Perturbed and spontaneous regional cerebral blood flow responses to changes in blood pressure after high-level spinal cord injury: the effect of midodrine

Aaron A. Phillips, Andrei V. Krassioukov, Philip N. Ainslie, and Darren E. R. Warburton

1Cardiovascular Physiology and Rehabilitation Laboratory, Physical Activity Promotion and Chronic Disease Prevention Unit, University of British Columbia, Vancouver, British Columbia, Canada; 2Experimental Medicine Program, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; 3International Collaboration of Repair Discoveries, University of British Columbia, Vancouver, British Columbia, Canada; and 4School of Health and Exercise Sciences, Faculty of Health and Social Development, University of British Columbia Okanagan, Kelowna, British Columbia, Canada

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Phillips AA, Krassioukov AV, Ainslie PN, Warburton DE. Perturbed and spontaneous regional cerebral blood flow responses to changes in blood pressure after high-level spinal cord injury: the effect of midodrine. J Appl Physiol 116: 645–653, 2014. First published January 16, 2014; doi:10.1152/japplphysiol.01090.2013.—Individuals with spinal cord injury (SCI) above the T6 spinal segment suffer from orthostatic intolerance. How cerebral blood flow (CBF) responds to orthostatic challenges in SCI is poorly understood. Furthermore, it is unclear how interventions meant to improve orthostatic tolerance in SCI influence CBF. This study aimed to examine 1) the acute regional CBF responses to rapid changes in blood pressure (BP) during orthostatic stress in individuals with SCI and able-bodied (AB) individuals; and 2) the effect of midodrine (alpha1-agonist) on orthostatic tolerance and CBF regulation in SCI. Ten individuals with SCI >T6, and 10 age- and sex-matched AB controls had beat-by-beat BP and mid and posterior cerebral artery blood velocity (MCAv, PCAv, respectively) recorded during a progressive tilt-test to quantify the acute CBF response and orthostatic tolerance. Dynamic MCAv and PCAv to BP relationships were evaluated continuously in the time domain and frequency domain (via transfer function analysis). The SCI group was tested again after administration of 10 mg midodrine to elevate BP. Coherence (i.e., linearity) was elevated in SCI between BP-MCAv and BP-PCAv by 35% and 22%, respectively, compared with AB, whereas SCI BP-PCAv gain (i.e., magnitudinal relationship) was reduced 30% compared with AB (all P < 0.05). The acute (i.e., 0–30 s after tilt) MCAv and PCAv responses were similar between groups. In individuals with SCI, midodrine led to improved PCAv responses 30–60 s following tilt (10 ± 3% vs. 4 ± 2% decline; P < 0.05), and a 59% improvement in orthostatic tolerance (P < 0.01). The vertebrobasilar region may be particularly susceptible to hypoperfusion in SCI, leading to increased orthostatic intolerance.

Cerebral autoregulation; orthostatic tolerance; alpha-1 agonist

SPINAL CORD INJURY (SCI) is a devastating chronic condition that results in not only motor and sensory deficits, but also autonomic dysfunction (22). As a consequence of decentralization of sympathetic fibers, those with SCI suffer from low resting blood pressure (BP) and episodes of severe hypotension when moving to an upright position (orthostatic hypotension) (8). Orthostatic hypotension has been shown to be an important independent risk factor for the development of stroke in able-bodied (AB) individuals (10), and stroke is two to three times more likely in those with SCI (51).

A fundamental property of cerebral vessels is their capacity to locally regulate cerebral blood flow (CBF). Effective cerebral autoregulation (CA) to buffer changes in BP requires an integrated response from myogenic, neurogenic, metabolic, and systemic factors (46). Brief disruptions in CBF caused by impaired BP control during orthostatic hypotension may cause irreversible neuronal cell death (2, 11). Consequently, poor BP control in individuals with SCI makes appropriate regulation of CBF crucial for preventing stroke.

