

Baroreflex sensitivity as a target for nonpharmacological interventions in elderly patients with supine hypertension and orthostatic hypotension

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Research Article

Keywords: Orthostatic hypotension, supine hypertension, autonomic nervous system, HRV, Valsalva maneuver, baroreflex

Posted Date: October 14th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11222315/v1>

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Additional Declarations: No competing interests reported.

Abstract

Orthostatic hypotension (OH) and supine hypertension (SH) are physiological indicators of autonomic dysfunction that are associated with an increased risk of major cerebrocardiovascular events. Since pharmacological interventions do not restore normal baroreflex control, improving the efficacy of nonpharmacological interventions that are suitable for these at-risk populations is needed. Heart rate variability (HRV) biofeedback (HRVB) intervention is a safe option to effectively target cardiovascular autonomic regulation and the baroreflex in this patient population. The objective of this study was to determine in elderly patients the relationship between autonomic biomarkers known to be increased by HRVB and impaired baroreflex responses in patients with systolic OH (sOH) and/or SH. This is a retrospective study of 273 patients (144 women; Age: 65–94 yrs) evaluated with a standardized testing protocol of the Autonomic Reflex Screen from 2015 to 2022. Analyses were performed to determine HRV indices and adrenal (BRS_a) and vagal (BRS_v) baroreflex responses during the Valsalva maneuver (VM). The study demonstrated that sOH was associated with a reduction in HRV metrics and the BRS_a , independent of SH. This study also demonstrated that SH was associated with a significant increase in Phase II_E of the VM and a reduction in the BRS_v , independent of sOH. Our results also showed that deficits in Phase II_L of the VM were only observed in patients with sOH and concurrent SH. These findings suggest a significant relationship between biomarkers known to improve with HRVB (SDNN and LF-HRV) and deficits in hemodynamic fluctuations in VM contributing to sOH and SH.

Introduction

Orthostatic hypotension (OH) is a sustained reduction in blood pressure (BP) that occurs when adaptive mechanisms fail to compensate for the reduction in venous return when assuming the standing position (Ricci et al., 2015). OH is considered a key manifestation of autonomic dysfunction and observed in patients with neurogenic (e.g., patients with diabetes mellitus, neurodegenerative disorders, high spinal cord lesions, autoimmune disorders, and small fiber neuropathies) and non-neurogenic disorders (e.g., volume depletion, anemia, polypharmacy and physical deconditioning) (Freeman et al., 2018; Ricci et al., 2015). OH has been independently associated with an increased risk of major cerebrocardiovascular events and may provoke symptoms of cerebral hypoperfusion, including fatigue, lightheadedness, blurry vision and syncope (Ricci et al., 2015).

There is evidence to suggest that nearly one-half of patients with OH develop supine hypertension (SH), which worsens OH in the morning (Fanciulli et al., 2018). SH could increase the risk of hypertensive emergencies, including cerebral hemorrhage, stroke, and myocardial infarction (Pinna et al., 2014). Since patients with SH are normotensive while seated and typically asymptomatic (Fanciulli et al., 2018), consensus panels of experts recommend that all patients newly diagnosed with OH should also be screened for SH (Fanciulli et al., 2016; Gibbons et al., 2017). Management in patients with concurrent OH and SH is complicated because both conditions are hemodynamic opposite; improving one may worsen the other (Fanciulli et al., 2018; Gibbons et al., 2017; Jordan et al., 2019; Mantovani et al., 2022).

Appropriate therapy for SH has yet to be defined and longitudinal studies are needed (Jordan et al., 2019; Mantovani et al., 2022).

The arterial baroreceptor reflex buffers acute fluctuations of arterial BP that occur during changes in posture, exercise, emotion, and other conditions (Benarroch, 2008). Dysfunction at central and/or peripheral sites in the baroreflex efferent pathway contributes to the development of OH (Freeman et al., 2018; Kaufmann et al., 2020) and have shown significant correlations with SH (Fanciulli et al., 2018; Mantovani et al., 2022). Current expert recommendations suggest both pharmacological and nonpharmacological interventions for OH (Freeman et al., 2018; Ricci et al., 2015). Since pharmacological interventions increase BP independent of posture and do not restore normal baroreflex control, nonpharmacological treatments are considered the foundation of OH management (Wieling et al., 2022). The use of nonpharmacological interventions has been shown to improve symptoms and the quality of life of OH patients (Freeman et al., 2018; Newton and Frith, 2018; Ricci et al., 2015) and represent the cornerstone of SH therapy (Mantovani et al., 2022). The prevalence of OH increases with age (Low, 2008) and the aging population is expanding rapidly (Cheng et al., 2020); therefore, improving the efficacy of nonpharmacological interventions that are suitable for these at-risk populations is needed.

Managing OH in patients with SH is a matter of debate and often requires prioritizing the treatment of OH over SH due to a greater risk of syncope and falls (Espay et al., 2016; Gibbons et al., 2017). However, this clinical prioritization has been challenged by evidence of poorer long-term outcomes in patients with concurrent OH and SH and evidence of more cardiovascular events in patients with SH, regardless of a diagnosis of OH (Earle et al., 2023; Palma et al., 2020). Since there are no pharmacological treatments that restore normal baroreflex control (Wieling et al., 2022), identification of optimal BP targets that are suitable for these at-risk populations is needed.

