Research Article

Test-retest reliability of the Valsalva maneuver in spinal cord injury

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Objective: To determine the test-retest reliability of quantitative and qualitative baroreflex sensitivity (BRS) parameters derived from the Valsalva maneuver (VM) in individuals with traumatic cervical SCI.
Design: Test-retest reliability.
Setting: Tertiary rehabilitation center.
Participants: Fourteen participants with cervical SCI (ranging from C3-C8 neurological level).
Outcome Measurements: Beat-to-beat systolic blood pressure (SBP) traces (finger photoplethysmography) were obtained during a 15-second forced expiration at two time points (7.6 ± 2.9 days between sessions) to assess VM reliability. Test-retest reliability of BRS metrics from derived from the VM (Valsalva ratio; VR, pressure recovery time; PRT, vagal baroreflex sensitivity; BRSv, adrenergic baroreflex sensitivity; $BRSa_1$, and total recovery; TR) were assessed by intra-class correlation coefficient (ICC, with 95% confidence interval; CI) and by qualitative reproducibility (V, N, or M pattern).
Results: ICCs for quantitative parameters were (CI): VR = 0.894 (0.703–0.965), TR = 0.927 (0.789–0.976), $BRSa_1$ = 0.561 (0.149–0.911), PRT = 0.728 (0.343–0.904), BRSv = 0.243 (−0.309–0.673). Qualitatively, 12 subjects (85.7%) demonstrated reproducible VM patterns at both time points (3 "M" pattern, 8 "V" pattern and one "N" pattern).
Conclusion: VR (a measure of cardiovagal function) and TR (a measure of sympathetic adrenergic function) are reliable quantitative parameters that can be derived from SBP response to VM in participants with SCI. Qualitative waveform analysis was reproducible in 12/14 participants. This provides the foundational evidence required to pursue further validity testing to establish a role for VM in the assessment of autonomic functions in SCI.

Keywords: Spinal cord injury, Baroreflex sensitivity, Valsalva maneuver, Test-retest reliability

Introduction

Autonomic dysfunction is a common and debilitating consequence of spinal cord injury (SCI).[1] In particular, autonomic cardiovascular control is critical in order to prevent syncope during orthostatic challenges such as sitting upright and standing.[2,3] In individuals with spinal cord lesions at or above T6, the capacity to regulate vascular tone via vasoconstriction can be impaired due to reduced sympathetic outflow to the splanchnic vascular bed resulting in orthostatic hypotension (OH), or in some cases, autonomic dysreflexia (AD).[4–6] Therefore, accurately assessing autonomic function in patients with SCI is of significant clinical importance. However, the complexity of the autonomic nervous system makes clinical assessment of autonomic function challenging. As such, there are no widely accepted methods for clinical measurement of autonomic functions in these patients.[7]

A complex and multi-factorial negative feedback system called the baroreflex is responsible for maintaining stable blood pressure (BP) through modification of heart rate (HR) and total peripheral resistance in response to BP perturbations.[8] This system employs both the sympathetic and parasympathetic autonomic divisions to maintain BP within a narrow range during changes in environmental condition or body position.[9]

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The baroreflex is impaired in many autonomic disorders, including in SCI.[10] Impaired arterial baroreflex sensitivity (BRS) is strongly linked to the development of life-threatening arrhythmias and increased cardiac morbidity and mortality in a variety of cardiovascular diseases.[3,11]

Consequently, comprehensive autonomic assessments are important for determining the function of the autonomic nervous system in different clinical settings. A simple non-invasive approach for assessing BRS, and in turn the autonomic nervous system, is the Valsalva maneuver (VM).[9] The VM provokes large perturbations in blood pressure due to increases in intrathoracic pressure (and reduced venous return) following forced expiration against a closed glottis. It also provides quantitative and qualitative analyses of central autonomic regulation of non-postural arterial BP changes during breathing activity and has been used to diagnose orthostatic intolerance in other disease conditions.[12] Of further importance, is the ability of the VM to detect orthostatic intolerance while supine, which is an important logistical consideration in non-ambulatory populations such as SCI. Our group previously demonstrated the utility of the VM in diagnosing both cardiovagal and sympathetic adrenergic dysfunction in patients with SCI, as part of the clinical autonomic battery.[5]

