The utility of Valsalva maneuver in the diagnoses of orthostatic disorders.

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ABSTRACT

Objective: 1) To assess hemodynamic responses and baroreflex sensitivity (BRS) indices during Valsalva maneuver (VM) and head-up tilt (HUT) testing in orthostatic intolerance (OI). Methods: Patients with neurogenic orthostatic hypotension (NOH, n=26), postural tachycardia syndrome (POTS, n=26) and symptomatic orthostatic intolerance (SOI, n=14) were compared to healthy population (Control, n=107) and inappropriate sinus tachycardia (IST, n=7). Hemodynamic assessment included patterning and quantification with vagal and adrenergic BRS (BRSv and BRSa/BRSa1). Results: In NOH, cardiovagal SBP decrements in VM and HUT were correlated (r=0.660, p<0.001); a “V” pattern of VM indicated alpha BRSa failure. Yet, BRSa1 did not reveal changes vs. Control (p>0.05) or was not applicable in 60% of NOH. In SOI, compared to Control cardiovagal SBP decrements were larger (p<0.05); higher BRSa1 contradicted higher adrenergic index (CASS). Overshoot in phase IV dipped below baseline or dropped ≥ 10 mmHg over 8 s in POTS (“N” pattern), but by 3 s in IST (“M” pattern”). Conclusions: Visualization of distinct VM patterns allows primary evaluation of autonomic dysfunction and differentiation of the various forms of OI. BRSa1 evaluation is compromised by pathological SBP patterns. Significance: VM patterning is a valuable non-postural supplement to HUT capable of detecting and differentiating OI.

Key words: Valsalva maneuver; hemodynamic patterns; adrenergic indices; orthostatic intolerance.
ABBREVIATED LIST

α-BRSA - experimental calculation of alpha-adrenergic BRS;
AAR - augmented autonomic response;
BAR - balanced autonomic response;
BRS - baroreflex sensitivity;
BRSA - adrenergic BRS;
BRSa1 - alternative calculation of adrenergic BRS;
BRSv - vagal BRS;
β-BRSA - experimental calculation of beta-adrenergic BRS;
BP - blood pressure;
bpm - beats per minute;
CASS - composite autonomic severity score;
Control - healthy population;
ΔHR - change in heart rate;
ΔSBP - change in systolic blood pressure;
HR - heart rate;
HUT - head-up tilt;
IST - inappropriate sinus tachycardia;
NOH - neurogenic orthostatic hypotension;
OH - orthostatic hypotension;
OI - orthostatic intolerance;
Phase IIe - early phase II;
Phase IIl - late phase II;
POTS - postural tachycardia syndrome;
PRT - pressure recovery time;
SAR - suppressed autonomic response;
SBP - systolic blood pressure;
SOI - symptomatic orthostatic intolerance;
VM - Valsalva maneuver;
VR - Valsalva ratio.
1. INTRODUCTION

Valsalva maneuver (VM) provides autonomic analyses of non-postural arterial blood pressure (BP) changes during breathing activity. Normally, hemodynamic fluctuation in VM is a quadriphasic process modulated through vagal (early phase II or phase II\textsubscript{c}), alpha-adrenergic (mainly in late phase II or phase II\textsubscript{l}) and beta-adrenergic (mainly in phase IV) activation, while phases I and III represent intrathoracic pressure deviations related to deep inhale and exhale, respectively (Figure 1). VM mutually offers qualitative and quantitative analyses of hemodynamic responses. Visual analysis is valuable as it allows instant screening of potential sympathetic or parasympathetic failure in autonomic dysfunction. Quantitative evaluation indirectly measures both vagal and adrenergic components of an important cardiovascular marker - arterial baroreflex sensitivity (BRS)(10, 16, 19, 20, 22, 26, 30). Estimated in VM, BRS is a validated marker, though vagal BRS (BRS\textsubscript{v}) appears to be a more reliable than adrenergic BRS (BRS\textsubscript{a})(17, 18, 25).

Hemodynamic responses in VM may demonstrate reproducible patterns. In young healthy populations VM patterns appear to be associated with BRS\textsubscript{a} value and, potentially, vasomotor tone(24). In autonomic dysfunction, VM responses are altered and capable of reflecting orthostatic intolerance (OI). For example, there is progressive BP decline in phase II\textsubscript{c} and slow recovery in phase IV in neurogenic orthostatic hypotension (NOH), and a notable BP overshoot in phase IV in postural tachycardia syndrome (POTS)(9, 29). Yet, definite hemodynamic patterns and associated BRS in OI have not been well elucidated. Specifically, it would be reasonable to explore postural and non-postural links of hemodynamic responses in OI. Patterning of linked to OI hemodynamic responses may enhance qualitative VM evaluation and, thus, improve the diagnosis of various autonomic disorders characterized by orthostasis. Improved VM assessment would be clinically beneficial as OI can be a
substantial cause of morbidity (2, 11, 21, 23, 27). Therefore, the present study’s aim was to clarify the contribution of the VM to the diagnosis of OI. Furthermore, we sought to identify potential non-postural markers of OI; the study specific objective was to analyze hemodynamic responses and associated BRS parameters during VM and HUT testing in pure symptomatic OI (SOI), NOH, POTS, IST, and a healthy population.

2. METHODS

2.1. Study design

Observational analytic study was designed in attempt to assess the association between SBP responses to VM and HUT in OI patients compared to the healthy group of population (Control). It was a prospective cohort study in regards of OI, though used as a cross-sectional study of interventions techniques (VM and HUT). The PICO model was: OI patients (Population), VM and HUT (Intervention), Control and IST patients (Comparison) and hemodynamic responses (Outcome).

2.2. Studied Population

The study included sixty-six patients (44 females) with OI: SOI, NOH and POTS (Table 1). NOH was defined as a reduction of systolic BP (SBP) $\geq 30$ mmHg without a compensatory postural tachycardia within 3 minutes of HUT (8). Clinical confirmation of NOH included: 1) persistent/consistent symptoms; and 2) unidentified non-neurogenic etiology (hypovolemia, medications, heart failure, excessive vasodilation, endocrinopathy, etc.) (8, 9). POTS was defined as a heart rate (HR) increment $\geq 30$ bpm within 5 minutes of HUT, without OH but with accompanying OI symptoms (14, 31). SOI was defined upon exclusion of HR and BP criteria for POTS and NOH, but manifested non-neuropathic OI symptoms (e.g., lightheadedness, vertigo, palpitations, dyspnea and near syncope). Additionally, IST patients (n=7; 6 females) were studied to compare POTS with non-postural tachycardia. IST was defined as resting sinus tachycardia $> 100$ bpm (23). All patients were compared to a Control group of 107 healthy
participants (67 females). Exclusion criteria for the Control group included any one of the following: i) exceeded 1 point each Composite Autonomic Severity Score (CASS) index (sudomotor, cardiovagal or adrenergic) complied from the Autonomic Reflex Screen; ii) pregnancy or lactation, iii) clinical autonomic dysfunction, iv) clinically significant coronary artery disease, v) usage of medications which could interfere with testing of autonomic function, and vi) failure of other organ systems or systemic illness that could affect autonomic function or the participant’s ability to cooperate. A neurologist performed all the clinical evaluations and diagnoses. This study was approved by the Health Science Research Board at the University of Western Ontario.