There is evidence to suggest that regular physical activity benefits baroreflex sensitivity (BRS) in the elderly and reduces the risk of cardiovascular morbidity and mortality (La Rovere and Pinna, 2014). However, nonpharmacological interventions involving physical activity may not be appropriate for frail patients at high risk of falls and injury, hence management of OH may require individualized care (Dani et al., 2022). Moreover, some nondrug treatments may not be safe for patients with comorbidities and/or disabilities (Logan et al., 2020; Robinson et al., 2022). Psychophysiological techniques like heart rate variability (HRV) biofeedback (HRVB) are a safe and promising option to effectively target cardiovascular autonomic regulation and the baroreflex in this patient population. HRVB has been shown to increase HRV amplitude and baroreflex gain (Lehrer et al., 2003; Lehrer and Gevirtz, 2014) and are well tolerated by older adults without adverse events (Park et al., 2019). A systematic review investigating the effects of HRVB on clinical outcomes in patients with cardiovascular disease found that HRVB was associated with improvements in both readmission rates and left ventricular ejection fraction and with a reduction in systolic BP (SBP) and diastolic BP (DBP) in pre-hypertensive patients (Burlacu et al., 2021). Evidence supporting the effectiveness of biofeedback on patients with OH is limited (Brucker and Ince, 1977; Ince, 1985; Rau et al., 2003). A recent study found that OH patients enrolled in a 12-week multidisciplinary

HRVB-based program increased the low-frequency (LF) power of HRV (LF-HRV) and reduced the orthostatic drops in SBP and DBP (Han et al., 2025). Patients in the HRVB-based program also reported fewer orthostatic symptoms. The increase of LF-HRV, an index of baroreflex function (Davies et al., 2002; Rahman et al., 2011), suggests that HRVB training increases baroreflex gain in patients with OH.

The Valsalva maneuver (VM), a test of reflex cardiovascular responses, has been used to demonstrate that OH is associated with a reduction in both the vagal and adrenergic components of the baroreflex (Palamarchuk et al., 2016; Sandroni et al., 1991; Schrezenmaier et al., 2007). We recently evaluated the effects of systolic OH (sOH) on adrenergic (α - and β -adrenergic mechanisms) and vagal mechanisms during the VM and head-up tilt (HUT) in patients with sOH (50–86 years of age) (Criado and Kalafut, 2024). The study supported previous findings showing reduced vagal and adrenergic baroreflex and demonstrated that reduced end-tidal CO₂ (EtCO₂) was a major contributor to orthostatic cerebral hypoperfusion in patients with OH. Interestingly, frequency-domain measures of HRV were only reduced when patients were in HUT, not in supine position. These results suggest that deficits in cardiovascular autonomic regulation associated with sOH are demonstrated when the arterial baroreflex response is triggered, during the VM and HUT. However, while SH was not controlled in the study, these results, and previous findings by Han et al (2025) indicate that both HRVB and biofeedback treatments targeting EtCO₂ may be effective nonpharmacological interventions complementing the standard of care in OH patients with symptoms of cerebral hypoperfusion. Despite this evidence, a better understanding of HRVB markers targeting cardiovascular autonomic regulation and baroreflex in patients with concurrent OH and associated SH are needed. Whether SH is only associated with autonomic deficits in supine position or also worsens HRV and/or baroreflex regulation in OH patients during orthostatic stress is not well understood. The objective of this study was to determine in elderly patients: a) whether adrenergic and vagal mechanisms are associated with deficits in SH, independent of sOH; b) whether deficits in the arterial baroreflex response in patients with sOH are exacerbated by SH; and, c) the relationship between biomarkers known to improve with HRVB and baroreflex deficits in patients with concurrent sOH and SH. Findings from this study aim at providing insight into the development of a nonpharmacological HRVB protocol that targets HRV metrics associated with hemodynamic and baroreflex impairments underlying sOH and SH.

Methods

This is a retrospective study of 273 participants (144 women; Age: 65–94 yrs) were evaluated at the Autonomic Laboratory at Scripps Clinic from 2015 to 2022. The study was approved by Scripps Health's Institutional Review Board of the Office for the Protection of Research Subjects as a minimal risk study. Participants were asked to refrain from consuming caffeine and alcohol and from smoking cigarettes for 8 hours prior to testing. Exclusion criteria included (1) pacemaker; (2) the use of vasodilators or vasoconstrictors that affect autonomic function, and (3) the VM with “flat-top” responses, where BP changes during phase II failed to fall below baseline. All participants performed a standardized testing

protocol of the Autonomic Reflex Screen in a temperature-controlled room (21–23° C) (Low et al., 2008; Novak, 2019).

The present study is reporting the results of brachial arterial BP, HR, respiration rate, and the beat-to-beat BP and HR responses to the Valsalva maneuver (VM). The HRV Acquire (WR Medical Electronics, Maplewood, MN) was used to record the electrocardiogram (ECG) while the BMEYE Nexfin device (Amsterdam, The Netherlands) and the CNAP Monitor 500 (CNSystems, Graz, Austria) were used to measure beat-to-beat BP. ECG and beat-to-beat BP were sampled at 200 Hz and analyzed using WR TestWorks software (WR Medical Electronics, Maplewood, MN). Brachial arterial SBP and DBP were obtained with Welch Allyn Connex 6400 Signs Monitor (Welch Allyn, Skaneateles Falls, NY).