A number of studies have examined static CA [i.e., the ability to maintain CBF during a range of steady-state (0 Hz) BPs] in those with SCI, and there is consistent evidence that static CA is preserved in this population [reviewed in (33)]. In contrast, the dynamic relationship between BP and CBF has been examined only in two studies (37, 49). Both static and dynamic CA are believed to be regulated by a combination of myogenic, metabolic, and neurogenic control mechanisms [for review see (32)]; however, static and dynamic CA may rely on relatively different influences from various regulatory factors (9). For example, it has been suggested that neural control more heavily influences dynamic CA as opposed to static CA (9), whereas endothelial (i.e., nitric oxide) dependence has been shown not to influence dynamic or static CA (52). The two studies on dynamic CA in individuals with SCI reported only spontaneous analyses of cerebral pressure-flow relationships (37, 49), which may not reflect how the cerebrovasculature responds to rapid perturbations in BP (30, 40, 41). In addition, the relationship between CBF and BP in a hemodynamically stable, closed-loop situation is unlikely to simulate the drastic reductions in cerebral perfusion pressure that occur during orthostatic challenges (40). In both these studies (37, 49), only metrics from the middle cerebral artery (MCA) were reported as opposed to arteries of the vertebrobasilar system; arteries that may be more related to orthostatic tolerance as it perfuses the medulla oblongata, which contains associated autonomic control centers and discrete regions responsible for consciousness (39). Furthermore, several studies have recently shown that the internal carotid/MCA region is differentially sensitive to orthostatic challenges compared with the vertebral/posterior cerebral artery (PCA) region (3, 38, 47, 48).

Midodrine, an alpha1 adrenoreceptor agonist, is used as a first line of defense to improve orthostatic tolerance in those with acute SCI (23). Although a 10-mg dose of midodrine has been shown to mitigate orthostatic hypotension in SCI, its

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influence on CBF is unclear (44, 45). One study reported no change in supine CBF velocity of the MCA (MCAv) after midodrine administration in individuals with SCI; however, reductions in MCAv during an orthostatic challenge were attenuated (45). In a follow-up study from that research group, MCAv was increased at baseline, and was not changed during an orthostatic challenge (44). Both of these studies, however, examined the relationship between MCAv in a homeostatic/steady-state situation (i.e., 0 Hz), and these findings are likely to be clarified and enhanced by an evaluation of the dynamic relationship between BP and CBF both at rest and during orthostatic stress. Furthermore, these studies used only self-reported symptoms of presyncope, and did not report any statistical analysis between trials (i.e., midodrine vs. no midodrine) (44, 45).

This study had four main objectives. The first was to compare static and dynamic regional CBF responses to orthostasis in SCI and AB individuals. The second was to evaluate how midodrine influences the static and dynamic regional CBF responses to orthostasis in SCI. The third objective was to evaluate orthostatic tolerance in individuals with SCI before and after midodrine. The final objective was to evaluate the relationship between dynamic systemic BP regulation and the cerebral pressure-flow relationship in individuals with SCI. We hypothesized that 1) static and dynamic CA in those with SCI would be preserved in both the MCA and PCA; 2) midodrine would not influence static CA but would partially normalize dynamic cerebral pressure-flow metrics to values reported in AB; 3) orthostatic tolerance would be improved after midodrine administration; and 4) dynamic cerebral pressure-flow relationships would be uncoupled from cardiac baroreflex function in individuals with SCI.

METHODS

Ten individuals with SCI participated in this study (C4–T5; American Spinal Cord Injury Association impairment scale A and B; Table 1). Eight participants were <1 yr postinjury; two were >1 yr postinjury (Table 1). All participants were referred for autonomic testing due to clinical observations. The control group consisted of 10 age- and sex-matched AB individuals. All testing took place at GF Strong Rehabilitation Centre, Vancouver, BC, Canada. Participant characteristics are presented in Tables 1 and 2. All participants were instructed to abstain from exercise and alcohol for 24 h before testing. No caffeine was permitted the day of testing. Additionally, participants abstained from all other medications on the day of testing, and had a small meal (e.g., a small yogurt) approximately 1 h before testing. Those who were smokers or had any history of cardiovascular disease were excluded from participation. All participants provided written informed consent in accord with the Clinical Research Ethics Board at the University of British Columbia, which approved this study.

Participants were tested over 2 days. Each testing day was separated by at least 48 h and took place between 10:00 a.m. and 12:00 pm. The testing days were identical except for the administration of 10 mg midodrine on one of the days. The order of days (i.e., whether baseline or midodrine trial went first) was randomized. On the midodrine day, a 10-mg oral dose was administered. Data from the SCI-with-midodrine group are referred to as SCImido, whereas data from the SCI-without-midodrine group are referred to as SCI. Midodrine is converted to the pharmacologically active metabolite desglymidodrine, which has a half-life of approximately 3 h (15). The setup for postmidodrine testing was initiated precisely 45 min after midodrine administration (Fig. 1A) to conduct physiological assessments at the time of peak response, which is approximately 1 h after ingestion (50). A 10-mg dose was chosen because it has been shown to elicit the greatest improvements in orthostatic hypotension and symptoms of orthostatic intolerance, with no additional side effects than a 5-mg dose (50). Participants rested quietly in the supine position for 15 min prior to initiation of testing.