2.3. Autonomic Tests

In one visit all participants performed standardized tests of the Autonomic Reflex Screen with the next sequence: 1) quantitative sudomotor axon reflex; 2) deep breathing testing; 3) VM; and 4) HUT. Autonomic study was started with an instruction to be relaxed and silent as long as possible during 20-min rest at the supine position. The results of Autonomic Reflex Screen were converted to the CASS to detect and quantify possible dysautonomia (19, 20, 22). Throughout all tests, beat-to-beat BP and HR were continuously measured using a BYEME Nexfin device (Amsterdam, The Netherlands) and an electrocardiography (ECG) device (Model 3000 Cardiac Trigger Monitor, IVY Biomedical Systems, Inc., Branford, CT) with ECG electrodes (Ambu® Blue Sensor SP, Glen Burnie, MD), respectively. All recordings were made using WR TestWorks™ software (WR Medical Electronics Co., Stillwater, MN). Waveforms of the hemodynamic responses to VM were analyzed with Spike 2 Version 7 software (Cambridge Electronic Design Ltd).

VM: Following supine rest after deep breathing testing (5-min at minimum but till the circulatory stability), participants rested quietly in the supine position for an additional one minute while “VM
baseline” recordings were acquired for further measuring as averaged BP and HR. Following VM baseline, patients were instructed to inhale deeply and subsequently exhale through a bulge with an air leak (to ensure an open glottis) and to maintain an expiratory pressure of 40 mmHg for 15 s as a standard to yield the most reproducible results(3, 22). Participants practiced series of VM to perform breathing at required level. As a standard, our VM analysis required 2 successful VM trails separated by a 2-min rest. VM trails were considered successful if the instructions were followed. A Valsalva ratio (VR) was calculated to provide information pertaining to cardiovagal function. The VR was calculated by obtaining the maximum HR (HR\text{max}) generated during the maneuver divided by the minimum HR (HR\text{min}) attained within 30 s of the peak HR [VR = \frac{HR\text{max}}{HR\text{min}}].

HUT: Patient rested quietly in the supine position for a minimum of 15 min prior to tilt. Following a one-minute “HUT baseline” recording, patients were tilted upward from the horizontal to an angle of 70 degrees. Patients remained upright for a maximum of 5 min. A physician was present during all HUT tests to monitor HR and BP changes and to determine whether tilt needed to end prior to the 5th min. Following tilt, patients were returned to the supine position where they remained for an additional 5 min while HR and BP were measured. A change in HR (ΔHR) was calculated by obtaining the average HR prior to tilt (HR\text{b}) and subtracting it from the maximal HR (HR\text{max}) achieved between the 2nd and 5th min of tilt [ΔHR = HR\text{max} - HR\text{b}]. Though OH can be identified in 50% to 100% of patients with autonomic dysfunction within 3 min of HUT, the extended analysis window to a 5th min was preferred to account for delayed OH, POTS and a predisposition to vasovagal syncope as well (34). A change in SBP (ΔSBP) was calculated by subtracting the minimal SBP (SBP\text{min}) obtained within 5 min in the upright posture from average baseline SBP (SBP\text{b}) [ΔSBP = SBP\text{b} - SBP\text{min}].

2.4. Evaluation of the hemodynamic response to Valsalva maneuver

2.4.1. Qualitative analysis
Qualitative VM analysis results were based on common features/shapes of two successful VM trails to conclude the potential pattern based on the reproducibility of a SBP curve alignment over the baseline and VM phase alteration (using the Spike program option to manually chose and frame the SBP curve fragment with further instant automatic calculation of SBP and time intervals deviations). Exclusions were for 6 VM records (2 IST, 3 POTS and one NOH), which did not obtain a second VM trail. Visual parameters of VM were comprised of three hemodynamic hallmarks following baseline: 1) “Valley”, where SBP decline arrests in phase IIe; 2) “Rise”, where SBP incline ceases in phase IIi; and 3) “Recovery”, where SBP returns to baseline in phase IV (Figure 1). These hallmarks were used to distinguish potential VM patterns: 1) Balanced Autonomic Response (BAR) with SBP dipping in phase IIe (“Valley” below baseline) followed by gradual recovery in phase IV; 2) Suppressed Autonomic Response (SAR) with non-dipping SBP in phase IIi (“Valley” over baseline); and 3) Augmented Autonomic Response (AAR) with prompt SBP overshoot above baseline in phase IIi (24).

2.4.2. Quantitative analysis

Quantitative analysis of VM included five main SBP changes (ΔSBP): 1) decrement in phase IIe from baseline to the “Valley” [“A”]; 3) increment in phase IIi from “Valley” to “Rise” [“C”]; 2) decrement in phase III from “Rise” to where SBP ceases to drop (start of phase IV) [“B”]; 4) increment in phase IV during pressure recovery time, PRT [“D”]; 5) baseline overshoot in phase IV [“E”]. The main time parameters were: \( t_1 \) - duration of phase IIe from peak of elevated SBP to the “Valley”; \( t_2 \) - duration of phase IIi; \( t_3 \) - duration of phase III, and PRT - duration of phase IV from the arrest of the SBP fall in phase III to the point SBP has reached baseline (Figure 1). Quantitative descriptive analysis was based on one of two successful VM trails, which usually was the first trail. Repeated calculations were applied to confirm SBP patterns in POTS and IST groups given the presence of some qualitative similarities. If the SBP response did not recover over 30 sec during phase IV, PRT was not calculated and VM response was
considered as “unrecovered”. Majority of the patients reached circulatory stability by 2nd min during rest period, if not – it was prolonged up to 3 min, which provided a sufficient time in all instances. BRSv was determined as a regression slope of the R-R interval (x, ms) over SBP (y, mmHg) during phase IIe \[ \sum (x - \bar{x}) \times (y - \bar{y}) / \sum (x - \bar{x})^2 \] (10, 22). BRSa was evaluated with alternative BRSa (BRSa1), which relates SBP decrements “A” (mmHg) and “B” (mmHg) to PRT (s) \[ \text{BRSa}_1 = (A + 0.75 \times B) / \text{PRT} \] (10, 22).