Valsalva maneuver (VM)

To perform the VM, participants were instructed to maintain an expiratory pressure at 30–40 mmHg for 15 s via a tube with an air leak to ensure an open glottis (Low & Sletten, 2008). Evaluation of the VM maneuver and determination of adrenergic baroreflex sensitivity (BRS_a) and vagal baroreflex sensitivity (BRS_v) required analysis of reproducible changes in the maneuver. The VM (Fig. 1A) consists of four phases initiated by phase I, where there are increases in intrathoracic and intra-abdominal pressure that produces mechanical compression of the aorta. During early phase II (phase II_E), the reduced venous return and stroke volume leads to a fall in cardiac output despite the tachycardia caused by cardiovagal withdrawal. The mechanism responsible for late phase II (phase II_L) is an increase in total peripheral resistance due to an increase in plasma epinephrine and efferent sympathetic discharges to muscle. After completion of the maneuver, phase III is produced by several factors including a sudden fall in intrathoracic pressure. While venous return and cardiac output have returned to normal, arteriolar bed remains vasoconstricted producing phase IV, which is an overshoot of BP above baseline values (Low and Sletten, 2008). The BP recovery time (PRT) was defined as the interval (in sec) between the lowest SBP of phase III and its return to baseline following the VM (Schrezenmaier et al., 2007).

The adrenergic baroreflex response (BRS_a) was defined as the SBP decrement during the VM (BP fall in phase II_E plus three-fourths of the amplitude of phase III) divided by the BP recovery time (Schrezenmaier et al., 2007). The vagal baroreflex response (BRS_v) was expressed as the regression slope of HR over SBP during phase II_E of the VM (Huang et al., 2007). Baseline supine HR, SBP, DBP and peak SBP changes for phase II_E, phase II_L, and phase IV were determined, as previously described (Huang et al., 2007; Schrezenmaier et al., 2007). The BRS_a , BRS_v and all phases of the VM were determined as the average of two successful maneuvers.

Head-up Tilt (HUT)

Participants were in resting supine position for at least 30 minutes and 5 min recordings were obtained during supine position and HUT. Time- [RMSSD (the square root of the mean squared successive

differences between interbeat interval (IBIs) (in ms); SDNN (standard deviation of the normal-to-normal interbeat interval], and frequency-domain measures of HRV [absolute LF-HRV power (0.04–0.15 Hz) and absolute high-frequency (HF-HRV) power (0.15–0.40 Hz)] were estimated while in supine position and during HUT using the Kubios HRV 2.1 software (Biosignal Analysis and Medical Imaging Group, Department of Applied Physics, University of Eastern Finland, Kuopio, Finland) as previously described (Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology, 1996). The unit for the frequency-domain measures is ms^2 . The effects of orthostatic challenge on SBP, DBP and HR (ΔSBP , ΔDBP and ΔHR) were defined as the difference between the average values during HUT from the average values in supine position. sOH was defined as a sustained reduction in SBP of at least 20 mmHg within 3 minutes of standing or HUT testing (Freeman et al., 2018). The presence of diastolic OH (a sustained reduction in DBP of at least 10 mmHg within 3 minutes of HUT) was documented but was not part of the analysis. In participants with supine systolic hypertension (SH) (defined as $\text{SBP} \geq 140$ mmHg), a decrease in SBP of at least 30 mmHg was the criterion for sOH (Freeman et al., 2018). Participants included in this study were grouped into four groups according to the SBP in supine position and in response to HUT (No SH/No sOH ($n = 109$); SH/No sOH ($n = 86$); No SH/sOH ($n = 33$); and SH/sOH ($n = 45$)). Procedures were performed between 7:30 AM and 4:00 PM.

Statistical analyses

Statistical analyses were performed by using Jamovi (version 2.6.44) (The jamovi project, 2025; Retrieved from <https://www.jamovi.org>). The Kolmogorov-Smirnov test was used to test normality and the Levene's test was used to test homogeneity of variance. Categorical variables were presented as number (%) and continuous variables as means $\pm$ standard error of the mean (SEM). One-way analysis of variance (ANOVA) was used to determine group differences in variables with normal distribution, whereas the Kruskal-Wallis test for variables that were not normally distributed. When appropriate, post hoc analysis utilized the Tukey's HSD test when the ANOVA was used or the Dwass-Steel-Critchlow-Fligner (DSCF) pairwise comparisons when the Kruskal-Wallis test was used. Chi-square test of independence was used to determine group differences in gender, Ethnicity, Race, and the time of the test (Morning: 7:30 AM to 11:30 AM; Afternoon: Noon to 4:00 PM). Nonparametric Spearman's rho correlations were used to determine the strength of the association between SDNN and LF-HRV with baroreflex indices (BRS_a and BRS_v) and hemodynamic responses to the VM. Statistical significance was set at probability level of $p < 0.05$ for all tests.

