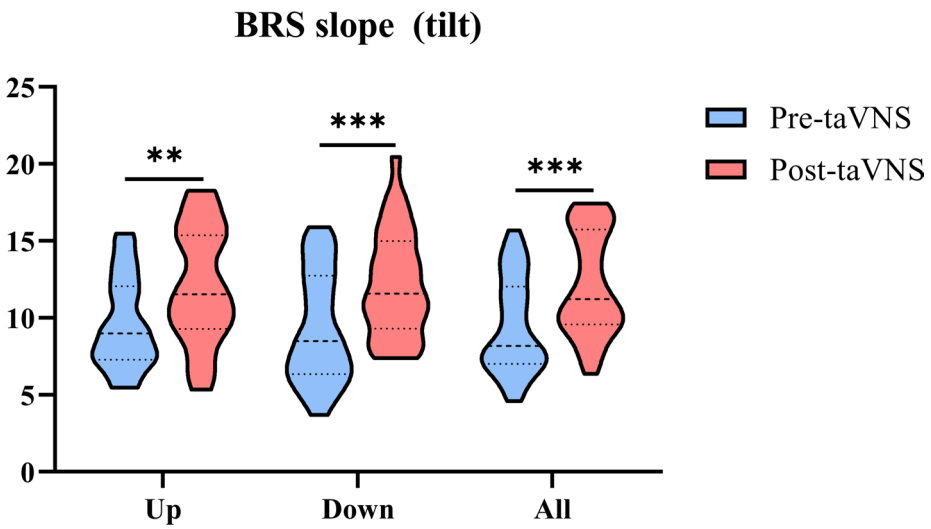


Fig. 2. Violin plots illustrating the distribution of BRS parameters across tilt sessions, pre- and post-taVNS. Blue represents pre-taVNS and red indicates post-taVNS values. Solid horizontal lines indicate the medians; dotted lines represent quartiles. ** $p < 0.01$, *** $p < 0.001$, paired t-tests or Wilcoxon signed-rank tests.

	Tilt (10 min)				
	Pre-sham		Post-sham		
Parameters	Mean	SD	Mean	SD	*p*-value
Up-slope	12.18	4.70	13.23	7.70	0.881
Down-slope	12.16	4.13	13.03	6.51	0.611
All-slope	12.17	4.19	13.13	6.79	0.848

Table 5. Comparison of BRS from Pre- to Post-sham Across Tilt Sessions.

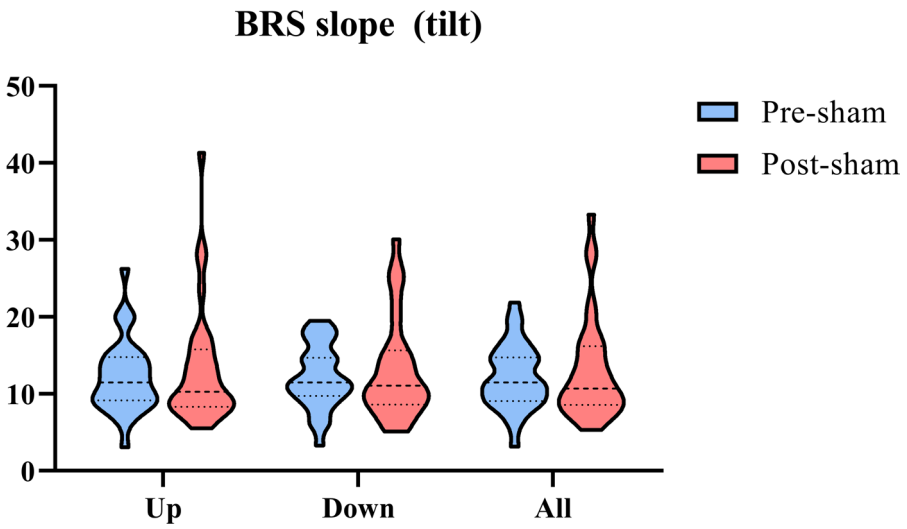


Fig. 3. Violin plots illustrating the distribution of BRS parameters across tilt sessions, pre- and post-sham. Blue represents pre-sham values and red indicates post-sham values. Solid horizontal lines indicate the medians; dotted lines represent quartiles. Statistical comparisons were performed using paired t-tests or Wilcoxon signed-rank tests, as appropriate.