The reliability of cardiovascular responses to the VM, including measures of cardiovagal and sympathetic adrenergic function, have been previously established.[13] While some components of the VM have been shown to provide acceptable reproducibility for BRS assessment,[13] there have been no studies on the reliability of the VM in SCI. Accordingly, in this study we assessed the test-retest reliability of BRS parameters obtained from HR and BP responses to VM in individuals with traumatic SCI and lesions above T6. We also performed qualitative assessment of the BP responses to VM based on tracings obtained from participants, as this has been shown previously to provide immediate clinical feedback regarding BRS functions.[12] Determining the reliability of VM parameters is an important step in validating this technique for bedside autonomic assessment in SCI.

Methods

Participants

We recruited 14 individuals (13 males and 1 female; 41.9 ± 15.5 years of age; C3-C8 neurological level) with traumatic, cervical SCI from a single tertiary rehabilitation center. Neurological level of injury was determined according to the International Standards for Neurologic Classification of spinal cord injury documented in the patients' hospital chart (performed by the attending physiatrist on the ward at the time of patient admission to inpatient rehabilitation). Only patients with recent (within 3–6 months) traumatic injuries at or above the level of T6 were included in the study. Patients were excluded if they had a tracheostomy, history of cardiopulmonary disease, severe cognitive dysfunction, or any unstable medical or psychiatric condition. Ethical approval for the study was obtained from the local institutional review committee. Written consent was obtained from each participant prior to commencing the study.

Valsalva maneuver

BP response to VM was measured as described previously.[5] All tests were conducted in the morning, prior to medication administration and food ingestion. Single-lead electrocardiography (ECG; ML 132; ADInstruments, CO Springs, CO), with electrodes over the anterior deltoids and left flank, was used to measure HR. Beat-to-beat BP recordings were obtained using finger cuff photoplethysmography (Finometer PRO, Finapres Medicine Systems, Amsterdam, Netherlands) with the cuff positioned around the distal phalanx of the second or third digit. Brachial BP was measured with an automated arm cuff (Dinamap Pro 300 V2; GE Healthcare, Milwaukee, WI) to verify the measures from the finger cuff. SBP data was normalized to account for differences in baseline BP between testing days. All data were collected at a sampling rate of 1000 Hz, analog-to-digital converted and saved for analysis using data collection software (Powerlab/16SP ML 795 and LabChart 7; ADInstruments, CO Springs, CO). During the VM, subjects were instructed to inhale deeply, subsequently exhaling through a mouthpiece with an air leak to ensure their glottis would remain closed while maintaining a manometer dial at an expiatory pressure of 40 mm Hg for 15 s. This forced expiratory pressure was selected as Low advises that pressures >60 mm Hg and <20 mm Hg result in unreliable waveform analysis.[7] All participants obtained the target pressure, but the ability to steadily maintain the target pressure fluctuated between participants (observed, but not directly measured). Two testing sessions were done for each participant and in each session the VM was performed at least twice. Each VM during the test was followed by a rest period of two minutes. Participants were tested again at a mean test-retest interval of 7.6 ± 2.9 days to avoid learning bias. The VM data collection and analysis protocols were performed by the same evaluator for

each subject and the same protocol was applied each time. Forced expiratory capacity is impaired in SCI patients. In order to minimize the impact of forced expiratory pressure as a potential confounding variable when assessing BRS, the investigator chose the VM that was performed with the most consistent effort and that met the criteria outlined by Low[7] for an acceptable trial (~40 mmHg and minimally labile expiratory pressure) for analysis.