Results

Demographics

The present study included a total of 273 participants (144 women, 53%) with a mean (SEM) age of 74.9 (0.4) and BMI of 25.9 (0.3). Participants in the sample were more likely to be White (85%) and Not Hispanic/Latino Spanish (94%). Statistical analyses showed that Age, BMI and the distribution of Gender,

Ethnicity, Race and Time of the Test (AM vs. PM) were not different among groups. Detailed comparisons are provided in Table 1.

Table 1
Demographic and descriptive characteristics

Variable	No SH/No sOH (n = 109)	SH/No sOH (n = 86)	No SH/sOH (n = 33)	SH/sOH (n = 45)
Age (years) ^b	73.5 (0.5)	75.8 (0.7)	74.5 (1.1)	76.6 (1.0)
BMI ^b	26.3 (0.5)	25.3 (0.5)	25.1 (0.8)	26.4 (0.9)
Gender				
F	64 (58.7%)	49 (57.0%)	14 (42.4%)	17 (37.8%)
M	45 (41.3%)	37 (43.0%)	19 (57.6%)	28 (62.2%)
Ethnicity				
Hispanic/Latino/Spanish	6 (5.5%)	1 (1.2%)	2 (6.1%)	3 (6.7%)
Not Hispanic/Latino/Spanish	102 (93.6%)	83 (96.4%)	29 (87.9%)	40 (88.9%)
Unknown	1 (0.9%)	1 (1.2%)	1 (3.0%)	1 (2.2%)
Declines to Answer	0 (0.0%)	1 (1.2%)	1 (3.0%)	1 (2.2%)
Race				
White	93 (85.3%)	76 (88.4%)	28 (84.8%)	37 (82.2%)
Black or African American	3 (2.8%)	1 (1.2%)	0 (0.0%)	0 (0.0%)
Asian	6 (5.5%)	5 (5.8%)	1 (3.0%)	2 (4.4%)
Other	4 (3.7%)	1 (1.2%)	1 (3.0%)	3 (6.7%)
Unknown	3 (2.8%)	3 (3.5%)	3 (9.1%)	3 (6.7%)
Time of Test				
AM	46 (42.2%)	31 (36.0%)	13 (39.4%)	18 (40.0%)
PM	63 (57.8%)	55 (64.0%)	20 (60.6%)	27 (60.0%)
Groups were compared using one-way ANOVA ^a or the Kruskal-Wallis ^b test for continuous variables and Pearson Chi-Square for dichotomous variables. Post hoc analyses utilized the Tukey's HSD test or Dwass-Steel-Critchlow-Fligner pairwise comparisons ($p < 0.05$). BMI body mass index. Values are mean (SEM).				

BP and Cardiovascular Autonomic Measures in Supine Position

Supine SBP and DBP were significantly higher in the SH/sOH and SH/No sOH groups than in the No SH/No sOH and No SH/sOH groups. Supine HR was not significantly different among the groups. Detailed comparisons are provided in Table 2. Time- and frequency-domain measures of HRV (SDNN, RMSSD, LF-HRV and HF-HRV) and respiration rates (breaths/min) in supine position were not significantly different among groups (Table 3).

Table 2
BP and HR responses during HUT

Variable	No SH/No sOH (n = 109)	SH/No sOH (n = 86)	No SH/sOH (n = 33)	SH/sOH (n = 45)
Supine SBP (mmHg) ^b	123 (0.9)	160 (1.8) ¹	121 (2) ²	165 (2.8) ^{1,3}
Supine DBP (mmHg) ^b	74 (0.6)	80 (0.9) ¹	73 (1.1) ²	80 (1.5) ^{1,3}
Supine HR (beats/min) ^a	64.6 (1)	65.6 (1.2)	68.5 (2.2)	62.2 (1.4)
ΔSBP (mmHg) ^b	-1.8 (1.3)	-10.0 (1.3) ¹	-29.6 (1.5) ^{1,2}	-47.2 (2.2) ^{1,2,3}
ΔDBP (mmHg) ^a	1.6 (0.7)	2.6 (0.8)	-13.2 (1.2) ^{1,2}	-9.6 (1.5) ^{1,2}
ΔHR (beats/min) ^b	10.4 (0.8)	8.1 (0.6)	12.2 (1.8)	8.6 (1.2)
Groups were compared using one-way ANOVA ^a or the Kruskal-Wallis test ^b for continuous variables. Post hoc analyses utilized the Tukey's HSD test or Dwass-Steel-Critchlow-Fligner pairwise comparisons (p < 0.05). Values are mean (SEM)				
SH Supine Systolic Hypertension; sOH Systolic Orthostatic Hypotension; SBP Systolic Blood Pressure; DBP Diastolic Blood Pressure; HR Heart Rate.				
¹ Significantly different from No SH/No sOH				
² Significantly different from SH/No sOH				
³ Significantly different from No SH/sOH				