Differences in heart rate variability from pre- to post-stimulation

Direct crossover and baseline HRV comparisons between taVNS and sham

In the secondary direct crossover analysis, differences in pre-to-post change averaged across the four analysis segments were significant for SDNN ($p = 0.046$) and pNN30 ($p = 0.017$), whereas pNN50 and the other HRV measures were not significant (Table S4). No Condition × Time × Analysis segment interaction was significant for any HRV measure (Tables S4 and S5). Pre-stimulation S-baseline HRV was also compared between the taVNS and sham sessions, and no significant differences were observed between the two conditions for any HRV parameter (Table S3).

Changes in HRV following taVNS stimulation

Within the taVNS condition, changes in HRV from pre- to post-stimulation were compared across the four analysis segments (Table S6 and Fig. 4). Several HRV parameters increased significantly from pre- to post-taVNS across the four analysis segments. In the time domain, SDNN, RMSSD, pNN30, and pNN50 increased after stimulation at every segment (SDNN: S-baseline $p = 0.007$, early-tilt $p < 0.001$, late-tilt $p = 0.041$, recovery $p = 0.004$; RMSSD: S-baseline $p = 0.004$, early-tilt $p = 0.002$, late-tilt $p = 0.003$, recovery $p = 0.006$; pNN30: S-baseline $p = 0.006$, early-tilt $p = 0.007$, late-tilt $p = 0.007$, recovery $p = 0.007$; pNN50: S-baseline $p = 0.004$, early-tilt $p = 0.012$, late-tilt $p = 0.017$, recovery $p = 0.012$). Mean HR decreased consistently across segments (S-baseline $p < 0.001$, early-tilt $p < 0.001$, late-tilt $p < 0.001$, recovery $p = 0.003$). In the frequency domain, LF showed no difference at S-baseline ($p = 0.342$) but increased during early-tilt and recovery (early-tilt $p < 0.001$, recovery $p = 0.020$). The LF/HF ratio decreased at S-baseline and late-tilt (S-baseline $p = 0.014$, late-tilt $p = 0.011$) but was not significantly different during early-tilt or recovery (early-tilt $p = 0.881$, recovery $p = 0.440$). In contrast, HF increased significantly at all segments (S-baseline $p = 0.004$, early-tilt $p = 0.003$, late-tilt $p = 0.007$, recovery $p = 0.002$).

Changes in HRV following sham stimulation

Using the same method as in the taVNS HRV analysis, we compared pre-sham and post-sham HRV across all four analysis segments. Segment-specific differences in HRV from pre- to post-sham are detailed in Table S7 and Fig. 5. Although several parameters reached statistical significance, there was no consistent pattern across parameters. Mean HR decreased significantly at S-baseline, early-tilt, and late-tilt (S-baseline $p = 0.008$, early-tilt $p = 0.002$, late-tilt $p = 0.028$), and SDNN showed a modest but nonsignificant increase at late-tilt ($p = 0.052$). In contrast, key parasympathetic-related parameters (RMSSD, HF power, and LF/HF ratio) did not exhibit consistent changes across segments. These within-visit results are descriptive; treatment-specific interpretation is based on the direct crossover models.

Exploratory associations between baseline autonomic tone and within-taVNS change

To explore whether baseline autonomic tone was associated with within-taVNS change, we conducted linear regression analyses between the pre-taVNS autonomic parameters and taVNS-induced changes. In our analysis of BRS, we observed changes during the tilt sessions. The changes in BRS down-slope ($R^2 = 0.22$, $p = 0.006$) and all-slope ($R^2 = 0.14$, $p = 0.036$) were inversely associated with baseline values (Fig. 6). Among the frequency-domain parameters, a strong negative association was found between the pre-taVNS LF/HF ratio and its post-taVNS change ($R^2 = 0.78$, $p < 0.001$). Given the limited physiological specificity of the LF/HF ratio and the