Quantitative analysis

Typical qualitative BP responses to a VM encompass four phases. The location and physiologic explanation of each phase is highlighted in Fig. 1. Inspecting the trace of the BP changes during the VM gives information regarding abnormalities in cardiovagal and adrenergic components of BRS. Quantitative parameters of the VM can be used as objective means of analyzing BRS.[2] The Valsalva ratio (VR) is known to be a measure of cardiovagal function during VM and is calculated as the maximum HR generated during the maneuver divided by the minimum HR occurring in the 30 s following the release of the maneuver ($VR = HR_{max}/HR_{min}$).[7] There are many ways reported for calculating the sympathetic adrenergic components of the VM.[14] The most commonly reported method is adrenergic baroreflex sensitivity (BRS_a) and alternate BRS_a (BRS_{a1}), which are calculated from the sympathetic adrenergic components of the BP trace (phase II_L and phase IV overshoot respectively).[2,15,16] Due to the absence of phase II_L in many pathologic conditions, these waveforms are not amenable to conventional analysis of BRS_a.[12] As such, another fundamental component of BRS_a is pressure recovery time (PRT) defined as time in seconds from the valley of phase III/start of phase IV to the return of phase IV to baseline.[17] $BRSa_1$ was defined as the SBP decrement divided by PRT [$BRSa_1 = (A + 0.75xB)/PRT$]. Cardiovagal baroreflex sensitivity (BRSv) was determined as the slope of regression of the R-R interval in milliseconds over SBP during early phase II $\left[\sum (x - \bar{x}) \times (y - \bar{y}) / \sum^{(x-\bar{x})} 2\right]$ (16). Novak examined the ability of several sympathetic indices derived from VM to detect differences between groups with no, mild, moderate and severe sympathetic adrenergic dysfunction (as determined by a battery of autonomic tests) (18). It was determined that the parameter most reflective of clinical dysautonomia was "Total Recovery" (TR), representing the relative change in SBP from baseline to the end of Phase II. Therefore, in addition to calculating conventional BRS_a, reliability parameters for TR are also presented. In order to control for variability in absolute resting blood pressure between testing sessions, TR was normalized to the pretest minimum SBP value for each test.

Qualitative analysis

The shape of the VM is closely related to indices of adrenergic function derived from phase II_L[15] and offers qualitative feedback regarding autonomic function.[12] Qualitative analysis of the VM has been previously described[12] and pertains to the shape of the SBP waveform in the context of presence versus absence of expected phases. A "V" pattern is indicative of

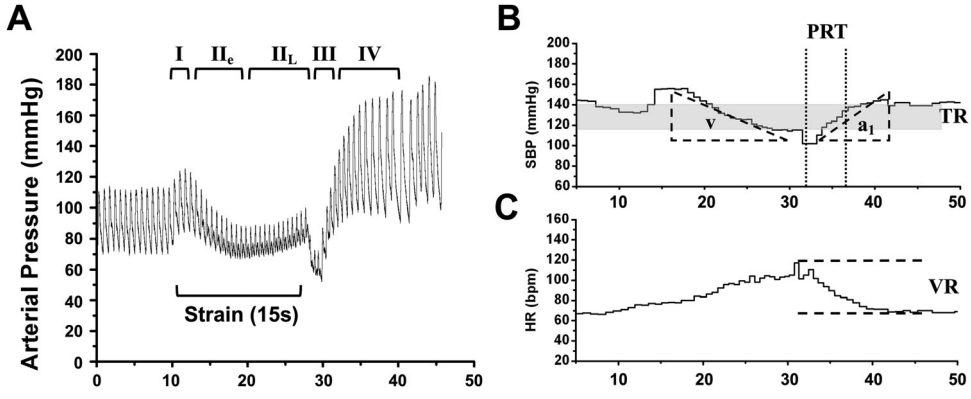

Figure 1 (A) Representative VM trace from one participant with an "N" shaped VM outlining the four phases of the VM. Phase I starting after onset of 15 s strain due to an increase in intrathoracic pressure. Early phase II_e modulated by vagal activation. Late phase II_L modulated by adrenergic activation from diminished venous return. Phase III representing the decrease in intrathoracic pressure upon exhalation and release of the maneuver. Phase IV indicates BP overshoot modulated by sustained vasoconstrictor response. Representative schematic of typical metrics derived from SBP (B) and HR (C) values during the VM. BRSv (v) indicates cardiovagal baroreflex sensitivity. Pressure Recovery Time (PRT) is the time from end of phase III to baseline during phase IV. $BRSa_1$ (a_1) indicates adrenergic baroreflex sensitivity. Total Recovery (TR) is the change in SBP from baseline to the end of phase II_L. Valsalva Ratio (VR) is the change in HR from peak back to baseline and is indicative of vagal modulation of HR.