Table 3
Cardiovascular autonomic measures and HR responses to HUT

Variable	No SH/No sOH (n = 97)	SH/No sOH (n = 72)	No SH/sOH (n = 24)	SH/sOH (n = 38)
Supine SDNN (ms) ^b	21.8 (1.4)	21 (1.5)	17.4 (2)	17.0 (1.6)
Supine RMSSD (ms) ^b	20.7 (1.6)	19.7 (1.7)	18.0 (2.6)	16.2 (1.4)
Supine LF-HRV (ms ²) ^b	318.1 (39.2)	344.2 (84.5)	184.5 (39.6)	221.8 (65.5)
Supine HF-HRV (ms ²) ^b	184.8 (32.3)	157.4 (35.8)	128.5 (42.9)	92.9 (16)
Supine Respiration (bpm) ^a	14.2 (0.4)	15.1 (0.5)	13.2 (0.9)	14.4 (0.6)
HUT SDNN (ms) ^b	17.2 (1.0)	16.0 (1.0)	10.7 (1.2)^{1,2}	12.4 (0.9)¹
HUT RMSSD (ms) ^b	14.7 (1.1)	14.3 (0.9)	9.8 (1.0)^{1,2}	12.3 (0.9)
HUT LF-HRV (ms ²) ^b	208.8 (38.3)	193.1 (40.7)	82.3 (22.6)^{1,2}	83.9 (17.7)^{1,2}
HUT HF-HRV (ms ²) ^b	92.4 (26.4)	69.9 (11.4)	30.4 (10.2)^{1,2}	46.3 (8.5)
HUT Respiration (bpm) ^a	16.5 (0.4)	17.3 (0.5)	14.9 (1.1)	16.9 (0.6)
Groups were compared using one-way ANOVA ^a or the Kruskal-Wallis test ^b for continuous variables. Post hoc analyses utilized the Tukey's HSD test or Dwass-Steel-Critchlow-Fligner pairwise comparisons ($p < 0.05$). Values are mean (SEM).				
<i>SDNN</i> Standard deviation of the normal-to-normal interval; <i>HF-HRV</i> absolute power of the high-frequency band, 0.15–0.4 Hz; <i>HUT</i> head-up tilt; <i>LF-HRV</i> Absolute power of the low-frequency band, 0.04–0.15 Hz; <i>RMSSD</i> root mean square of successive differences between normal-to-normal heartbeats.				
¹ Significantly different from No SH/No sOH				
² Significantly different from SH/No sOH				
³ Significantly different from No SH/sOH				

BP and Cardiovascular Autonomic Measures in Response to HUT and the VM

Statistical analyses demonstrated that groups with sOH (No SH/sOH and SH/sOH groups) showed larger Δ SBP and Δ DBP than groups with no sOH (No SH/No sOH and SH/No sOH groups). The SH/No sOH group also showed a larger Δ SBP than the No SH/No sOH group, whereas the SH/sOH group

showed a larger Δ SBP than the No SH/sOH group. Changes in HR (Δ HR) were not significantly different among groups. Detailed comparisons are provided in Table 2.

Analyses of time- and frequency-domain measures of HRV during HUT showed significantly lower SDNN, RMSSD, and HF-HRV in the No SH/sOH group than in the No SH/No sOH and SH/No sOH groups. The SH/sOH group also had lower SDNN than the No SH/No sOH group. The SH/sOH and No SH/sOH groups showed lower LF-HRV than the No SH/No sOH and SH/No sOH groups. Respiration rates (breaths/min) during HUT were not significantly different between groups. Detailed comparisons are provided in Table 3.

Analyses of the beat-to-beat BP response to the VM showed significant differences in Phase II_E, Phase II_L, PRT, and Phase IV among groups. Post hoc analyses demonstrated that participants in both groups with SH (SH/sOH and SH/No sOH groups) showed significantly higher Phase II_E than the No SH/No sOH group. The SH/sOH group also showed significantly lower Phase II_L and Phase IV than the No SH/No sOH and SH/No sOH groups. Phase IV was lower in the No SH/OH group than in the No SH/No sOH group. The SH/OH group showed a longer BP recovery time (PRT) than the No SH/No sOH and SH/No sOH groups, whereas the No SH/sOH group showed longer PRT than the No SH/No sOH group. Detailed comparisons are provided in Table 4.

Table 4
Cardiovascular autonomic measures and HR responses to the VM

Variable	No SH/No sOH (n = 91)	SH/No sOH (n = 72)	No SH/sOH (n = 27)	SH/sOH (n = 38)
PHASE II _E (mmHg) ^b	31.8 (1.7)	45.0 (2.6)¹	34.5 (2.0)	44.4 (3.6)¹
PHASE II _L (mmHg) ^b	11.3 (1.0)	13.9 (1.7)	8.6 (1.9)	5.7 (1.6)^{1,2}
PRT (sec) ^b	5.9 (0.8)	10.0 (1.3)	14.6 (2.7)¹	15.3 (1.7)^{1,2}
PHASE IV (mmHg) ^b	15.0 (1.3)	10.8 (2.3)	3.6 (3.2)¹	-1.5 (2.9)^{1,2}
BRS _a (mmHg/s) ^b	18.9 (1.9)	19.6 (2.9)	10.1 (2.6)^{1,2}	11.2 (2.4)^{1,2}
BRS _v (ms/mmHg) ^b	3.5 (0.2)	2.4 (0.2)¹	2.3 (0.2)	2.6 (0.6)¹
Groups were compared using one-way ANOVA ^a or the Kruskal-Wallis test ^b for continuous variables. Post hoc analyses utilized the Tukey's HSD test or Dwass-Steel-Critchlow-Fligner pairwise comparisons (p < 0.05). Values are mean (SEM)				
<i>BRS_a</i> Adrenergic baroreflex sensitivity, <i>BRS_v</i> Vagal baroreflex sensitivity, <i>Phase II_E</i> early phase II, <i>Phase II_L</i> late phase II, <i>PRT</i> blood pressure recovery time.				
¹ Significantly different from No SH/No sOH				
² Significantly different from SH/No sOH				
³ Significantly different from No SH/sOH				