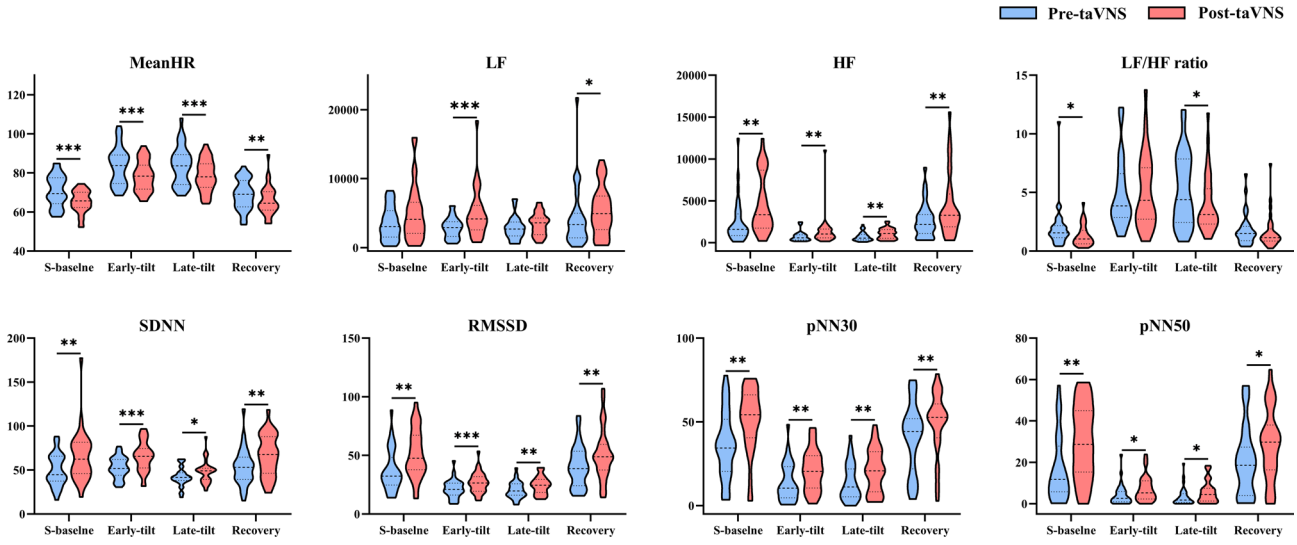


Fig. 4. Violin plots illustrating the distribution of HRV parameters across the four analysis segments (S-baseline, early-tilt, late-tilt, recovery), pre- and post-taVNS. Blue represents pre-taVNS and red indicates post-taVNS values. Solid horizontal lines indicate the medians; dotted lines represent quartiles. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, paired t-tests or Wilcoxon signed-rank tests.

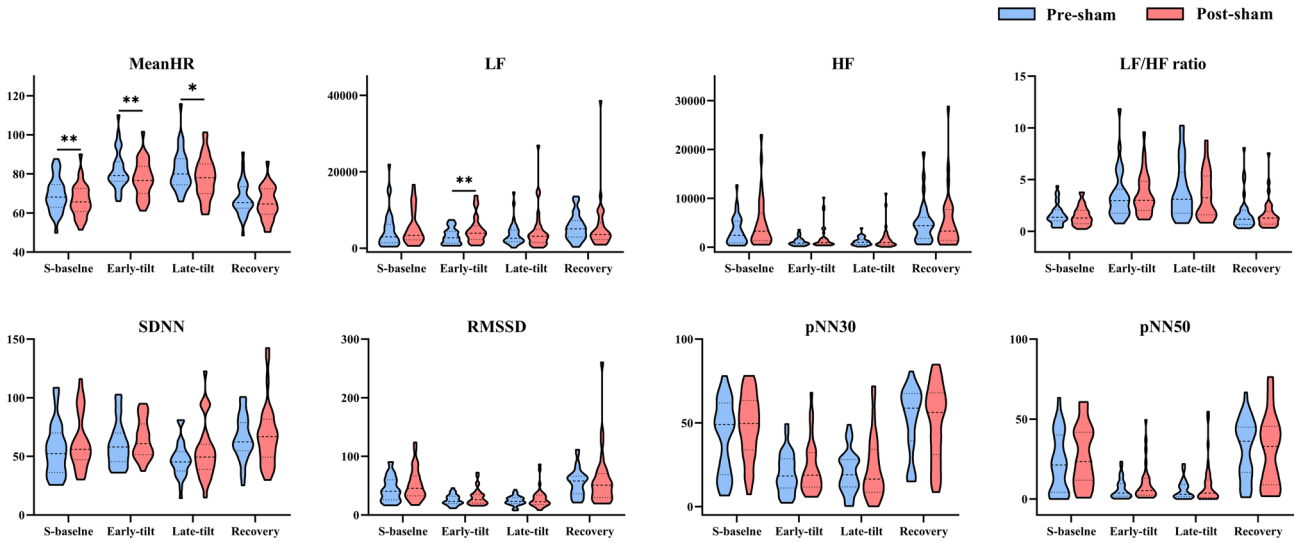


Fig. 5. Violin plots illustrating the distribution of HRV parameters across the four analysis segments (S-baseline, early-tilt, late-tilt, recovery), pre- and post-sham. Blue represents pre-sham, and red indicates post-sham values. Solid horizontal lines indicate the medians; dotted lines represent quartiles. * $p < 0.05$, ** $p < 0.01$, paired t-tests or Wilcoxon signed-rank tests.