2.4.3. Experimental calculations

Additionally, we proposed evaluating α- and β-adrenergic components of BRSa discretely as α-BRSa and β-BRSa. The primary purpose in analyzing α and β components separately was that adrenergic insufficiency of one component (e.g., alpha) may be concealed in total BRSa (e.g., BRSa1) by a relative hyper-response of complementary adrenergic limb (e.g., beta). Discrete BRSa evaluation was based on evidences of a mainly α-adrenergic response in phase IIe and a mainly β-adrenergic response in phase IV (22, 28). Therefore, parameters of α-BRSa were represented by phase IIe (C and \( t_2 \)), parameters of β-BRSa - by phase IV (D and PRT). Calculations of α- and β- BRSa were based on trigonometric function “cosine” to reflect SBP “rise over horizontal run” equivalently to the “slope” calculations for BRSv. In this manner, α-adrenergic SBP “rise C” over “run \( t_2 \)” was principally reflected by adjusted hypotenuse \( k_\alpha \), and β-adrenergic SBP “rise D” over “run PRT” by adjusted hypotenuse \( k_\beta \) (Figure 1). Therefore, α-BRSa was estimated as a cosine of angle between hypotenuse \( k_\alpha \) and \( t_2 \) [α-BRSa = \( (t_2 \times C) / k_\alpha \), where \( k_\alpha = \sqrt{t_2^2 + C^2} \)]. Similarly, β-BRSa was measured as a cosine of angle between hypotenuse \( k_\beta \) and PRT [β-BRSa = \( (D \times \text{PRT}) / k_\beta \), where \( k_\beta = \sqrt{D^2 + \text{PRT}^2} \)].

2.4.4. Statistical Analysis

Hemodynamic, BRS, and patient characteristic data were compared between groups using the one-way ANOVA model with a Bonferroni Post-Hoc analysis to reveal significant differences between groups.
Repeated measures ANOVA were applied to estimate significance of certain factors (within and between the subjects) associated with the SBP patterns observed in both VM trails. Correlation analysis with a Pearson’s test was used to determine significant relationships between VM and HUT hemodynamic reductions. All tests were two-tailed and a p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS statistical software, version 21 for Windows (SPSS Inc, Chicago, IL).

3. RESULTS

3.1. Neurogenic orthostatic hypotension

Main characteristics of population and autonomic findings. NOH patients were significantly older than individuals of all other groups (p<0.001; Table 1). Half of our NOH population manifested chronic autonomic failure due to Parkinson’s disease (n = 2), multiple system atrophy (n = 10) and pure autonomic failure (n = 6). One NOH patient with multiple system atrophy and two with pure autonomic failure could not complete the second VM trail. The CASS in NOH patients differed from all groups due to higher cardiovagal and adrenergic indices (p<0.01). Compared to Control and POTS, NOH had also higher sudomotor index (Table 1).

Quantitative HUT and VM analyses. Cardiovagal alterations in HUT (ΔHR) and VM (VR) were significantly lower in NOH compared to the others groups (Table 2). There were no significant differences in BRSv (VM) between any of the groups (Table 2). As we did expect BRSv in NOH to be significantly different from Control given the differences in the VR and Δ HR, we analyzed potential impact of dysautonomia type, such as pre- and postganglionic impairment in multiple system atrophy and pure autonomic failure respectfully(13). The results of these NOH subgroups revealed that BRSv values among the groups were still insignificant (p>0.05). In NOH, ΔHR correlated to BRSv. Only within NOH and Control groups did the
postural and non-postural cardiogal alterations (ΔHR and VR) correlated. Both low VR and ΔHR demonstrated links between α-BRSa but not between β-BRSa (Table 5; Figure 2).

Not only did a lack of phase II indicate BRSa failure, but it also equally complicated BRSa1 and α-BRSa evaluations, making these calculations impossible in 40% of NOH patients. Additionally, BRSa1 was compromised when “PRT” was absent (impossible in 20% of NOH). In NOH, both BRSa1 and α-BRSa were lower compared to the other patient populations (p<0.01), yet only α-BRSa was significantly lower compared to the Control group (p<0.05). Moreover, value of experimental β-BRSa was much larger in NOH compared to all other groups (p<0.01; Table 2). Only in Control group BRSa1 correlated to VR (Table 5).

Baseline beat-to-beat BP recordings revealed 60% of the NOH population had supine hypertension (>140 mmHg), which corresponded to a significantly higher mean SBP compared to all other groups (p<0.05). In response to VM, NOH patients had the largest drop in SBP during phase IIe [“A”], which translated into a significantly longer arrest time [“t1”] compared to the other groups (p<0.001, Tables 3 and 4). Only within NOH and Control groups did this drop in SBP significantly correlate with the SBP fall in HUT (Table 5). In Control group “A” also correlated to VR (Table 5). The SBP overshoot [“E”] seen in phase IV, was significantly lower in NOH compared to the other patient populations but not compared to Controls. Additionally, “A” and “E” were significantly correlated inversely within NOH and unilaterally within Control group (Table 5, Figure 2).

**VM patterning.** Compared to all groups, NOH patients demonstrated either an absent (40%) or reduced phase IIe [“t2”] (p<0.001; Tables 3 and 4). Overall, insufficient hemodynamic response in VM featured a V-shaped (or “V”) pattern with a prolonged hyper-dip in phase IIe followed by a “Syncline” instead of a “Valley” and a significantly delayed or completely absent PRT in phase IV (Table 4, Figure 3). The “V”
pattern was reproducible as there were no significant differences accordingly to the pairwise comparison of “A”, “t”, and PRT obtained from a second trail within subjects (Table 6). The NOH patients, who could not complete the second VM trail, demonstrated a clear V-shaped SBP response as well.

3.2. Postural tachycardia syndrome

Main characteristics of population and autonomic findings. Compared to all OI patients, POTS and IST were significantly younger (p<0.01) and mainly females (p>0.05). POTS patients had greater body mass index compared to the Control only, whereas IST patients had greater body mass index compared to the all groups (Table 1). POTS and IST did not differ from Control in terms of CASS /its individual indexes (Table 1).

Quantitative HUT and VM analyses. HUT results and VR of POTS and IST patients did not differ from Control either (Table 1). Nonetheless, BRSa was higher in POTS against Control (Table 2). Only within POTS and Control groups did BRSa correlate to the overshoot “E”, α-BRSa, and β-BRSa (Table 5). Similar to SOI and Control groups, α-BRSa correlated to β-BRSa (Table 5; Figure 2).

VM patterning. One out 25 POTS patients and two out 6 IST patients did not perform the second trail of VM. VM responses in POTS and IST appeared analogous; yet, with closer visual inspection, two hemodynamic spikes “C” (SBP increments in phase II) and “E” (overshoot in phase IV) distinguished IST. First, POTS presented different patterns (12 AAR, 11 BAR and 2 SAR), while IST was mostly AAR (aka 5 patterns with “C” rise over baseline, though one was BAR). Also, IST had higher incline “C” than the Control group (p<0.05), but not against POTS (Table 3). Second, POTS had a relatively sustained decline of “E” from its peak (non-dropping ≥ 10 mmHg by 7 s at the average; Table 6); though, there was no clear overshoot “E” in 1 POTS patient (BAR). Conversely, IST showed a rapid SBP dip below baseline in
majority (n=4/6) of participants or SBP drop of ≥ 10 mmHg in the rest of group within 3.5 s (Table 6; Figure 3). Overall, in IST prominent spikes “C” (rising over the baseline) and “E” (rapidly declining) represented an M-shaped (“M”) pattern compared to POTS, where prolonged decline of “E” was relatively perceived as an N-shaped (“N”) pattern (Figure 3).