Statistical analyses also showed significant differences in BRS_a and BRS_v among groups. Post hoc analyses showed that BRS_a was lower in the No SH/sOH and SH/sOH groups than in the No SH/No sOH and SH/No sOH groups. BRS_v was lower in the SH/No sOH and SH/sOH groups than in the No SH/No sOH group. Detailed comparisons are provided in Table 4.

Correlations between SDNN-HRV and hemodynamic responses to VM and the adrenal and vagal baroreflex during HUT

SDNN demonstrated a significant correlation with PRT, Phase IV and BRS_a in the No SH/sOH and SH/sOH groups. SDNN significantly correlated with Phase II_L in SH/sOH group and with BRS_v in all groups. Detailed comparisons are provided in Table 5. SDNN showed a positive correlation with RMSSD, HF-HRV and LF-HRV in all groups (see Supplementary Table S1).

Table 5
Correlation analyses of SDNN and LF-HRV during HUT with hemodynamic responses to VM and the adrenal and vagal baroreflex

Variable	No SH/No sOH (n = 87)	SH/No sOH (n = 61)	No SH/sOH (n = 21)	SH/sOH (n = 32)
SDNN				
Phase II _E (mmHg)	0.058	-0.142	-0.266	-0.219
Phase II _L (mmHg)	0.080	-0.162	0.383	0.389¹
PRT (sec)	-0.091	0.227	-0.671²	--0.518²
Phase IV (mmHg)	0.100	-0.233	0.531¹	0.619³
BRS _a	0.145	-0.239	0.642²	0.382¹
BRS _v	0.469³	0.486³	0.692²	0.392¹
LF-HRV				
Phase II _E (mmHg)	0.077	-0.044	-0.207	-0.127
Phase II _L (mmHg)	0.154	-0.048	0.256	0.486²
PRT (sec)	-0.200	0.044	-0.685³	--0.646³
Phase IV (mmHg)	0.171	-0.048	0.547¹	0.694³
BRS _a	0.236¹	-0.017	0.662²	0.568³
BRS _v	0.441³	0.486³	0.676²	0.516²
<i>BRS_a</i> Adrenergic baroreflex sensitivity; <i>BRS_v</i> Vagal baroreflex sensitivity; <i>LF-HRV</i> Absolute power of the low-frequency band, 0.04–0.15 Hz; <i>SDNN</i> Standard deviation of the normal-to-normal interval. <i>Phase II_E</i> early phase II, <i>Phase II_L</i> late phase II, <i>PRT</i> blood pressure recovery time. Correlations were determined using Spearman rank correlation. ¹ p < 0.05; ² p < 0.01; ³ p < 0.001.				

Correlations between LF-HRV and hemodynamic responses to VM and the adrenal and vagal baroreflex during HUT

LF-HRV significantly correlated with PRT, Phase IV and BRS_a in the No SH/sOH and SH/sOH groups. LF-HRV also showed a significant correlation with BRS_a in the No SH/No sOH group. LF-HRV demonstrated a significant correlation with Phase II_L in the SH/sOH group and with BRS_v in all groups. Detailed comparisons are provided in Table 5. LF-HRV showed a positive correlation with SDNN, RMSSD, and HF-HRV in all groups (see Supplementary Table S1).

Discussion

Pharmacological interventions implemented to treat OH aim at reducing symptoms with minimal side effects, not to restore normal baroreflex and BP (Freeman et al., 2018; Wieling et al., 2022). While nonpharmacological treatments have been shown to improve the quality of life of OH patients, most are limited to reducing or preventing OH symptoms (e.g., patient education/lifestyle changes, bolus water drinking, compression stockings, abdominal compression, physical counter-maneuvers, etc.) and do not restore normal baroreflex (Freeman et al., 2018; Newton and Frith, 2018; Ricci et al., 2015; Wieling et al., 2022). There is evidence to suggest that exercise training can slow the age-related decline in cardiovagal BRS (Monahan et al., 2000). Exercise interventions improve HRV and cardiovascular health factors in the elderly (Grassler et al., 2021). Findings in an experimental model showed that 6 weeks of daily exercise training increased the HF-HRV and decreased the occurrence of ventricular fibrillation during myocardial ischemia (Hull et al., 1994). While these results support the effectiveness of exercise training increasing cardiovagal baroreflex function, poor tolerability and frail patients at high risk of falls and injury restricts its use (Dani et al., 2022; Frith et al., 2014; Robinson et al., 2018). As a result, the need for nonpharmacological interventions targeting baroreflex control for this at-risk population is considered a research priority (Dani et al., 2022).