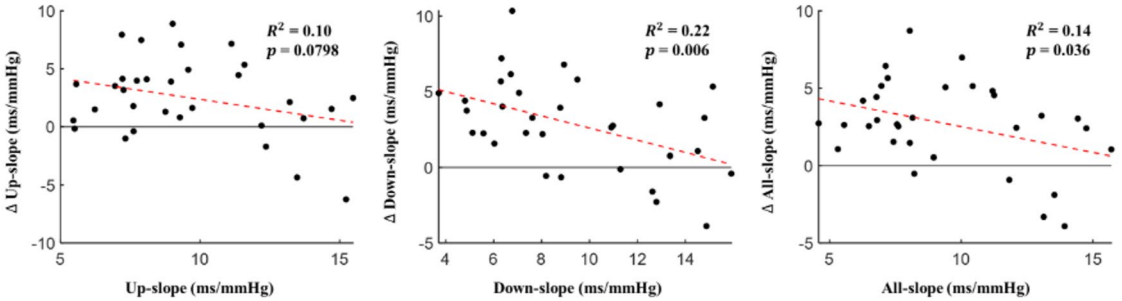


Fig. 6. Scatterplots showing the association between pre-taVNS BRS parameters and the changes induced by taVNS. All BRS parameters are from the tilt sessions.

potential for mathematical coupling between baseline values and change scores, this association was considered exploratory and was not interpreted as evidence of greater sympathetic predominance at baseline. The mean pre-taVNS HR also showed a significant negative correlation with its change ($R^2 = 0.50$, $p < 0.001$). In the time domain, moderate negative correlations were observed between the baseline parasympathetic markers, RMSSD ($R^2 = 0.17$, $p = 0.020$), pNN30 ($R^2 = 0.35$, $p < 0.001$), and pNN50 ($R^2 = 0.20$, $p = 0.010$), and their respective changes. These inverse associations may reflect baseline-dependent variation in within-taVNS changes, although mathematical coupling or regression to the mean cannot be excluded (Fig. 7). Sex-coded versions of these exploratory plots are provided in Supplementary Figure S1. Exploratory sex-interaction analyses did not identify significant sex-related variation in the intervention response for any BRS or HRV measure (Table S10). Because baseline is included in the change score, these associations may reflect mathematical coupling or regression to the mean. In complementary models including both crossover conditions, Baseline × Condition interactions were not significant for any of the three BRS measures or for seven of the eight HRV measures; only the LF/HF ratio remained significant ($p < 0.001$; Table S11).

Discussion

In this study, we investigated the effects of taVNS on autonomic function by using the HUTT both pre- and post-stimulation. BRS was specifically analyzed during the tilt phase to evaluate autonomic responsiveness during induced blood pressure perturbation, whereas HRV was compared across the S-baseline, tilt, and recovery phases. The direct crossover and baseline-adjusted BRS analyses were nonsignificant. Among the secondary HRV outcomes, direct crossover differences averaged across analysis segments were significant for SDNN and pNN30, whereas no analysis segment-specific interaction was significant. Therefore, the findings provide preliminary evidence of cardiovagal modulation, while BRS-specific, mechanistic, and clinical interpretations require caution.