To evaluate reproducibility of “M” and “N” patterns we conducted a one-way repeated ANOVA (rANOVA). Measured differences between trail 1 and trail 2 within subject’s VM were presence of AAR type of overshoot “E” and time of E decline over 10 mmHg or to the baseline. The results of rANOVA indicated no pairwise differences within subjects for time of “E” decline but for AAR pattern constancy in a repeated VM trail for both IST (n=4) and POTS (n=22) groups. Pairwise comparison between subjects of these factors involved in shaping of “M” and “N” patterns demonstrated significant differences (Table 6).

3.3. Symptomatic orthostatic intolerance

Main characteristics of population and autonomic findings. Patients with SOI did not differ by demographic characteristics. SOI presented with a greater adrenergic index (p<0.05) compared to Control and a higher CASS than POTS (Table 1).

Quantitative HUT and VM analyses. In HUT, ΔHR was significantly lower in SOI compared to POTS (Table 2) and correlated to BRSv (Table 5). Compared to Control, BRSA1 was higher in SOI, as well in IST and POTS, while α-BRSA had the highest value only in IST (Table 2). In SOI and Control groups, α-BRSA correlated to β-BRSA (Table 5; Figure 2). SOI showed greater SBP drop “A” compared to the Control group (p<0.05) and lower overshoot “E” compared to IST (p<0.005, Table 3).

VM patterning. Overall, compared to Control group (43 BAR, 30 AAR and 16 SAR), the SOI VM patterns were unremarkable, though absent SAR patterns (11 BAR patterns and 3 AAR).
4. DISCUSSION

The present study examined VM parameters (qualitative vs. quantitative) in specific clinical conditions (SOI, POTS and NOH vs. Control group and IST)) to extend previous findings obtained in healthy subjects to that in dysautonomia characterized by OI(24). Our results support the following conclusions: i) In OI, VM is a valuable supplement to HUT; ii) In VM, qualitative analysis may provide significant benefit to aid diagnosis; iii) In BRSa, separate alpha- and beta-adrenergic evaluation may improve autonomic screening.

First, our results demonstrate VM patterns are valuable non-orthostatic supplement to HUT given its capacity to detect OI and differentiate non-postural autonomic dysfunction. For example, post late phase IV BP changes in IST ("M" pattern) versus POTS ("N" pattern; Figure 3). We further explain this capacity by the presence of significant unilateral correlations among hemodynamic (ΔSBP and “A”, that is consistent with α-adrenergic response) and cardiac (ΔHR and “VR”, that is consistent with vagal response) alterations in VM and HUT in healthy populations (Control group). In NOH, the significance of the associations between postural (ΔSBP) and non-postural (“A”) hemodynamic falls is strengthened with adrenergic impairment (Figure 2). As well, low VR and ΔHR in NOH were associated with low adrenergic modulation (BRSa), which may indicate a reduced adrenergic control of HR in NOH patients.

As a result, NOH presents with a well-known hemodynamic response to VM, which we term a “V” pattern per its reproducibility in repeated VM trails within subjects. Specifically, the main features of the “V” pattern such as decreased phase IIe [“t2”] and prolonged PRT did not differ in a repeated VM trail within NOH subjects (Table 5). Though NOH was significantly older population compared to the all groups and there might be potential group characteristics (e.g., physical activity status), only adrenergic
failure contributes into both phase II \textsubscript{L} reduction /absence and prolonged PRT over 6 s \textsuperscript{22}, which were found only in NOH. We claim that HUT, as a primary diagnostic tool in OI, will benefit from analyses of VM patterns, which provide instant visual markers, to monitor OI in a dynamic (e.g., recovery of phase II \textsubscript{L} and/or lesser PRT/greater overshoot in phase IV would indicate \(\alpha\)- and/or \(\beta\)-adrenergic improvement respectively, which may not be figured out of single \(\Delta\text{SBP}\)). This addition is important given the severity of NOH is linked to BRS insufficiency and a greater 4-year mortality rate \textsuperscript{21, 27}. Similarly, VM analysis is a diagnostic aid in postural tachycardia when clinical symptoms are in question. The “M” pattern alone might be similar to AAR pattern and, likewise, contributed by the younger age and higher training status. However, prolonged to over 7 s duration of “E” overshoot decline of \(\geq 10\) mmHg or to the baseline level, which is reproducible within POTS subjects but significantly different between POTS and IST groups in repeated VM trails (Table 6) would rather confirm POTS in instances of postural tachycardia. We hypothesize that the “N” pattern is due to \(\beta\)-adrenergic hypersensitivity as it is shaped by relatively sustained overshoot in phase IV (“E”). Moreover, only in POTS and Control group did “E” correlate to BRS\(_{\alpha}\) (BRS\(_{\alpha 1}\)), which exposed greater link to \(\beta\)-BRS within POTS but greater link to \(\alpha\)-BRS\(_{\alpha}\) within the Control. However, further studies are necessary for the clarifications\textsuperscript{1} and validation of \(\alpha\)- and \(\beta\)-BRS calculations with muscle sympathetic neuronal activity and pharmacological dissection.

Second, visualization of VM patterns allows instant evaluation of potential clinically important findings but not quantitative measures, which break down with OI progression (i.e. NOH). For an example, both \(\alpha\)- and \(\beta\)-adrenergic insufficiency in NOH were featured by the “V” pattern. In contrast, parasympathetic impairment in NOH was not recognized by BRS\(_{v}\); as well, BRS\(_{\alpha}\) did not reveal significant adrenergic insufficiency in NOH compared to the healthy subjects. As we did expect BRS\(_{v}\) in NOH to be significantly different from Control given the differences in the VR and \(\Delta\) HR, we further studied the potential impact of central and peripheral autonomic failure addressing that BRS pathways, which are involved in
vasopressin release, are impaired in multiple system atrophy but are normal in pure autonomic failure (13). However, the results revealed that BRSv values among the NOH subgroups groups were still insignificant. Thus, we suggest that classic calculation of BRSv may be an inappropriate measure applied to VM. First, classic calculation of BRSv is not focused on the R-R interval response to the BP rise following phase III, even though it is important (33) (mainly with regards to NOH, were both phases IIe and IV are severely altered with a “V” pattern). Second, hemodynamic responses to VM are instant; thus, in those healthy individuals with excessively rapid changes in BP (>50 mmHg over a few seconds) estimated BRSv values might be relatively low due to missed/unrecorded BP fluctuations (33).

The BRSa evaluation was compromised in pathological VM patterns (i.e., BRSa1 was not applicable to 60% of NOI). Furthermore, appearance of potential “Valley” of phase IIe over time would indicate NOH improvement (Figure 4); whereas in SOI, visualized reduction of phase IIe and prolongation of PRT would reflect progressive α-adrenergic insufficiency, which results in a “Syncline” pattern indicative of severe adrenergic failure. Likewise, visual analysis of VM patterns may provide greater recognition of postural tachycardia when treatment of POTS patients overlaps with deconditioning, somatic hypervigilance (31) or IST (4, 12). Hence, qualitative evaluation would be as a reasonable differentiating tool: change/resolution of the “N” pattern over time could be indicative of POTS improvement, or the presence of an “M” type pattern would suggest the presence of IST (Figure 5).