impairment or absence of sympathetic adrenergic mediated phases II_L (syncline pattern of phase II_e, instead of a typical valley shape) and phase IV (delayed or absent with no typical overshoot of baseline SBP). An "M" pattern is defined by the typical sympathetic adrenergic mediated increments in SBP during phase II_L and phase IV. Although Palamarchuk *et al.*[12] described this pattern as pathologic in participants with exaggerated responses due to sinus tachycardia syndrome, we use the "M" descriptor to denote the presence of all expected phases of the SBP response VM. An "N" pattern is indicative of a prolonged overshoot of baseline SBP during phase IV, possibly secondary to heightened adrenergic activity below the level of SCI. Representative figures are presented in the results section.

Statistical analysis

Test-retest reliability was assessed using a Model 2 (two-way random, consistency) single measure intra-class correlation coefficient (ICC; SPSS® Statistics 20, SPSS, Inc, Hong Kong).[18] Test-retest reliability was defined as poor (<0.5), moderate (0.5–0.75) and good (>0.75).[19] 95% confidence intervals (CI) are presented to estimate the ICC range.

Results

Test-retest reliability results for each parameter are presented in Table 1. Quantitative parameters displayed variable test-retest reliability. TR as a measure of the change in SBP from baseline to the end of phase II was the most reliable quantitative parameter with narrow range (ICC = 0.927; CI: 0.789–0.976). VR as a measure of cardiovagal activity was similarly reliable (ICC = 0.894; CI: 0.703–0.965). PRT as a measure of sympathetic adrenergic mediated normalization of SBP demonstrated moderate reliability (ICC = 0.728; CI: 0.343–0.904), in comparison to the more simply calculated TR. Although $BRSa_1$ demonstrated a moderate ICC according to our *a priori* definition (0.561), wide CIs (0.149–0.911) preclude it from being a reliable measure in the present context. BRSv demonstrated negligible reliability with low ICC (0.243) and wide CIs (−0.309–0.673).

Table 1 Intra-rater reliability of Valsalva maneuver parameters.

	Test 1 ± SD (Min-Max)	Test 2 ± SD (Min-Max)	ICC	95% CI
VR	1.56 ± 0.43 (1.16–2.89)	1.47 ± 0.34 (1.21–2.30)	0.894	0.703–0.965
PRT (s)	11.92 ± 9.29 (0.89–34.00)	11.18 ± 8.71 (0.60–27.00)	0.728	0.343–0.904
$BRSa_1$ (mmHg/s)	9.68 ± 11.14 (1.84–39.12)	12.60 ± 15.21 (1.30–43.75)	0.561	0.149–0.911
BRSv (ms/mmHg)	2.68 ± 1.87 (0.14–7.33)	2.67 ± 1.72 (0.14–5.90)	0.243	−0.309–0.673
TR	0.76 ± 0.59 (2.26 − −0.04)	0.62 ± 0.60 (1.89 − −0.07)	0.927	0.789–0.976

Note: SD: standard deviation.

In terms of qualitative reliability, three subjects (21%) demonstrated an "M" pattern at both time points. Eight subjects (57%) demonstrate a "V" pattern at both time points. One subject demonstrated an "N" pattern. One subject demonstrated a "V" pattern for the first visit and an "M" pattern for the second visit, while another subject demonstrated a "V" pattern for the first visit and an "N" pattern for the second visit. Figure 2 illustrates an example of the test-retest reliability traces for participants with an "M", "N" and "V" pattern, using SBP traces.