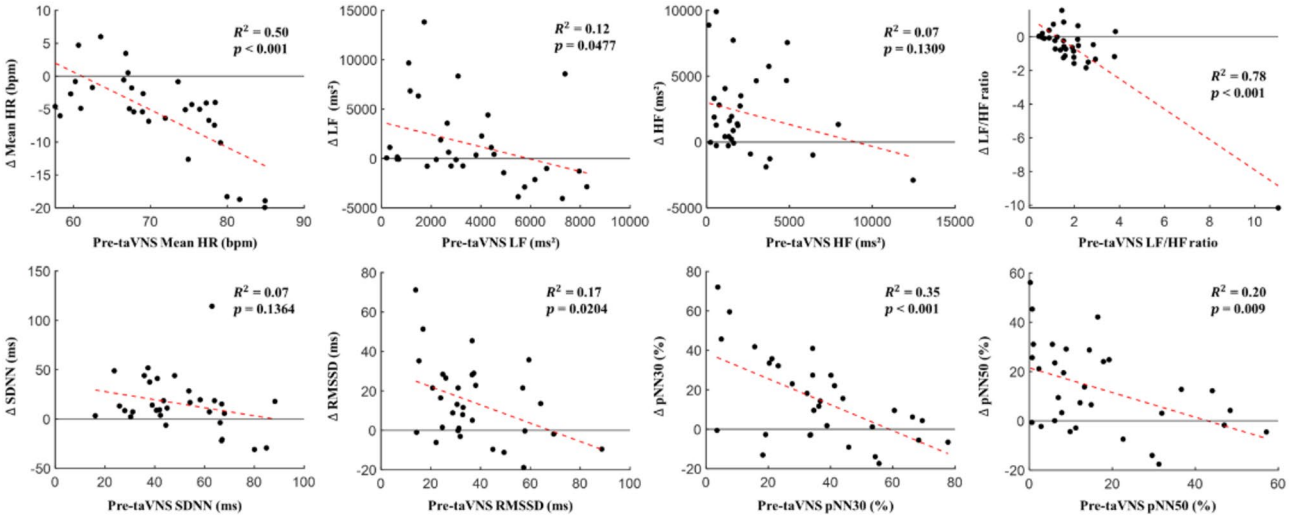


Fig. 7. Scatterplots showing the association between pre-taVNS HRV parameters and the changes induced by taVNS. All HRV parameters are from the S-baseline phase.

Baroreflex sensitivity during orthostatic stress

We assessed BRS to quantify reflex control of HR in response to blood pressure changes–a physiologically critical mechanism for short-term cardiovascular stability[44,45]. Importantly, compared with HRV, which provides indirect insights into autonomic modulation, BRS offers a more mechanistically specific index of baroreflex-mediated autonomic control because it directly reflects the dynamic interplay between SBP and IBI.

In this study, we examined BRS during the tilt phase, a condition of orthostatic stress that physiologically induces gravitational pooling and compensatory autonomic responses[46,47]. The direct crossover analysis did not demonstrate a significant Condition × Time effect for any BRS measure (Table 3). Pre-stimulation BRS was lower before taVNS than before sham (Table S1), and the baseline-adjusted sensitivity analysis likewise showed no significant between-condition differences (Table S2). Within the taVNS visit, up- and down-slope BRS increased (Table 4; Fig. 2), a pattern compatible with greater IBI responsiveness to spontaneous SBP fluctuations[48]. However, these within-visit increases were descriptive and did not establish a taVNS-specific BRS effect.

In contrast, in the sham condition, BRS showed no significant within-visit change (Table 5; Fig. 3). This result is descriptive and does not by itself establish treatment specificity, which is evaluated by the direct crossover analyses.

Reduced BRS is strongly associated with increased cardiovascular risk, including in patient populations with hypertension, orthostatic hypotension, and autonomic dysfunction[49,50]. The present observations may therefore provide a rationale for further investigation of taVNS in populations with impaired autonomic regulation, but they do not establish clinical or antihypertensive efficacy.

In sum, BRS increased within the taVNS visit, but neither the direct crossover nor the baseline-adjusted between-condition analysis demonstrated a significant taVNS-specific effect. These within-visit BRS findings should therefore be considered preliminary and interpreted descriptively rather than as evidence of improved cardiovascular reflex regulation during orthostatic stress. BRS during tilt nevertheless remains a clinically relevant physiological measure of autonomic cardiovascular regulation[51].

