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Original Article

Comparison of Baroreflex Responses to Lower Body Negative Pressure and Valsalva Maneuver in Healthy Subjects

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Abstract

Lower body negative pressure (LBNP) technique has been used for simulating orthostasis by producing preload reduction. Valsalva maneuver (VM), a commonly employed test for autonomic function evaluation, operates on similar principle. Previous literature recommends LBNP as a substitute to VM but has not compared them from a baroreflex perspective. We have compared baroreflex responses to VM and LBNP in apparently healthy adult male subjects (n=22) by assessment of baroreflex sensitivity (BRS). BRS values during Phase II and IV of VM and during suction (dLBNP) and immediate post suction (pLBNP) phases of LBNP were compared. There was no significant difference between Phase IIVM and dLBNP (4.598 (2.945-5.917) ms/mm Hg versus 4.228 (2.199-5.266) ms/mm Hg, p=0.84, Wilcoxon signed rank test). Also, there was no significant difference between Phase IVVM and pLBNP (4.892 (4.165-5.921) ms/mm Hg versus 7.650 (4.278-9.354) ms/mm Hg, p=0.11, Wilcoxon signed rank test). While there was no significant difference amongst the BRS values obtained, Bland Altman analysis revealed existence of bias between BRS derived using VM and LBNP. It may be concluded that the two maneuvers operate via different mechanisms and interchangeable use of Valsalva maneuver and Lower body negative pressure for BRS assessment may not be tenable.

Introduction

The reduction of preload serves as a potent stimulus to engage the cardiovascular system. It may be brought about by different maneuvers such as Head up tilt, Valsalva maneuver and Lower body negative pressure. The perturbation brought about by the decrement in venous return engages reflex cardiovascular regulatory mechanisms leading to restoration of blood pressure and heart rate to resting levels.

The baroreflex is one of the key mechanisms responsible for modulation of blood pressure. Efficacy of the baroreceptors to buffer oscillations in blood pressure can be assessed using Baroreflex sensitivity (BRS) which quantifies the relationship between heart rate and blood pressure. BRS estimation may be done by studying spontaneous fluctuations in systolic

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blood pressure (SBP) and heart rate or by inducing perturbations using drugs or maneuvers such as Head up tilt or Valsalva maneuver. The relationship between change in RR intervals in response to SBP fluctuations helps to quantify BRS (1).

Lower body negative pressure (LBNP) has been employed to simulate orthostatic stress by passive suction on the lower half of the body. Different grades and time durations have been reported in literature (2,3). While low intensity LBNP (upto-20 mm Hg) is said to selectively unload cardiopulmonary receptors, higher intensities are reported to additionally engage aortic and carotid baroreceptors (4). Therefore LBNP demonstrates potential utility in assessment of baroreflex integrity.

Previous literature has suggested use of LBNP as a substitute to Valsalva maneuver (VM) (5). It has been reported that passive suction employed in LBNP mitigates the reflexes activated by other maneuvers for preload reduction such as Valsalva maneuver and Head up tilt. This may be useful for elderly subjects and patients with neurological disorders who may not be able to perform VM (5). Description of hemodynamic changes brought about by LBNP has been documented. But the efficacy of LBNP to assess BRS is not adequately addressed by previous literature.

We conducted the present study to examine the potential of LBNP as a tool for baroreflex evaluation. We also assessed cardiovascular responses to Valsalva maneuver to compare both maneuvers from a baroreflex perspective.

Methods

Our study was a cross sectional, observational study conducted at Autonomic and Vascular function laboratory, Department of Physiology, All India Institute of Medical Sciences (AIIMS), New Delhi. The study was approved by Institute Ethics committee. Twenty two healthy male volunteers (mean age = 26.6±6.23 years, BMI = 21.5±2.65 kg/m^2) of Delhi-NCR region were recruited for the study. All subjects were apparently healthy and did not have any co morbidities likely to affect autonomic function. Before inclusion in the study, detailed history of the subjects was taken to ensure that there was no contraindication for performance of Valsalva maneuver i.e. any history suggestive of retinopathy, elevated intraocular pressure, intra-ocular lens implantation or any surgical scar on the abdomen. Written informed consent was obtained from all participants after detailed explanation of the study protocol.

The subjects were requested to abstain from tea/ coffee on the morning of the test. Abstinence from tobacco, heavy exercises and any medication likely to affect the autonomic nervous system was also ensured. All the subjects were fit to perform Valsalva maneuver, as described earlier. They were requested to wear loose fitting and comfortable clothing on the day of the test.