Discussion

The present study aimed to assess the test-retest reliability of the VM in individuals with cervical SCI. To our knowledge, this is the first study to provide an assessment of test-retest reliability for BRS derived from the VM in patients with SCI. We found that VR and TR demonstrated good reliability. Furthermore, qualitative assessment of the VM waveform showed a high degree of reproducibility between testing days. Our novel findings demonstrate that certain aspects of the VM can be used as a reliable, non-invasive tool for the assessment of BRS and autonomic function in this population.

Previous work by Novak[14] suggests that TR is the optimal method for calculation of global sympathetic index and allows for easy and reliable differentiation of individuals with worsening sympathetic failure. Our study showed that overall TR had the best reliability (ICC = 0.93) of the parameters assessed. Additionally, VR also demonstrated good reliability in SCI (ICC = 0.89), which aligns with reproducibility data for VR presented by Palamarchuck *et al.* in healthy populations (ICC = 0.87).[13] These results suggest that BRS parameters associated with phases II_L and III are more reliable than those associated with phase IV or phase II_e (PRT, $BRSa_1$, and BRSv). This is likely due to the strong relationship between sympathetic vasomotor activation, as measured by muscle sympathetic nerve activity (MSNA), and changes in BP during phase II_L.[19] In support of this notion, individuals with autonomic failure have a strong linear relationship between the MSNA response to phase II_e and the change in

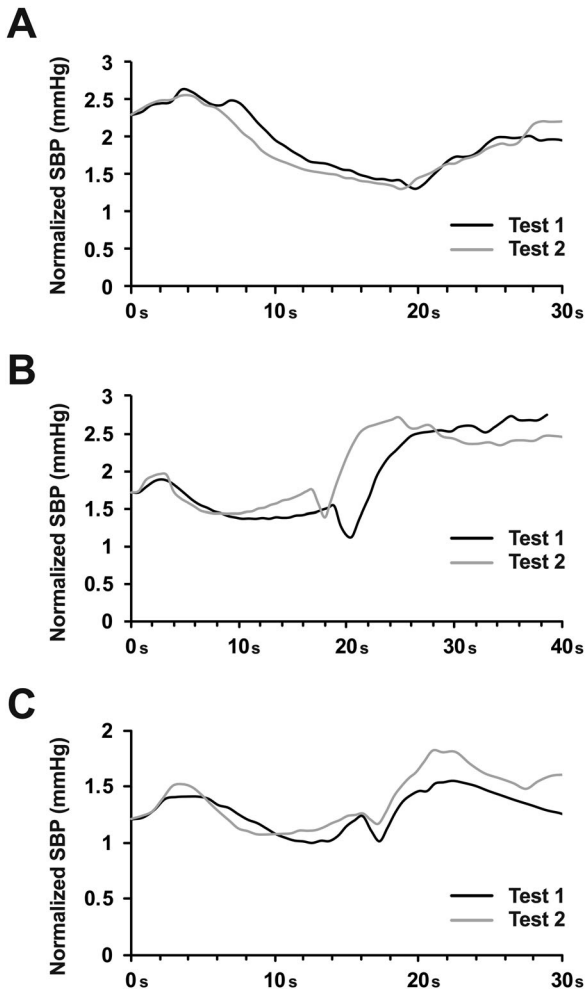

Figure 2 Representative test-retest reliability traces of qualitative hemodynamic responses to VM. (A) displays a "V" pattern, (B) an "N" pattern and (C) an "M" pattern. A "V" pattern is indicative of impairment or absence of sympathetic adrenergic mediated phases II_L (syncline pattern of phase II_e, instead of a typical valley shape) and phase IV (delayed or absent with no typical overshoot of baseline SBP). An "M" pattern is defined by the typical sympathetic adrenergic mediated increments in SBP during phase II_L and phase IV. Although Palamarchuk *et al.*[12] described this pattern as pathologic in participants with exaggerated responses due to sinus tachycardia syndrome, we use the "M" descriptor to denote the presence of all expected phases of the SBP response VM. An "N" pattern is indicative of a prolonged overshoot of baseline SBP during phase IV, possibly secondary to heightened adrenergic activity below the level of SCI.