Autonomic regulation reflected in HRV responses to taVNS

In the S-baseline phase, most of the parasympathetic HRV parameters, particularly RMSSD, pNN50, and HF power, increased significantly within the taVNS visit (Table S6 and Fig. 4). For example, Geng et al. (2022) reported significant increases in parasympathetic HRV parameters following short taVNS sessions in young adults[36]. Also, Clancy et al. (2014) reported a reduction in the LF/HF ratio[31]. However, the LF/HF ratio did not show a significant taVNS-specific effect in the direct crossover analyses, which may reflect differences in stimulation protocols and physiological context. Accordingly, the LF/HF ratio findings were considered together with the broader pattern of time- and frequency-domain HRV responses. In the secondary direct crossover analysis, differences averaged across analysis segments were significant for SDNN and pNN30, whereas pNN50 and the other HRV measures were not significant (Table S4). No Condition × Time × Analysis segment interaction was significant for any HRV measure (Tables S4 and S5). Taken together, these limited secondary HRV findings are compatible with possible cardiovagal modulation but do not support a broad or analysis segment-specific effect[52]. By contrast, in the sham condition, some parameters reached statistical significance, but no consistent pattern was observed across parameters or analysis segments. In particular, key parasympathetic markers (RMSSD and HF) did not show consistent changes. Thus, the overall HRV findings suggest a possible contribution of taVNS to cardiac autonomic modulation, while the magnitude and phase specificity of these effects should be interpreted cautiously.

During tilt, gravitational pooling typically elicits an increase in sympathetic activity and suppression of vagal activity[53,54]. The within-taVNS HRV pattern may be compatible with attenuated cardiovagal withdrawal during orthostatic stress. Afferent ABVN input to the NTS is one plausible pathway[55–57].

The HRV changes observed in this study are compatible with possible involvement of afferent ABVN–NTS pathways, which may contribute to modulation of vagal (parasympathetic) efferent activity. Moreover, the pattern of HRV changes during the tilt phase may indicate maintained or enhanced cardiovagal modulation during orthostatic stress, although analysis segment-specific intervention effects were not consistently observed. In contrast, in the sham condition, some parameters reached statistical significance, but no consistent pattern emerged across parameters or phases. Hemodynamic and respiratory responses also varied across HUTT analysis segments without significant intervention-specific three-way interactions (Tables S8 and S9), reducing the likelihood that differences in orthostatic loading or respiratory-rate changes alone accounted for the observed HRV patterns. However, the absence of tidal-volume measurements limits mechanistic interpretation. Taken together, our findings are consistent with a possible contribution of taVNS to cardiac autonomic modulation, while nonspecific or time-dependent effects cannot be completely excluded.

Exploratory associations with baseline autonomic tone

The results of the regression analysis indicate that within-taVNS changes in autonomic measures may vary according to their baseline levels. Lower baseline BRS was also associated with greater within-taVNS changes in baroreflex function; however, complementary crossover models did not identify significant Baseline × Condition interactions for BRS, limiting interpretation of baseline BRS as a stimulation-specific predictor. The inverse association between baseline LF/HF ratio and its subsequent change may be consistent with baseline-dependent response heterogeneity, although this relationship should be interpreted cautiously given the limited physiological specificity of LF/HF and the mathematical coupling between baseline values and change scores[58]. Similarly, greater within-taVNS changes in RMSSD, pNN30, and pNN50 among participants with lower baseline values may reflect baseline-dependent variation in cardiovagal responses rather than a uniform stimulation effect[59,60]. Across HRV measures, Baseline × Condition interactions were not significant for seven of eight indices, with a significant interaction observed only for the LF/HF ratio (Table S11). Given the exploratory nature of these analyses and the limited physiological specificity of the LF/HF ratio, this isolated finding does not establish baseline-dependent taVNS responsiveness. Nevertheless, the broadly inverse associations observed across several autonomic measures suggest that baseline autonomic state may remain relevant for future studies of response heterogeneity. Future studies should prespecify moderator analyses and validate baseline-dependent response patterns in independent samples, particularly in populations with autonomic dysfunction.

Novelty and contributions

Most prior taVNS studies have assessed autonomic modulation at rest, used short stimulation durations, and focused on HRV. Even when BRS was assessed, measurements were typically restricted to resting conditions without sufficient blood pressure perturbation, limiting the physiological relevance and interpretability of baroreflex responsiveness. To evaluate the effects of taVNS in more physiologically meaningful conditions, we applied 60-min of taVNS at rest and continued stimulation during the subsequent 30-min HUTT, for 90-min of total exposure. With its phased structure (supine–tilt–recovery), the HUTT enables standardized observation of autonomic regulation at S-baseline, during orthostatic stress, and throughout recovery, thereby providing a standardized framework for evaluating autonomic responses to orthostatic stress adaptability beyond resting conditions.