Finally, our study results let us advocate necessity of separate alpha- and beta-adrenergic evaluation to enhance BRSa accuracy in analysis of pathological responses to VM. Particularly, evident by CASS there is definite adrenergic insufficiency in NOH which was not revealed by BRSa1. Nevertheless, our experimental calculation of α-BRSa, though not yet validated, was capable of detecting adrenergic insufficiency in 20% more of the NOH population. Likewise, in SOI compared to Control, a higher CASS adrenergic index would rather alter BRSa, yet higher BRSa1 does not explain this finding on its own.
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Tables 1 and 2). Presumably, such discrepancy in BRSa1 was influenced by presence of SAR pattern (which has shown lower BRSa vs. AAR(24)) in the Control group. Based on our finding of an inverse relationship between alpha and beta BRSa, we suggest that other forms of BRSa analysis where these two adrenergic components are not treated as separate entities, such as in BRSa1, could be compromised when one altered component (e.g., alpha) is counterbalanced by the other (e.g., beta). This may also explain the significantly augmented $\beta$-BRSa in NOH compared to the all other groups, which is in agreement with Tamura et al. study (32).

We would conclude that VM provides valuable qualitative evaluation in OI while BRSa evaluation is compromised and not as informative. We recommend BRSa calculation requires distinct, alpha and beta adrenergic assessment in VM. Avoiding the general BRSa description may enhance BRS accuracy, which is important for both autonomic research and clinical evaluation.

**Perspectives and Significance**

Present study shows that postural BP responses are implicated in specific BP patterns during VM. Hemodynamic responses to VM in orthostatic dysfunction are probably associated with adrenergic BRS, which estimation is often compromised in autonomic impairment. However, qualitative BP patterning allows VM utilization beyond compromised quantification. If validated, VM patterning would improve the diagnosis of orthostasis, or potentially broaden the research window when HUT is limited.

**Study limitation**

The present study is limited to the biases of selection, confounding and information. Selection bias, which is prevalent in cross-sectional studies(7), is due to the mostly younger aged control population, relatively small IST sample size and a female predominance in IST and POTS groups. As age and gender of the subjects might have a considerable bearing on hemodynamic responses to VM and HUT, there is a
confounding bias. To a certain degree, the physical activity status would have some effects on the VM responses given the evidence supports beneficial cardiovascular adaptations to training. Our subjects' physical activity levels were not recorded. However, the studies demonstrate that BRSa (which is associated with VM patterns in healthy population(24)) is not altered with both aerobic conditioning and resistance training(5, 6, 15). In contrast, BRSv is increasing after 4 weeks of cycling but remains unchanged after 8 weeks of high-intensity strength training(5, 6, 15). Yet BRSv does not differ among those patients groups, associated potential fitness impact (unlikely in NOH where BP responses have rather classic features) has to be studied further.

Finally, information bias in the cohort study is necessitating further large sample sizes and long follow-up. As an observer bias, it requires intra- and inter-rater reliability evaluations. Inadequate respiratory effort in VM may limit parasympathetic response abating BP decrease and chances are that the results may be misinterpreted. Existing methodological differences in the choice of the VM and HUT analysis window may complicate the comparison between our findings and the findings of individual authors. Thus, further testing is required with different time durations of VM and HUT. Experimental α- and β-BRSa require further study with validation against direct muscle sympathetic nerve activity, which is currently undergoing in our autonomic laboratory. The single case reports of VM patterns in NOH and POTS are inconclusive but are of potential research interest looking into the hemodynamic changes in OI in response to non-postural stimuli.

**Conclusion**

The present study defines hemodynamic patterns of VM in NOH, POTS and IST. The revealed VM patterns indicate that OI is detectable during non-postural testing. This approach to autonomic investigation enhances OI studies by use of a supplementary non-postural technique. In addition, we
argue separate evaluation of α- and β-adrenergic responses has to be considered for more selective autonomic screen with BRSa.

CONFLICT OF INTEREST STATEMENT

None of the authors have potential conflicts of interest to be disclosed.

ACKNOWLEDGEMENTS

None

FUNDING SOURCE

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DISCLOSURES

All authors have approved the final article and have no financial or other conflicts of interest to declare.

REFERENCES


FIGURES AND LEGENDS

**Figure 1.** Parameters for baroreflex sensitivity (BRS) evaluation in Valsalva maneuver (VM).

Figure 1 presents BRS parameters in VM: **A** – systolic blood pressure (SBP) decrement in early phase II; **B** – SBP decrement in phase III; “Baseline”- supine SBP level before VM; **C** – SBP increment in late phase II; **D** – SBP increment during PRT; **E** – SBP overshoot in phase IV; \( k_\alpha \) – \( \alpha \)-adrenergic coefficient “rise of C over \( t_2 \)” as a hypotenuse adjusted to angle \( \alpha \); \( k_\beta \)– \( \beta \)-adrenergic coefficient “rise of D over PRT” as hypotenuse adjusted to angle \( \beta \); “Overshoot”- the peak of SBP recovery in phase IV; **PRT** – pressure recovery time in phase IV; “Rise”- the peak of SBP incline in late phase II; \( t_1 \) – duration of early phase II; \( t_2 \) - duration of late phase II; \( t_3 \) - duration of phase III; “Valley” – the point of SBP fall arrests in early phase II. **Solid line** represents SBP fluctuation in VM; **arrows** show main SBP changes in VM (A-E); **traced triangles** display indices of experimental \( \alpha \)-adrenergic (\( \alpha \)-BRSa) and \( \beta \)-adrenergic (\( \beta \)-BRSa) BRS calculations respectively generated out of late phase II and phase IV parameters.

**Figure 2.** Correlations between postural and non-postural variables.

Figure 2 depicts correlations among systolic blood pressure (SBP) and heart rate (HR) variations during both Head-up tilt test and Valsalva maneuver and within single Valsalva maneuver. Presented correlations are significant at the levels: \( p<0.05 \) (*), \( p<0.01 \) (†) and \( p<0.001 \) (‡). Unilateral correlations are represented with open arrows, inverse correlations – with diamond arrows. Abbreviations: \( \alpha \)-BRSa,
alpha-adrenergic baroreflex sensitivity (BRS); BRSα₁, alternative adrenergic BRS; BRSv, vagal BRS; β-BRSα, beta-adrenergic BRS; VR, Valsalva ratio.