Protocol

Participants were transferred to the tilt table and rested supine for 15 min while baseline hemodynamic data were recorded (Fig. 1B). Participants were progressively tilted from supine to 30°, 45°, and 60°. Five minutes of continuous data were collected at each tilt level, and participants were instructed to keep their eyes open throughout the test. Transition between tilt levels was achieved in less than 5 s. Participants were asked about the presence of presyncopal symptoms (i.e., dizziness, light-headedness, nausea) at the beginning, middle, and end of each stage. Participants were asked to rate their symptoms between 1 and 10 (with 5 being slightly dizzy and 10 being about to lose consciousness or vomit), and were also instructed to notify the testing team if at any point their rank of symptoms became greater than 7/10. The stage and time (in seconds) at which each participant withdrew or was withdrawn from tilt were recorded. Orthostatic

<table>
<thead>
<tr>
<th>Participant</th>
<th>SCI level</th>
<th>DOI, duration of injury, in weeks; AIS, American Spinal Injury Association impairment scale. *Postsecondary years.</th>
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<tbody>
<tr>
<td>1</td>
<td>T1</td>
<td>11 A</td>
</tr>
<tr>
<td>2</td>
<td>T1</td>
<td>324 A</td>
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<tr>
<td>3</td>
<td>C2</td>
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<td>8 A</td>
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<td>10</td>
<td>C2</td>
<td>11 A</td>
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</table>

Table 1. Individual demographic information for participants with spinal cord injury
<table>
<thead>
<tr>
<th>Participant</th>
<th>SCI level</th>
<th>DOI, duration of injury, in weeks; AIS, American Spinal Injury Association impairment scale. *Postsecondary years.</th>
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<td>1</td>
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<td>10</td>
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Table 2. Selected cardiovascular variables of study participants
<table>
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<th>Variable</th>
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<th>SCI</th>
<th>P</th>
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<tr>
<td>Age, yr</td>
<td>31 ± 11</td>
<td>29 ± 10</td>
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<tr>
<td>Mass, kg</td>
<td>71 ± 15</td>
<td>68 ± 14</td>
<td>0.57</td>
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<tr>
<td>BMI, kg·m⁻²</td>
<td>24.5 ± 3.5</td>
<td>22.6 ± 3.7</td>
<td>0.12</td>
</tr>
<tr>
<td>Education, years postsecondary</td>
<td>1.8 ± 2.1</td>
<td>2.3 ± 1.6</td>
<td>0.38</td>
</tr>
<tr>
<td>No. of women participants</td>
<td>3</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>TBI</td>
<td>0</td>
<td>1</td>
<td>NA</td>
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</tbody>
</table>

AB, able-bodied controls; n = 10; SCI, high-level spinal cord injury, n = 10; BMI, body mass index; TBI, traumatic brain injury; N/A, not applicable.
A tolerance index (OTi) was calculated by the formula \( \text{OTi} = \frac{[\text{Final tilt degree}]}{[\text{time (s) the last stage was tolerated}]} \).

### Data Acquisition

For each participant, brachial BP was measured (BpTRU-BP-100; Coquitlam, VSM Medical, Vancouver, BC, Canada) on the right arm at least two times at each stage of tilt. Beat-by-beat BP via finger photoplethysmography (Finometer PRO; Finapres Medicine Systems, Amsterdam, The Netherlands), heart rate (electrocardiogram ML 132; ADInstruments, Colorado Springs, CO), end-tidal carbon dioxide partial pressure (PetCO2) (17515 CO2 Analyzer Gold Edition; Vacu-Med, Ventura, CA), left MCAv and right PCAv blood flow velocity (PCAv) (Doppler-Box, Compumedics DWL, Singen, Germany) was measured. Using two 2-MHz probes mounted bilaterally on the temporal bones using a fitted head strap, the PI segment of the PCA was insonated at depths between 60–70 mm; the MCA was insonated at 45–55 mm. Arteries were confirmed using ipsilateral common carotid artery compression, ensuring an increase in PCA velocity and decrease in MCA velocity. All data were collected at 1,000 Hz using an analog-to-digital converter (PowerLab/16SP ML 795; ADInstruments) interfaced with data acquisition software (LabChart 7; ADInstruments) on a laptop computer. Finger photoplethysmograph signal was corrected to the brachial level.