The recordings were done in a noise and temperature controlled environment at Autonomic and Vascular function laboratory at the Department of Physiology at All India Institute of Medical Sciences, New Delhi. All the recordings were performed between 09.00 am and 1.00 pm. Upon arrival to the lab, the subjects were asked to empty their bladder and were provided supine rest for 10 minutes to allow vital parameters such as heart rate, blood pressure and respiratory rate to come to the baseline.

Valsalva maneuver: VM was performed in supine position. The subjects were requested to blow into a disposable mouth piece connected to a sphygmomanometer to maintain an expiratory pressure of 40 mm Hg for 15 seconds, as described previously (6, 7). A small leak was created in the mouthpiece to ensure open glottis and sustained effort throughout the maneuver. Post maneuver, the subjects were requested to breathe as normally as possible.

Lower body negative pressure: The lower half of the body of the subject was sealed in the LBNP device (Vacusport™, Weyergans High care AG, Germany) at the level of the iliac crests, as recommended in literature (2). Lower body suction of -40 mm Hg was applied for 15 seconds in supine position. The subjects were requested to breathe as normally as possible during and after the suction period. A sham trial of LBNP was given before the start of protocol during which no data acquisition was performed. The purpose of sham exposure was to familiarize the subjects with LBNP suction and prevent undue anxiety during the actual trial.

Beat to Beat Blood pressure and ECG: Beat to beat blood pressure was recorded by finger plethysmography using volume clamp technique (Finometer™ model 2, Finapres Medical Systems, Amsterdam, Netherlands). The technique provides a reliable non invasive estimate of blood pressure and is comparable to intra-arterial recordings (8, 9). Lead II ECG was sampled after amplification using bioamplifier and application of band pass filter of 0.5 and 35 Hz. RR intervals were derived in real time using the raw signal. A digital data acquisition system, Power Lab™ system (AD Instruments, Australia) was used to acquire the blood pressure and ECG signals at sampling rate of 1 kHz. Lab Chart Pro™ version 7 Software (AD Instruments, Australia) was used for data acquisition and storage for subsequent offline analysis.

Baroreflex Sensitivity analysis: Analysis of baroreflex sensitivity (BRS) was performed for VM and LBNP. Phase II and IV of VM were chosen for BRS assessment as they entail active engagement of baroreflex. The systolic blood pressure (SBP) values from peak to nadir were identified during Phase II. The slope of the regression curve between corresponding RR interval and SBP values from peak to nadir was computed as a measure of BRS (10–13). Similarly, the nadir to peak values of SBP were chosen during Phase IV of VM and regressed against subsequent RR intervals. The slope of the regression curve was taken as a measure of BRS. These values help to estimate the vagal component of BRS (BRS_v↓ and BRS_v↑) (10, 12, 13). We designated them as PhaseIIVM and PhaseIVVM respectively. The slope was chosen for only those regression curves with r values 0.5 or better.

We utilized a similar methodology for evaluation of BRS using LBNP. Identification of SBP values during suction phase (from peak to nadir) and immediate post suction phase (from nadir to peak) were performed. Subsequent RR intervals were regressed against these SBP values and slopes were determined as measures of BRS. The values thus derived were designated as dLBNP and pLBNP (representing ‘during’ LBNP and ‘immediate post’ LBNP respectively). Since BRS using LBNP has not been reported adequately in literature, we choose two arbitrary criteria for describing the baroreflex response to LBNP as adequate – fall of atleast 10 mm Hg in SBP and r value of 0.5 or better for the regression curve. dLBNP and pLBNP were evaluated for subjects, only if both criteria were met.

Statistical analysis: Gaussian fit of data was checked using D’Agostino and Pearson Omnibus normality test. Values were expressed as Mean±SD or Median (Interquartile range) depending on gaussian fit. Wilcoxon signed rank test was used for statistical comparison between BRS values. The level of statistical significance was set at p value of <0.05.

Bland Altman test was used to check the bias and agreement between BRS values derived using Phase IIVM and dLBNP & Phase IVVM and pLBNP respectively.

Results

Twenty two healthy male subjects (mean age = 26.6±6.23 years, BMI = 21.5±2.65 kg/m^2) participated in the study. All subjects were able to perform Valsalva maneuver at 40 mm Hg for 15 seconds. Also, all subjects were able to tolerate LBNP suction of -40 mm Hg for 15 seconds. None of them reported any discomfort or presyncopal symptoms on application of LBNP suction.