**Figure 3.** The shaped patterns of hemodynamic responses to Valsalva maneuver (VM).

Figure 3 presents “V”, “M” and “N” patterns of systolic blood pressure (BP, upper channel) and beat-to-beat BP (middle channel) in response to VM (mouth pressure (MP) is depicted in lower channel). In neurogenic orthostatic hypotension, the **V-shaped pattern** is distinguished by prolonged hyper-dip of systolic BP (A) as a “Syncline” (S) instead of “Valley” (V) in early phase II (IIₑ) and altered phase III (reduced, absent or indefinite). In inappropriate sinus tachycardia, the **M-shaped pattern** is distinguished by two systolic BP peaks: 1) prominent incline (C) in late phase II (IIₐ) that results in “Rise” (R) over “Baseline” (B); and 2) rapid decline of “Overshoot” (E) in phase IV (≥ 10 mmHg or dipping below “Baseline” within 3 s). In postural tachycardia syndrome, the **N-shaped pattern** is distinguished by rather sustained “Overshoot” (E) in phase IV (non-dropping ≥ 10 mmHg over 8 s).

**Figure 4.** Potential visual tracers of adrenergic insufficiency in neurogenic orthostatic hypotension (NOH).

Figure 4 presents dynamic changes in the “V” pattern in response to VM in an NOH patient (33 year old female with an autoimmune autonomic ganglionopathy) over 3 months after standard measures for orthostatic dysfunction including oral medication such as midodrine, fludrocortisone. **Visit 1** (upper channel): In the absence of late phase II (yet preserved “Valley”) and phase III, the systolic blood pressure (SBP) has a prolonged hyper-dip (A) in early phase II followed by a prolonged phase IV (Valsalva ratio 1.87; ΔSBP – 59.7 mmHg and ΔHR 51.4 bpm in Head-up tilt test). **Visit 2** (lower channel): Shortened in time the SBP decline (A) is following by recovered late phase II, which reflects improvement of α-adrenergic response; faster SBP gaining in phase IV is potentially indicative of enhanced β-adrenergic
response (Valsalva ratio 1.92; ΔSBP - 24.6 mmHg and ΔHR 33.7 bpm in Head-up tilt test). Hemodynamic changes were associated with significant improvement of orthostasis.

**Figure 5.** Potential visual tracers of adrenergic response in postural tachycardia syndrome (POTS).

Figure 5 presents dynamic changes in the “N” pattern in response to VM in a POTS patient (26 year old female) over the course of one year after standard measures for orthostatic dysfunction but changing oral medication (increasing bisoprolol from 1.25 mg to 10 mg daily). **Visit 1** (upper channel): The systolic blood pressure (SBP) overshoot in phase IV (E) is sustained for 20 s (Valsalva ratio 2.2; ΔSBP - 16.4 mmHg and ΔHR 30.2 bpm in Head-up tilt test, which was difficult to interpret given the patient’s various medications, including midodrine). **Visit 2** (lower channel): Overshoot “E” is reduced by twice and dipping by 20 s, which may reflect improvement of improved/adequate β-adrenergic response (Valsalva ratio 1.7; ΔSBP - 22.8 mmHg and ΔHR 4 bpm in Head-up tilt test). Patient reported resolution of postural palpitations and presyncope.
Correlations between postural and non-postural variables:

- HEALTHY POPULATION
- NEUROGENIC ORTOSTATIC HYPOTENSION
- POSTURAL TACHYCARDIA SYNDROME
- SYMPTOMATIC ORTHOSTATIC INTOLERANCE

**VALSALVA MANEUVER**

- SBP drop "A"
- SBP overshoot "E"
- α-BRSa
- BRSa₁
- β-BRSa
- BRSv
- VR

**HEAD-UP TILT TEST**

- SBP drop "ΔSBP"
- ΔHR
Table 1. Studied groups characteristics

<table>
<thead>
<tr>
<th></th>
<th>NOH</th>
<th>POTS</th>
<th>IST</th>
<th>SOI</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females, n / total, n</strong></td>
<td>8/26</td>
<td>22/26</td>
<td>6/7</td>
<td>8/14</td>
<td>62/107</td>
</tr>
<tr>
<td>[%]</td>
<td>[31%]</td>
<td>[85%]</td>
<td>[86%]</td>
<td>[57%]</td>
<td>[58%]</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>66 ± 10§</td>
<td>31 ± 11**†</td>
<td>27 ± 14**†</td>
<td>48 ± 14*§</td>
<td>32 ± 15</td>
</tr>
<tr>
<td>[min-max]</td>
<td>[42-83]</td>
<td>[13-56]</td>
<td>[14-50]</td>
<td>[17-71]</td>
<td>[16-75]</td>
</tr>
<tr>
<td><strong>BMI b</strong></td>
<td>25.31 ± 3.90‡</td>
<td>28.53 ± 4.18§</td>
<td>36.83 ± 13.42§</td>
<td>28.36 ± 1.33‡</td>
<td>24.18 ± 3.15</td>
</tr>
<tr>
<td>[min-max]</td>
<td>[19.01-28.73]</td>
<td>[24.31-36.20]</td>
<td>[23.62-50.46]</td>
<td>[26.57-29.80]</td>
<td>[16.22-32.51]</td>
</tr>
<tr>
<td><strong>CASS</strong></td>
<td>5.61 ± 2.46§</td>
<td>0.35 ± 0.78**†</td>
<td>0.40 ± 0.55*</td>
<td>1.67 ± 1.97*§</td>
<td>0.28 ± 0.51</td>
</tr>
<tr>
<td>[n=23]*</td>
<td>[n=23]*</td>
<td>[n=6]*</td>
<td>[n=12]*</td>
<td>[n=106]*</td>
<td></td>
</tr>
<tr>
<td><strong>Sudomotor index</strong></td>
<td>0.92 ± 1.21§</td>
<td>0.21 ± 0.66*</td>
<td>0.33 ± 0.52</td>
<td>0.77 ± 1.01</td>
<td>0.23 ± 0.49</td>
</tr>
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<td>[n=24]</td>
<td>[n=24]</td>
<td>[n=6]</td>
<td>[n=13]</td>
<td>[n=106]</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovagal index</strong></td>
<td>1.25 ± 0.68§</td>
<td>0.08 ± 0.27*</td>
<td>0.29 ± 0.76*</td>
<td>0.29 ± 0.61* [n=13]</td>
<td>0.04 ± 0.19</td>
</tr>
<tr>
<td>[n=24]</td>
<td>[n=26]</td>
<td>[n=7]</td>
<td>[n=107]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adrenergic index</strong></td>
<td>3.46 ± 1.21§</td>
<td>0.04 ± 0.20*</td>
<td>0.00 ± 0.00*</td>
<td>0.46 ± 0.78*§</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>[n=26]</td>
<td>[n=25]</td>
<td>[n=6]</td>
<td>[n=14]</td>
<td>[n=107]</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± standard deviation. * - significantly different from NOH (p<0.01); † - significantly different from SOI (p<0.05); ‡ - significantly different from IST (p<0.05); § - significantly different from Control (p<0.05); a – CASS was generated only for individuals presented with all three autonomic indices; b – Control n=88, POTS n=8, IST n=3, SOI n=4, and NOH n=5.
VALSALVA MANEUVER PATTERNS IN ORTHOSTATIC INTOLERANCE