SBP during phase II_L. Those with autonomic failure have lower MSNA during phase II_e and as such have large sustained drops in BP during phase II_L.[20,21] Alternatively, VR is representative of vagal restoration of HR to baseline levels following the release of the VM. Interestingly, we have previously shown that VR is lower in patients with SCI compared to healthy controls.[5] This evidence suggests that even though VR is easily reproducible due to the direct action of the vagus nerve on HR, overall cardiovagal function is impaired in SCI. The mechanisms for this dysfunction have not been elucidated and this is still a matter of debate in the literature.[22] Aside from their high degree of reproducibility, TR and VR have the added benefit of being easy to calculate. This allows clinicians the ability for rapid quantification and interpretation of autonomic function without the need for lengthy calculations.

Other phases of the VM are not only dependent on autonomic regulation of the vasculature (which elicit repeatable responses) but have a significant dependence on mechanical factors such as the degree of superior and inferior vena cava occlusion, sufficient intrathoracic pressure generation, or blood volume levels that can vary between trials or testing days. Particularly, our study showed that BRSv demonstrated poor reliability (ICC = 0.24) in SCI compared to Palamarchuck and colleagues' findings in healthy individuals.[13] BRSv is calculated from phase II_e and represents cardiovascular adaptation due to reductions in venous return and cardiac output. As such, BRSv represents not only adaptations in autonomic tone, but also mechanical factors. While participants were told to maintain an expiratory pressure of 40 mmHg, the consistency of pressure generation may contribute to the poor reliability of BRSv. Previous studies have shown that SCI patients (particularly those with cervical SCI) demonstrate reduced capability to generate and maintain expiratory pressure during the VM due to impaired regulation of accessory expiratory muscles.[24]

PRT, and $BRSa_1$ both demonstrated moderate reliability in our SCI population which is in accordance with the reliability observed in healthy subjects.[13] Both PRT and $BRSa_1$ are derived from components phase IV of the VM which is due to persistent vasoconstriction that begins during phase II. Individuals with SCI demonstrate longer PRT and a less steep increase in phase IV indicative of adrenergic failure. The moderate reliability of these parameters may depend on a number of factors such as vascular reactivity to autonomic signaling, restoration of venous return, or sympathetic instability.[22] Sympathetic instability is likely the most notable contributor in SCI patients. Variability in descending sympathetic drive and thus the adrenergic components of the VM could depend on the completeness of the injury. However, larger scale studies at various neurological levels would be required to assess this aspect.

Our second aim was to assess the reliability of qualitative assessments of the VM.

We found that majority of patients (86%) had a qualitatively reproducible VM between testing sessions. The majority of the participants (57%) displayed a "V" pattern following SCI characterized by a steep drop in SBP during phase II and prolonged PRT. In autonomic diseases such as neurogenic orthostatic hypotension, the "V" pattern provides a repeatable qualitative method to diagnose autonomic failure.[12] Only adrenergic failure/insufficiency contributes to both the absence/reduction of phase II_L and prolonged PRT. As such, patterning of the VM waveform can be a valuable tool for identifying sympathetic failure in SCI patients, as we have previously reported.[5] Few participants demonstrated the "M" pattern, representing intact sympathetic adrenergic function. This further underscores the usefulness of the VM in measuring autonomic function after SCI, as the prevalence and magnitude of autonomic dysfunction in SCI is variable and only partially corresponds to lesion level and severity.[5] Only two participants displayed different patterns between the first and second visit. Interestingly, one patient exhibited a sustained overshoot in phase IV and was classified as an "N" pattern. This could be due to β-adrenergic hyperactivity below the level of injury resulting in autonomic dysreflexia.[12] Although our results for qualitative analysis are interesting and suggest that significant information regarding sympathetic adrenergic function can be observed, we cannot say that waveforms alone are reproducible enough between tests, given that two participants demonstrated waveform variability. Further studies are needed to substantiate the reproducibility of these waveforms in response to common perturbations affecting SCI participants, including medications changes, acute illness (e.g. urinary tract infections) and bouts of autonomic dysreflexia.