The hemodynamic response to VM and LBNP for a representative male aged 26 years is represented in Fig. 1. A reference regression plot between RR interval and systolic blood pressure which was used for BRS estimation is represented in Fig. 2.

We observed ‘flat top’ morphology of BP response to Valsalva maneuver in 5 subjects. As described previously (10–12), SBP does not fall below the baseline during Phase II in ‘flat top’ morphology of

(A)

(B)

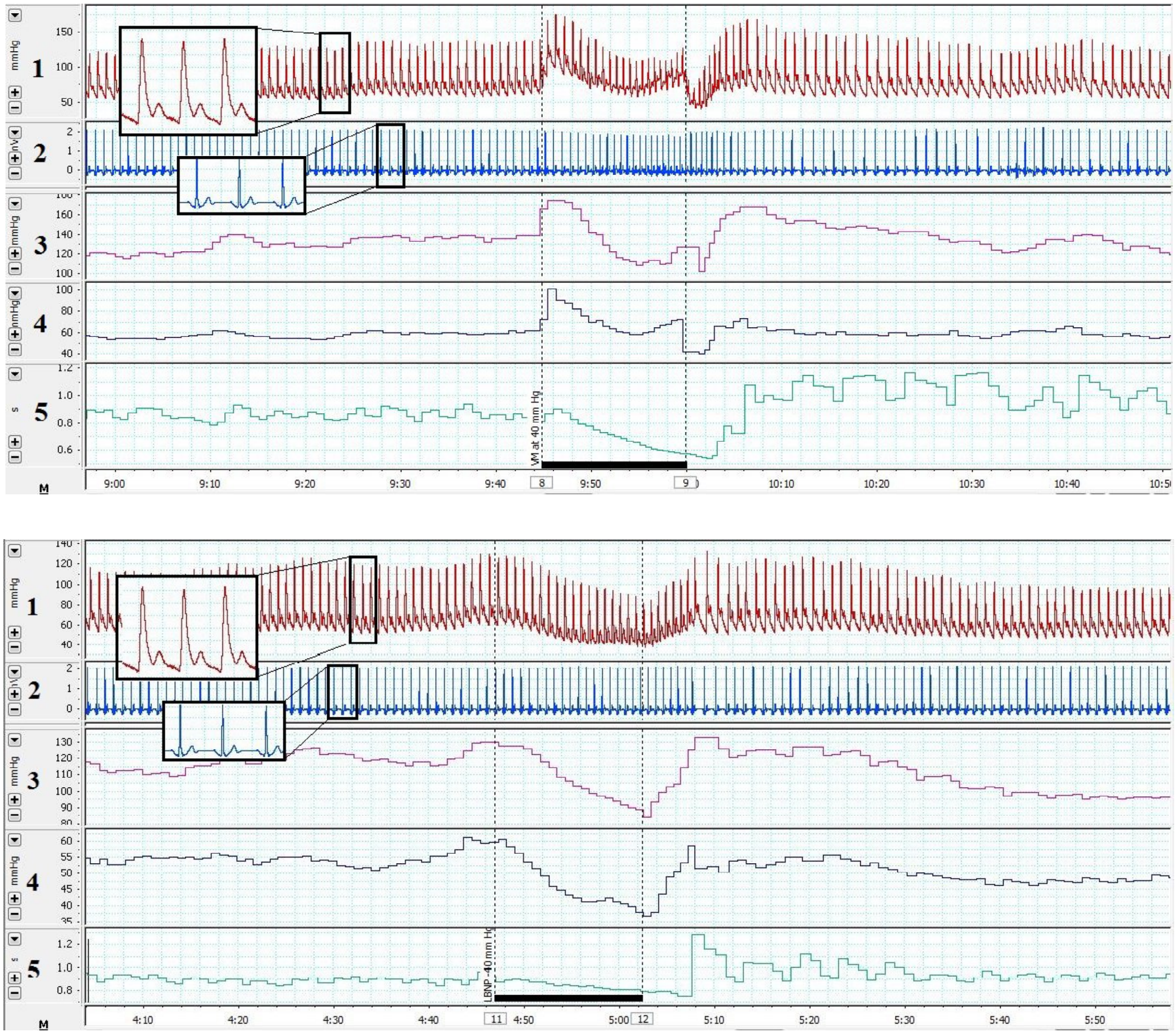

Fig. 1 : Representative records of Valsalva maneuver and LBNP in a male subject aged 26 years.