Abbreviations: CASS, Composite Autonomic Severity Score; IST, inappropriate sinus tachycardia; NOH, neurogenic orthostatic hypotension; POTS, postural tachycardia syndrome; SOI, symptomatic orthostatic intolerance.
Table 2. Cardiovagal response and baroreflex sensitivity (BRS) in autonomic tests

<table>
<thead>
<tr>
<th>Groups</th>
<th>NOH (n = 25)</th>
<th>POTS (n = 25)</th>
<th>IST (n = 6)</th>
<th>SOI (n = 13)</th>
<th>Control (n = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Valsalva maneuver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valsalva Ratio</td>
<td>1.30 ± 0.25§</td>
<td>2.22 ± 0.54†</td>
<td>2.03 ± 0.19†</td>
<td>1.87 ± 0.51†</td>
<td>1.96 ± 0.39</td>
</tr>
<tr>
<td>BRSv, ms/mmHg</td>
<td>2.73 ± 6.79⁺</td>
<td>2.66 ± 4.32</td>
<td>1.51 ± 1.98</td>
<td>5.90 ± 10.58</td>
<td>4.93 ± 5.40</td>
</tr>
<tr>
<td>BRSa₁, mmHg/s</td>
<td>4.42 ± 4.36⁺</td>
<td>33.72 ± 31.36⁺</td>
<td>52.33 ± 32.16⁺</td>
<td>48.33 ± 68.21⁺</td>
<td>17.12 ± 14.51</td>
</tr>
<tr>
<td>α-BRSa, mmHg</td>
<td>1.69 ± 1.38 ⁵§</td>
<td>7.90 ± 2.82*</td>
<td>10.88 ± 2.02⁺</td>
<td>7.29 ± 3.93*</td>
<td>5.92 ± 3.80</td>
</tr>
<tr>
<td>β-BRSa, mmHg</td>
<td>23.00 ± 12.45⁺</td>
<td>1.78 ± 1.10 ⁵⁺</td>
<td>1.26 ± 1.23⁺</td>
<td>3.38 ± 2.94⁺</td>
<td>2.68 ± 2.26</td>
</tr>
<tr>
<td><strong>Head-up tilt test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔHR, bpm</td>
<td>13.92 ± 9.86§</td>
<td>40.59 ± 16.37⁺</td>
<td>32.34 ± 8.63†</td>
<td>30.48 ± 14.55⁺</td>
<td>30.48 ± 11.48</td>
</tr>
<tr>
<td>ΔSBP, mmHg</td>
<td>-83.58 ± 34.27⁺</td>
<td>-29.22 ± 12.42⁺</td>
<td>-17.63 ± 8.07⁺</td>
<td>-30.08 ± 13.79⁺</td>
<td>-24.00 ± 11.96</td>
</tr>
</tbody>
</table>

* - significantly different from NOH (p<0.01); † - significantly different from NOH (p<0.005); ‡ - significantly different from POTS (p<0.05); § - significantly different from Control (p<0.05); a - in 5/25 NOH, 1/25 POTS and 1/13 SOI subjects SBP did not recover to the baseline level and, thus, compromised calculations; b – in 10/25 NOH absent late phase II (“V” pattern) and, thus, compromised calculations; c – 1 NOH patient with MSA, who could not complete the second VM trail, was excluded from BRSv analysis due to potential artifact effect on SBP curve in early phase II.

Abbreviations: BRSa₁, alternative adrenergic BRS; α-BRSa, α-adrenergic BRS; β-BRSa, β-adrenergic BRS; BRSv, vagal BRS; ΔHR, heart rate change; ΔSBP, systolic blood pressure change; IST, inappropriate sinus tachycardia; NOH, neurogenic orthostatic hypotension; POTS, postural tachycardia syndrome; SBP, systolic blood pressure; SOI, symptomatic orthostatic intolerance.
Table 3. Hemodynamic response (mmHg) to Valsalva maneuver

<table>
<thead>
<tr>
<th>Groups</th>
<th>NOH (n = 25)</th>
<th>POTS (n = 25)</th>
<th>IST (n = 6)</th>
<th>SOI (n = 13)</th>
<th>Control (n = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP at baseline</td>
<td>154.41 ± 31.52†</td>
<td>112.88 ± 18.11*</td>
<td>119.87 ± 9.97*</td>
<td>120.14 ± 13.76*</td>
<td>117.88 ± 16.85</td>
</tr>
<tr>
<td>SBP in phase II</td>
<td>91.49 ± 30.43</td>
<td>88.42 ± 20.10</td>
<td>96.34 ± 18.32</td>
<td>86.92 ± 15.98</td>
<td>101.62 ± 19.12</td>
</tr>
<tr>
<td>&quot;A&quot; - Decrement in early phase II</td>
<td>62.61 ± 27.48†</td>
<td>24.46 ± 17.48*</td>
<td>23.54 ± 10.89*</td>
<td>33.22 ± 16.60*†</td>
<td>16.25 ± 17.90</td>
</tr>
<tr>
<td>&quot;B&quot; - Decrement in phase III</td>
<td>23.12 ± 15.44 b</td>
<td>21.10 ± 6.79</td>
<td>23.92 ± 14.33</td>
<td>20.54 ± 13.08</td>
<td>22.96 ± 8.92</td>
</tr>
<tr>
<td>&quot;C&quot; - Increment in late phase II</td>
<td>10.06 ± 13.50 b</td>
<td>20.27 ± 13.41</td>
<td>34.15 ± 9.17†</td>
<td>23.92 ± 15.56*</td>
<td>13.92 ± 11.08</td>
</tr>
<tr>
<td>&quot;D&quot; - Increment during PRT</td>
<td>72.13 ± 25.36*†</td>
<td>25.29 ± 16.10**</td>
<td>13.31 ± 7.18*</td>
<td>29.84 ± 23.74*†</td>
<td>25.29 ± 16.69</td>
</tr>
<tr>
<td>&quot;E&quot; - Overshoot in phase IV</td>
<td>9.68 ± 8.16†</td>
<td>30.11 ± 16.95*†</td>
<td>47.73 ± 31.17†</td>
<td>24.67 ± 12.71*†</td>
<td>15.64 ± 12.20</td>
</tr>
</tbody>
</table>

Values are means ± standard deviation. * - significantly different from NOH (p<0.05); † - significantly different from control (p<0.05); ‡ - significantly different from IST (p<0.005) a - in 5/25 NOH, 1/25 POTS and 1/13 SOI subjects SBP did not recover to the baseline level; b – in 10/25 NOH absent late phase II ("V" pattern); 3N – in 3/25 NOH subjects absent phase III. Abbreviations: IST, inappropriate sinus tachycardia; NOH, neurogenic orthostatic hypotension; POTS, postural tachycardia syndrome; PRT, pressure recovery time; SBP, systolic blood pressure; SOI, symptomatic orthostatic intolerance.
Table 4. *Phasic time parameters (s) in Valsalva maneuver*