HRVB is a nonpharmacological, non-invasive, and safe intervention that is well tolerated by elderly individuals and has been shown to increase both HRV amplitudes and baroreflex gain (Lehrer et al., 2003; Lehrer and Gevirtz, 2014). Lehrer et al. (2003) found that HRVB reinforced breathing at a “resonance frequency” produced marked increases in the vagal baroreflex after 10 sessions compared to a control group. Findings from Han and colleagues (Han et al., 2025) suggest that HRVB training as part of an integrated program (that also included education about OH, exercise/physical activity, telephone counseling and relaxation therapy) increased LF-HRV, improved OH symptoms and reduced orthostatic drops in SBP and DPB in patients with OH. While it is not clear how HRVB contributed to this multidisciplinary program, these promising findings encourage further investigating the effectiveness of HRVB on cardiovascular autonomic and baroreflex dysfunction in OH patients.

Our previous studies suggest that deficits in cardiovascular autonomic regulation associated with sOH were only demonstrated when the arterial baroreflex response is triggered during the VM and HUT (Criado and Kalafut, 2024). Orthostatic stress or when moving to the upright position results in a decrease in venous return to the heart and a transient decrease in BP (Freeman et al., 2018; Gibbons et al., 2017; Ricci et al., 2015). Arterial baroreceptors in the carotid sinuses and aortic arch detect this reduction in BP and triggers the arterial baroreflex response (Benarroch, 2008). The arterial baroreceptor reflex buffers acute fluctuations of arterial BP that occur during changes in posture, exercise, emotion, and other conditions (Benarroch, 2008). The present study evaluated hemodynamic fluctuations in VM that are modulated by vagal (phase II_E), α -adrenergic (phases II_E and II_L) and β -adrenergic mechanisms (phase IV) and allows determination of the vagal and adrenergic components of the baroreflex (Palamarchuk et al., 2016; Sandroni et al., 1991; Schrezenmaier et al., 2007). Our findings demonstrated that both groups with sOH (No SH/sOH and SH/sOH) showed significant increases in PRT and

reductions in the adrenergic baroreflex (BRS_a) and in Phase IV amplitude of the VM. Both groups with sOH also showed a significant reduction in SDNN, an estimate of the overall HRV (Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology, 1996), and in LF-HRV, an index of baroreflex function (Davies et al., 2002; Rahman et al., 2011), during HUT. These findings suggest that sOH is associated with a reduction in HRV metrics and the adrenergic baroreflex (BRS_a) when the arterial baroreflex response is triggered (HUT or VM), independent of SH.

This study also demonstrated that both groups with SH (SH/No sOH and SH/sOH groups) showed a significant increase in Phase II_E and a reduction in the vagal baroreflex (BRS_v). These findings suggest that SH is associated with a reduction in vagal and adrenergic mechanisms, independent of sOH. Our results also showed that while deficits in time- and frequency-domain measures of HRV in patients with sOH were not exacerbated by SH, deficits in Phase II_L were only observed in patients with sOH and concurrent SH. These findings suggest significant reduction in α -adrenergic control and evidence of adrenergic failure (Palamarchuk et al., 2016; Sandroni et al., 1991; Schrezenmaier et al., 2007). The present study also found a significant relationship between biomarkers known to be increased with HRVB (SDNN and LF-HRV) and baroreflex (adrenergic and vagal) and hemodynamic fluctuations in VM contributing to sOH and SH. Moreover, only patients with concurrent sOH and SH showed a significant relationship between SDNN and LF-HRV with Phase II_L. Finally, SDNN and LF-HRV showed strong correlations with RMSSD and HF-HRV during HUT. Overall, these findings provide evidence of the relationship between HRV metrics known to be improved by HRVB and hemodynamic and baroreflex impairments underlying sOH and SH.

A limitation in the study is that the sample may not be representative since only retrospective data from patients referred to the Autonomic Laboratory without age-matched control group were studied. Patients with sOH included those with and without neurogenic OH. Patients with neurogenic OH do not show the HR increase to compensate for the orthostatic reduction in BP (Freeman et al., 2018; Ricci et al., 2015). However, the present results showed no group differences in HR change in response to HUT. Although there is a view that all types of OH have a neurogenic component (Biaggioni 2023), future studies are needed to understand supine hypertension in OH patients with and without neurogenic OH. Evidence also suggests that the time of the day when a patient is tested may influence the magnitude of the orthostatic HR response (Sheldon et al., 2015), which could potentially alter orthostatic BP responses in patients with different severities of OH. However, the distribution of patients tested in the morning, and afternoon was similar between the groups tested. While sOH was defined as a sustained reduction in SBP within 3 min of HUT, the present study did not evaluate patients with delayed OH, which is a slow and gradual decrease in BP that occurs after 3 min of standing (Freeman et al., 2018; Ricci et al., 2015). Evidence suggests that patients with delayed OH may have less severe autonomic dysfunction but with a risk of progressing to early OH (Freeman et al., 2018; Ricci et al., 2015). Despite the limitations, the present study contributes to our understanding of neurobiological biomarkers for autonomic and baroreflex dysfunction in sOH patients with SH. These results support future research using HRVB as a

nonpharmacological intervention to improve HRV metrics and baroreflex function in sOH patients having difficulties incorporating nonpharmacological interventions to their standard of care.