The above pictures show representative records from a 26 year old male performing Valsalva maneuver (A) and when exposed to LBNP (B). The channels 1 and 2 show raw signals of continuous beat to beat blood pressure and Lead II ECG while channels 3,4 and 5 show Systolic BP, Diastolic BP and RR interval derived in real time using raw signals in 1 and 2. The inset boxes show magnified views of raw BP and ECG signals. The black bar at the bottom shows the duration of the maneuvers (15 seconds each).

VM. BRS evaluation is not recommended in these subjects and therefore we excluded them from BRS analysis. Also, we observed that 7 subjects did not fit our criteria for BRS evaluation using LBNP i.e. fall of at least 10 mm Hg in SBP and r value of 0.5 or better for the regression curve. Therefore BRS (dLBNP and pLBNP) could not be computed for these subjects. Therefore statistical comparison of BRS values of 17 subjects for Valsalva maneuver and 15 subjects for LBNP was finally performed.

Baroreflex sensitivity assessed by VM (Phase IIVM and Phase IVVM) and LBNP (dLBNP and pLBNP) are depicted in Figure 3. There was no significant difference between Phase IIVM and dLBNP (4.598 (2.945-5.917) ms/mm Hg versus 4.228 (2.199-5.266) ms/mm Hg, p=0.84, Wilcoxon signed rank test). Also, there was no significant difference between Phase IVVM and pLBNP (4.892 (4.165-5.921) ms/mm Hg versus 7.650 (4.278-9.354) ms/mm Hg, p=0.11, Wilcoxon signed rank test).

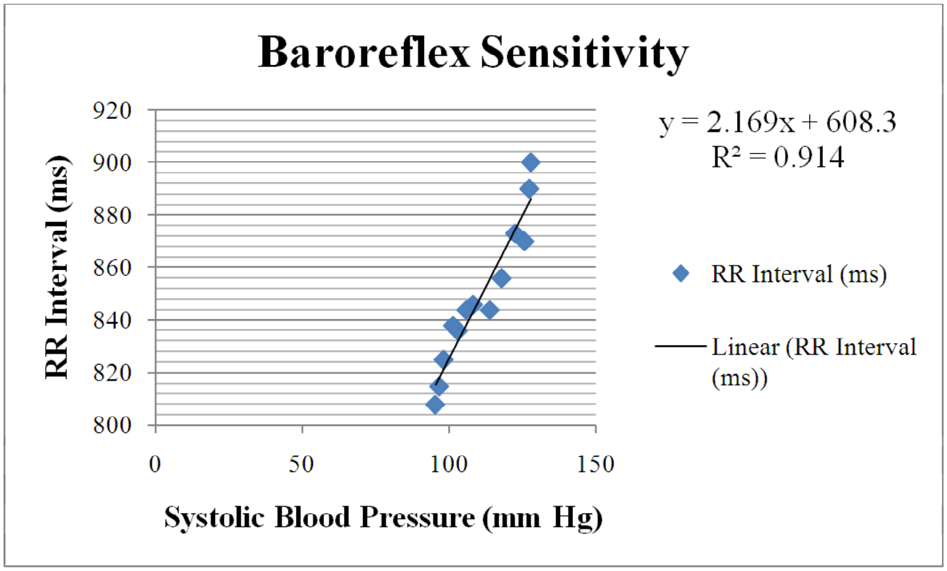

Fig. 2 : Representative linear regression curve used for estimation of Baroreflex sensitivity.

The above graph depicts linear regression of RR intervals (ms) against Systolic blood pressure (mm Hg) for dLBNP for the representative subject in Figure 1. The slope of the regression curve (2.169 ms/mm Hg) is an estimate of Baroreflex sensitivity.