Our combined analysis of BRS and HRV data collected using this design characterized autonomic responses across S-baseline, tilt, and recovery phases. BRS increased from pre- to post-stimulation within the taVNS visit; however, the direct crossover analysis for the primary BRS outcome did not demonstrate a significant taVNS-specific effect. Several cardiovagal HRV parameters, including HF and RMSSD, showed increases during the taVNS condition, whereas in the secondary direct crossover analysis, differences averaged across analysis segments were significant only for SDNN and pNN30, with no significant analysis-segment-specific interaction. Thus, these findings suggest possible modulation of cardiovascular autonomic responses during orthostatic stress, but do not establish that taVNS improves baroreflex or blood pressure regulation. The main contribution of this study is therefore the physiological characterization of BRS and HRV responses during HUTT under taVNS and sham conditions.

In addition, the inclusion of a sham condition provided context for changes related to time and nonspecific study procedures. In the sham sessions, BRS showed no significant within-visit changes, and although changes in some HRV parameters reached significance, the findings did not form a consistent pattern. Nevertheless, treatment-specific inference is more appropriately based on the direct crossover analyses than on separate within-condition comparisons. Collectively, the observed autonomic patterns are compatible with possible modulation through ABVN–NTS pathways, but they do not confirm this mechanism or fully exclude expectancy, visit, or other nonspecific effects.

Limitations

This study has several limitations. First, although our design induced blood pressure perturbation to evaluate autonomic responsiveness beyond resting conditions, our study population consisted of healthy adults, which limits the clinical generalizability of our results. In patient populations with autonomic abnormalities (e.g., hypertension, orthostatic hypotension, autonomic failure), responses to taVNS might differ. Therefore, follow-up studies with those groups are warranted. Second, because our participants were predominantly young adults, our findings might not fully capture age-related differences in autonomic responsiveness and taVNS effects. Given that autonomic flexibility and baroreflex function typically decline with age, taVNS efficacy could vary

across age groups, underscoring the need for studies that include a broader age range. Third, we examined acute responses within a single session; therefore, we could not assess the cumulative effects of repeated or prolonged stimulation or potential residual effects after stimulation cessation. Future investigations using longitudinal designs are needed to determine the durability and stability of taVNS effects. In addition, the trial was registered retrospectively after completion of data collection rather than prospectively before participant enrollment. The use of a 0-mA sham may have allowed participants to distinguish between stimulation conditions, and blinding effectiveness was not formally assessed. Therefore, potential expectancy effects related to incomplete blinding cannot be excluded.

In light of those limitations, future work should apply the present protocol to patients with hypertension or autonomic dysfunction and compare their responses with healthy controls to more clearly establish the therapeutic relevance of taVNS. Moreover, repeated and long-term stimulation with follow-up assessments of HRV and BRS will be important to determine whether taVNS offers sustained or cumulative benefits for blood pressure regulation and autonomic function. Such studies will be needed to determine whether taVNS may have therapeutic relevance for blood pressure regulation and autonomic dysfunction.

Conclusion

This study quantitatively evaluated autonomic responses to taVNS during blood pressure perturbation by analyzing BRS and HRV. The direct crossover analysis for the primary BRS outcome and the baseline-adjusted sensitivity analysis did not establish a taVNS-specific BRS effect. Among the secondary HRV outcomes, differences averaged across analysis segments were significant only for SDNN and pNN30, with no significant analysis-segment-specific interaction. Within-visit increases in BRS and several HRV measures were descriptive. Thus, the findings extend assessment of taVNS beyond resting conditions and provide preliminary evidence compatible with cardiovagal modulation during HUTT, while not demonstrating improved baroreflex function or blood pressure regulation. Further studies in clinically relevant populations are needed.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Geonhee Lee: Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. Donghun Kang: Writing – original draft, review & editing, Methodology, Formal analysis, Data curation, Conceptualization. Jiseok Lee: Data curation. Jongshill Lee: Writing – review & editing, Supervision. Jeyeon Lee: Writing – review & editing, Supervision, Project administration. In Young Kim: Writing – review & editing, Supervision, Funding acquisition.

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Declarations

Competing interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Clinical trial
The clinical trial described in this paper was registered at https://cris.nih.go.kr/cris/index/index.do under the registration number KCT0011752 (first trial registered 20/03/2026, retrospective registration).

Additional information
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