Limitations

While our study provides good rationale for the reliability of some parameters for VM in SCI, it is not without its limitations. The present study was conducted in a relatively small sample size leading to large standard deviations in our quantitative BRS parameters. However, previous studies have used similar sample sizes to assess the reliability of BRS using a variety of techniques including the VM.[13] Thus, our sample size of 14 is likely sufficient to address the reliability of the BRS parameters assessed. Additionally, it is also likely that the large standard deviations in our quantitative BRS parameters is due to variability in descending sympathetic drive between participants. This may depend on the extent of damage to sympathetic networks in these individuals and warrants further investigation. As follows from this, our study sample contains bias which may have influenced out results. First, although the inclusion criteria called for participants with injuries T6 and above, our sample reflects the responses of only those with cervical level injuries. It is possible that participants with more caudal injuries would be better able to recruit accessory muscles of breathing, which could alter hemodynamic responses (particularly parameters dependent on intrathoracic pressure dynamics), however the present sample does not allow us to test this hypothesis. Second, participants were heavily biased toward male sex and it is unknown whether sex differences exist in response to VM in SCI, although it has previously been shown that VR is not different between sexes across the life spectrum[20,21] and to our knowledge there is no plausible mechanism as to why responses would be different between sexes.

A second limitation is that VM depends extensively on the amount of effort the participant puts into forced expiration. All participants were able to maintain forced expiration of 15 s, although the ability to sustain 40 mmHg was variable. To mitigate this as a confounding factor we asked the participants to repeat the VM at least twice and chose the best attempt for analysis purposes. The ability to achieve and sustain a pressure of 40 mmHg is required to occlude venous return to a sufficient extent to facilitate VM.[23] While the degree of intrathoracic pressure may affect some quantitative parameters of the VM, all of our participants had notable changes in BP during the VM suggesting that a sufficient pressure was maintained throughout the maneuver. As discussed earlier, some phases of the VM are tightly linked to autonomic function, while other phases are developed from a combination of mechanical and autonomic factors. Furthermore, Legg *et al.*[24] measured VM responses to a conventional VM versus a shorter forced expiratory maneuver in participants with SCI and found that the shorter maneuver produced similar results to a longer VM.[24] Last, the trial chosen for analysis was at the discretion of a single author (HN) and we did not specifically test the interrater reliability of our analyses.

A further limitation of the current design is that participants completed testing before medication administration, including medication that regulates autonomic control of BP (e.g. midodrine and fludrocortisone). It would be interesting to determine

whether reliability of responses (particularly the unreliable BRS_a and BRS_v) is affected by commonly prescribed medications and this is a logical extension of our findings for future studies focused more on the validity of the VM.

Our results also have implications to the clinical applicability of VM. Although VM is easily administered at the bedside and non-invasive (as long as specialized equipment is available), quantitative analysis would likely necessitate waveform analysis by experienced clinicians or technicians, thus precluding *ad hoc* use by a general SCI clinician.

Conclusion

In conclusion, we demonstrate that VR and TR demonstrate good reliability. While TR has been used in previous studies to stratify individuals with varying degrees of autonomic failure, it has not been widely used for the screening of SCI patients. As such, assessment of autonomic function using TR in SCI could be included in future studies. Additionally, we showed that the identification of "V", "M", and "N" patterns from the VM waveform provided a reproducible method in the evaluation of autonomic function in SCI, in most participants, but likely requires further refinement and characterization in multiple contexts (e.g. response to medications, environmental perturbations etc.), before recommending it for routine clinical use. Collectively, our results suggest that some aspects of the VM can provide reliable information regarding autonomic function in individuals with SCI. Using the VM as a tool for the bedside assessment of autonomic dysfunction may enhance understanding regarding the completeness injury to autonomic circuits within the spinal cord following SCI.

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Conflicts of interest Authors have no conflict of interests to declare.

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