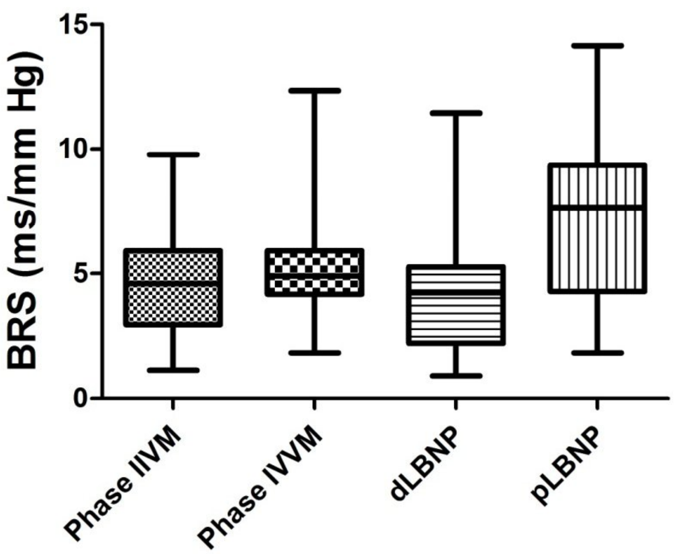

Fig. 3 : Comparison of Baroreflex sensitivity (BRS) values derived using Valsalva maneuver and LBNP.

Baroreflex sensitivity values derived using Valsalva maneuver (Phase IIVM and Phase IVVM) and LBNP (dLBNP and pLBNP). Data expressed as Median (Interquartile Range). There was no significant difference between Phase IIVM & dLBNP and Phase IV & pLBNP, as assessed by Wilcoxon Signed Rank test (p=0.84 and 0.11 respectively).

Bland Altman analysis revealed bias in both positive and negative directions between BRS derived from both maneuvers (Fig. 4). The mean bias between dLBNP and Phase IIVM & pLBNP and Phase IVVM were 0.094 and 2.064 ms/mm Hg respectively.

Discussion

Baroreflex sensitivity has demonstrated efficacy as a parameter for assessment of autonomic nervous system integrity. BRS assessment has value to a clinician, as impairment may have prognostic value in various disorders. Previous literature has shown impaired BRS to be related to prognosis in heart failure and myocardial infarction (14). Therefore BRS assessment can offer useful information both in health and disease.

The gold standard method for BRS assessment is pharmacological method which involves serial injections of phenylephrine and nitroprusside to bring about blood pressure increments and decrements. Simultaneous assessment of heart rate responses helps us quantify BRS. Other commonly used methods for BRS quantification are Sequence method, Head up tilt and Valsalva maneuver (1).

The common mechanism operant in Head up tilt, Valsalva maneuver and Lower Body Negative pressure

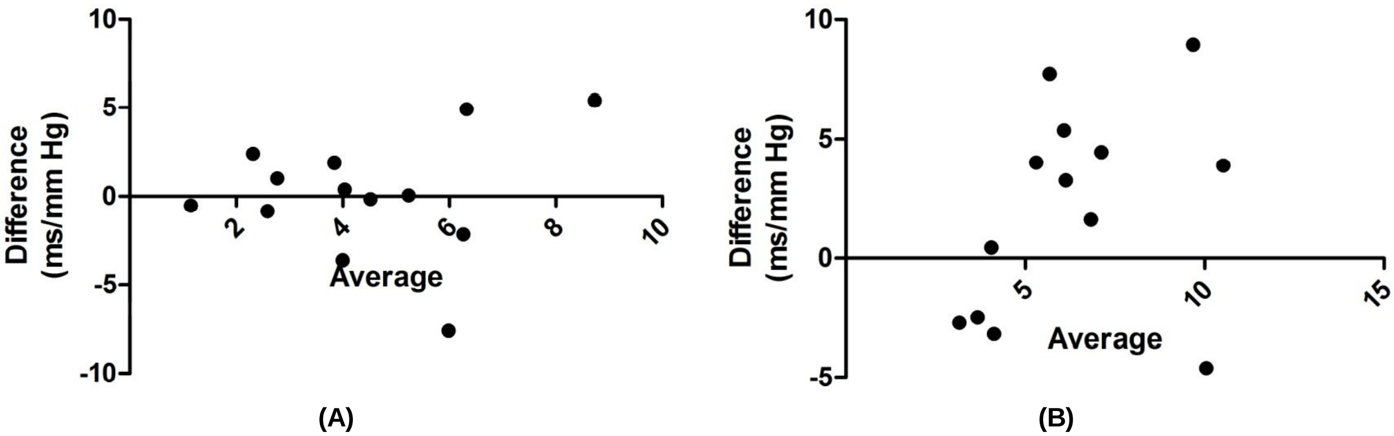

Fig. 4 : Bland Altman agreement analysis between BRS derived from Valsalva maneuver and LBNP.
Above figures show Bland Altman agreement analysis between dLBNP and Phase IIVM (A) and pLBNP and Phase IVVM (B). The mean bias in (A) and (B) are 0.094 and 2.064 ms/mm Hg respectively.