<table>
<thead>
<tr>
<th>Groups</th>
<th>NOH (n = 25)</th>
<th>POTS (n = 25)</th>
<th>IST (n = 6)</th>
<th>SOI (n = 13)</th>
<th>Control (n = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early phase II [t1]</td>
<td>13.89 ± 2.93†</td>
<td>8.92 ± 3.30*</td>
<td>8.40 ± 2.14*</td>
<td>9.77 ± 2.63*</td>
<td>8.63 ± 2.43</td>
</tr>
<tr>
<td>Late phase II [t2]</td>
<td>2.18 ± 1.61†</td>
<td>9.64 ± 2.54*</td>
<td>11.51 ± 2.05*</td>
<td>7.96 ± 4.01*</td>
<td>8.22 ± 3.83</td>
</tr>
<tr>
<td>Phase III [t3]</td>
<td>2.34 ± 2.39f</td>
<td>1.82 ± 0.80f</td>
<td>1.06 ± 0.27</td>
<td>1.90 ± 0.49</td>
<td>1.97 ± 1.07</td>
</tr>
<tr>
<td>Pressure recovery time [PRT]</td>
<td>23.24 ± 11.76†</td>
<td>1.79 ± 1.11*</td>
<td>1.28 ± 1.24*</td>
<td>3.43 ± 3.00**</td>
<td>2.95 ± 2.72</td>
</tr>
</tbody>
</table>

* - significantly different from NOH (p<0.001); † - significantly different from Control (p<0.001); a - in 5/25 NOH, 1/25 POTS and 1/13 SOI subjects SBP did not recover to the baseline level; b – in 10/25 NOH absent late phase II (“V” pattern); c – in 3/25 NOH subjects absent phase III. Abbreviations: IST, inappropriate sinus tachycardia; NOH, neurogenic orthostatic hypotension; POTS, postural tachycardia syndrome; SOI, symptomatic orthostatic intolerance.
Table 5. Pearson correlations of postural and non-postural autonomic variables

<table>
<thead>
<tr>
<th>VR</th>
<th>“A” mmHg</th>
<th>“E” mmHg</th>
<th>BRSv ms/mmHg</th>
<th>α-BRSa a s*mmHg</th>
<th>β-BRSa a s*mmHg</th>
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</thead>
<tbody>
<tr>
<td>ΔHR, bpm</td>
<td>NOH</td>
<td>0.633†</td>
<td>0.474*</td>
<td>0.470*</td>
<td>0.857†</td>
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<td></td>
<td>SOI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.619†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔSBP, mmHg</td>
<td>NOH</td>
<td>0.66‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.383†</td>
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<tr>
<td>Within Valsalva maneuver</td>
<td>NOH</td>
<td>0.730*</td>
<td></td>
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<td>Control</td>
<td>0.422†</td>
<td>0.195*</td>
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<tr>
<td>“A”, mmHg</td>
<td>NOH</td>
<td>-0.457*</td>
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<tr>
<td></td>
<td>Control</td>
<td>0.336†</td>
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<tr>
<td>BRSa1, mmHg/s</td>
<td>POTS</td>
<td>0.425*</td>
<td>0.477†</td>
<td>-0.504*</td>
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<td>0.199*</td>
<td>0.438†</td>
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<td>0.489†</td>
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<td>α-BRSa, s*mmHg</td>
<td>POTS</td>
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<td>-0.647†</td>
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<td></td>
<td>SOI</td>
<td></td>
<td>-0.906†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.233*</td>
<td></td>
<td></td>
<td>-0.241*</td>
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</tbody>
</table>

* - Correlation significant at the level p<0.05; † - Correlation significant at the level p<0.01; ‡ - Correlation significant at the level p<0.001; a - in 5/25 NOH, 1/25 POTS and 1/13 SOI subjects SBP did not recover to the baseline level and, thus, compromised “PRT” in calculations; b – in 10/25 NOH absent late phase II (“V” pattern); c – 1 NOH patient was excluded from BRSv analysis due to potential artifact effect on SBP curve in early phase II. Abbreviations: "A" - Decrement in early phase II; BRSa1, alternative adrenergic BRS; α-BRSa, α-adrenergic BRS; β-BRSa, β-adrenergic BRS; BRSv, vagal BRS; Control – healthy population (n=107); ΔHR, heart rate change; ΔSBP, systolic blood pressure change; "E" - Overshoot in phase IV; IST, inappropriate sinus tachycardia (n=6); NOH, neurogenic orthostatic hypotension (n=25); POTS, postural tachycardia syndrome (n=25); SBP, systolic blood pressure; SOI, symptomatic orthostatic intolerance (n=13).
Table 6. *Pairwise comparison of factors involved in shaping of “M”, “N” and “V” patterns*

<table>
<thead>
<tr>
<th></th>
<th>Trail 1</th>
<th>Trail 2</th>
<th>Wilks’ Lambda</th>
<th>F</th>
<th>Partial Eta Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>“N” PATTERN VERSUS “M” PATTERN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor “AAR” [%] *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POTS (n=25)</td>
<td>17</td>
<td>17</td>
<td>0.944</td>
<td>1.596</td>
<td>0.56</td>
</tr>
<tr>
<td>IST (n=4)</td>
<td>100</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor “E” [s] *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POTS (n=24)</td>
<td>7.68 ± 6.16</td>
<td>7.16 ± 4.43</td>
<td>0.969</td>
<td>1.000</td>
<td>0.002</td>
</tr>
<tr>
<td>IST (n=4*)</td>
<td>1.30 ±1.62</td>
<td>0.90±0.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>“V” PATTERN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor “t2” [s]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOH (n=22)</td>
<td>1.34 ± 1.70</td>
<td>1.40 ± 2.48</td>
<td>0.999</td>
<td>0.031</td>
<td>0.01</td>
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<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Factor “PRT” [s]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOH (n=22)</td>
<td>16.98 ± 14.19</td>
<td>17.50 ± 13.14</td>
<td>0.997</td>
<td>0.064</td>
<td>0.003</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Factor “A” [mmHg] †</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOH (n=22)</td>
<td>61.27 ± 27.39</td>
<td>74.48 ± 29.70</td>
<td>0.676</td>
<td>10.066</td>
<td>0.003</td>
</tr>
</tbody>
</table>

The table presents results of a one-way repeated ANOVA in postural tachycardia syndrome (POTS), IST (sinus tachycardia) and neurogenic orthostatic hypotension (NOH). Measured differences between trail 1 and trail 2 of VM were: 1) Factor “AAR” - presence of augmented autonomic response; 2) Factor “E” - duration of overshoot “E” (in phase IV) decline over 10 mmHg or to the baseline; 3) Factor “t2” – duration of late phase II; 4) Factor “PRT” – pressure recovery time; 5) Factor “A” - decrement in early phase II. Symbols: * - the factor “E” analysis did not include one IST patient per possible artifact in phase IV. Symbols: * - significantly different multivariate effect between subjects (p<0.05); † - significantly different multivariate effect within subjects (p<0.05).