Abbreviations

Abbreviations

Adrenergic baroreflex sensitivity	BRS _a
Analysis of variance	ANOVA
Baroreceptor sensitivity	BRS
Blood Pressure	BP
BP recovery time	PRT
Body mass index	BMI
Diastolic BP	DBP
Early phase II	Phase II _E
Electrocardiogram	ECG
End-tidal CO ₂	EtCO ₂
Head-up tilt	HUT
Heart Rate	HR
Heart Rate Variability	HRV
Heart Rate Variability Biofeedback	HRVB
High Frequency power of HRV	HF-HRV
HRV Biofeedback	HRVB
Head-up tilt	HUT
Interbeat interval	IBI
Late phase II	Phase II _L
Low Frequency	LF
Low Frequency power of HRV	LF-HRV
Millimeter of mercury	mmHg
Analysis of variance	ANOVA
Orthostatic hypotension	OH
Standard deviation of the normal-to-normal interbeat interval	SDNN
Standard error of the mean	SEM

Supine Hypertension	SH
Systolic BP	SBP
Systolic OH	sOH
The square root of the mean squared successive differences between interbeat interval	RMSSD
Vagal baroreflex sensitivity	BRS _v
Valsalva maneuver	VM

Declarations

Acknowledgements: The authors thank Anna Kim, RVT for expert technical assistance. This study is funded by Scripps Clinic Medical Group Research Fund and from the Hearst Endowment. The Scripps Clinic Medical Group Research Fund and the Hearst Endowment had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Author Contributions J.R.C. and M.A.K. conceived and designed research, interpreted results of the study; J.R.C. prepared figures, tables and drafted the manuscript. R.N.G. assisted in the interpretation of the results of the study and in the draft of the manuscript. M.A.K. approved the final version of the manuscript.

Data Availability No datasets were generated or analyzed during the current study

Conflict of interest The authors declare that they have no conflicts of interests.

Informed Consent All patients were over 18 years of age. The study was approved by the Scripps Health's Institutional Review Board of the Office for the Protection of Research Subjects as a minimal risk study and written consent was waived.

Competing Interests The authors declare no competing interests.

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Figures

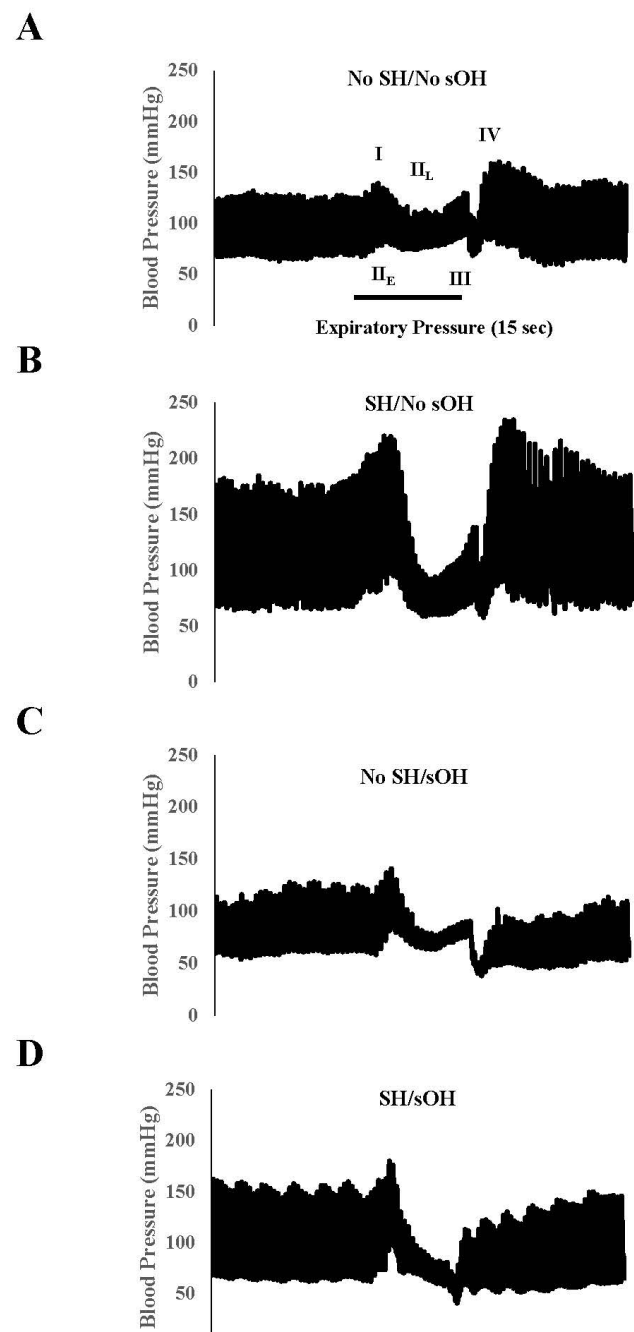


Figure 1

The VM consists of four main phases: phase I (I), phase II_E (II_E), phase II_L (II_L), phase III and phase IV. The first two phases of the VM are generated while the patient maintains an expiratory pressure between 30–40 mmHg for 15s. Phases III and IV are generated after completion of the maneuver. Representative BP response during the Valsalva maneuver in the four groups: A. No SH/No OH; B. SH/No OH; C. No SH/OH; and D. SH/OH.

Supplementary Files

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