is preload reduction. The reduced venous return to the heart engages compensatory baroreflex mediated changes to maintain cardiovascular homeostasis. Valsalva maneuver has been regularly employed in autonomic function assessment as a strategy for preload reduction and baroreflex sensitivity assessment. The maneuver can be divided into 4 different phases based on the hemodynamic profile (15, 16). Phase II and IV of the maneuver lead to active engagement of the baroreflex and therefore have been used for BRS estimation in literature (17). Our BRS values (PhaseIIVM and Phase IVVM) show good agreement with previously described values (10, 17, 18). Though we observed 'flat top' responses in some subjects (n=5), the same has been described as a normal variant of Valsalva maneuver and is observed in healthy subjects performing VM in supine position (18,19).

We observed that BRS values for Phase IIVM and dLBNP and Phase IVVM and pLBNP were statistically comparable. But since we also wanted to validate LBNP as a substitute to VM for BRS assessment, Bland Altman analysis was performed to evaluate the agreement and bias between BRS values. We observed considerable bias between BRS values derived using both maneuvers. The bias extended in both positive and negative directions. This supported the concept that VM and LBNP may not be substituted for each other for purpose of BRS assessment.

Another interesting observation in our study was that approximately one-third of our subject population did not show typical hypotensive response to LBNP suction of -40 mm Hg for 15 seconds duration. This observation may be attributed to the following reasons. Previously authors used LBNP suction of -40 mm Hg for 30 seconds with seal at the level of lower border of xiphisternum (5). But we used the seal location at the level of iliac crests, in accordance with recommendations in previous literature (2). It has been suggested seal at level of xiphisternum may create severe hemodynamic alterations and may impede with diaphragm movement interfering with respiration (20). Therefore we preferred seal around iliac crest in our study. Seal around iliac crests spares the highly compliant splanchnic and renal vascular beds. Also, we applied suction for duration of 15 seconds to ensure comparability of VM and LBNP on a temporal scale. This shorter duration of suction along with sparing of splanchnic and renal vascular beds may be responsible for the absence of hypotensive response to LBNP in a subset of our study population.

Our study has several novelty factors. Though LBNP has been used widely for study of cardiovascular and hemodynamic regulatory mechanisms, we came across only few reports of BRS evaluation using LBNP. BRS evaluation has been done in these reports by sequence method (21) or frequency domain approach (22) using LBNP application for prolonged durations. Ours is the first study to report BRS using blood pressure oscillations produced by LBNP leading directly to baroreflex engagement. In addition to the above novelty, our data investigated the previous notion of LBNP being a substitute for VM, especially with respect to BRS estimation. LBNP is a passive suction on the lower half of the body while VM involves active patient effort. Active volition by the subject is likely to engage central command. As pointed out previously (5), interaction between neural centers due to inherent active subject effort may influence the end response. Also concomitant activation of mechanoreceptors and thoracic stretch receptors (23) is likely to have a bearing on the overall hemodynamic response. Therefore, while it is true that preload reduction is the common mechanism underlying baroreflex activation in VM and LBNP, concurrent engagement of above mentioned physiological factors may be probable reason for the bias between BRS values between VM and LBNP. So, we may infer that LBNP and VM may not be interchangeably used when assessing baroreflex function.

There are few limitations to our study. A larger sample size with subjects across the age spectra may yield more insight into the differences between VM and LBNP. We chose a safe suction limit of -40 mm Hg to avoid any syncopal episodes in our subjects. Also we included only male subjects as there are contradictory reports of the effect of menstrual cycle phases on BRS (24,25).

Conclusion

Our study serves as a pilot investigation for using LBNP to produce blood pressure perturbations to engage the baroreflex. The use of LBNP may be extended to patient groups, especially those with baroreflex impairment, to establish its utility as a technique for autonomic and baroreflex assessment. We compared baroreflex sensitivity as assessed by Valsalva maneuver and Lower body negative pressure and observed that though both maneuvers are similar from a preload reduction standpoint, they are essentially different with respect to engagement of other reflex mechanisms. Therefore, the exchangeable use of the techniques from a baroreflex sensitivity evaluation standpoint may not be plausible. Further investigations into these maneuvers may help us differentiate them with respect to underlying regulatory mechanisms.

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Conflict of Interest

The authors declare that no conflict of interest, financial or otherwise, exists.

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