### Data Analysis

Following 2 min of acclimation to the new tilt stage, 3 min of steady-state BP, heart rate, and PetCO2 were recorded. Systolic and diastolic BP (DBP), and peak MCAv/PCAv and minimum MCAv/PCAv were then extracted to generate mean steady-state values for the given stage. From these values, mean arterial pressure (MAP) as \( (2 \times \text{DBP} + \text{systolic BP})/3 \) and mean MCAv/PCAv as \( (2 \times \text{MCAv/PCAv minimum} + \text{MCAv/PCAv maximum})/3 \) were calculated. This also allowed for the calculation of cerebrovascular conductance (CVC) as mean MCAv/PCAv/MAP. To estimate myocardial work, rate pressure product was calculated as \( \text{heart rate} \times \text{systolic blood pressure} \).

**Time-domain pressure-flow relationships.** For evaluation of time-domain dynamic pressure-flow relationships during a clinically relevant orthostatic stimulus, acute changes in BP and CBF velocity (CBFv) for 15 s prior and 60 s after tilt were evaluated. The BP, MCAv, and PCAv responses occurring after each tilt stage were averaged for each participant. Not every tilt resulted in large decreases in BP in all participants. As such, to be included in the average response the tilt had to result in a decrease in MAP >15 mmHg over the first 30 s. All signals were visually inspected for artifacts or noise, and corrected by linear interpolation. CBFv signals were filtered by a low-pass filter with a cutoff frequency of 10 Hz (LabChart 7). All hemodynamic variables were sampled on a heart beat-by-beat basis (as detected by the electrocardiogram), whereas PetCO2 was sampled on a breath-by-breath basis (as detected by the peak of the first derivative of the PetCO2 waveform). All signals were then transferred to Excel software (Microsoft, Redmond, WA) with a custom-designed cubic spline interpolation package that allowed for resampling at 5 Hz. Mean CBFv and CVC were calculated according to the above formulas. After resampling, a mean response from the various orthostatic trials was generated for 60 s after tilt for each participant. Average and peak changes in CBFv and conductance of the MCA and PCA were recorded over the first 60 s of tilt. The 60 s was separated into two 30-s-long segments. The 30-s period immediately after tilt was also divided into six 5-s-long averages for analysis. It was not possible to insonate the PCA in one SCI participant. As such, steady-state and perturbed dynamic pressure-flow metrics for the PCA are limited to nine individuals.

**Transfer function analysis.** Using transfer function analysis, the dynamic relationships between spontaneous oscillations in BP and MCAv/PCAv were evaluated. Beat-by-beat R-R interval, MAP, and CBFv signals were resampled at 4 Hz and divided into five successive windows that overlapped by 50% and then passed through a Hanning window and were fast Fourier transformed (49). Briefly, the transfer function \( H(f) \) between the signals was calculated as \( H(f) = S_{xy}(f)/S_{xx}(f) \), where \( S_{xy}(f) \) denotes the cross-spectrum between the two signals, and \( S_{xx}(f) \) is the autospectrum of the input signal (i.e., BP). The relationship between BP and CBFv with regard to amplitude and time were denoted as transfer function gain and phase shifts in the low (0.07–0.20 Hz) frequency. The low frequency range was chosen because it is the most established range for examining transfer function analysis in humans (4). The fraction of output power that can be linearly related to input power at each frequency is denoted by the coherence function. The coherence function is similar to a correlation coefficient in that values approximating 0 may indicate a nonlinear relationship, such as severe extraneous noise in the signals or no relationship between signals, whereas a coherence value approaching 1 reflects a strong influence of BP to CBFv. Gain describes the magnitude of change in BP that is reflected by CBFv. A reduction in phase suggests that BP is driving CBFv, or that changes in CBFv rapidly occur after changes in BP. According to previous applications of this methodology, an intact pressure-flow relationship would be associated with reductions in gain and increases in phase. Conversely, the absence of an intact pressure-flow response would manifest as increases in gain, with reductions in phase. Transfer function metrics were conservatively analyzed using only band points with coherence greater than 0.5 arbitrary units (au) as per convention (35, 40). Finally, to provide insight into systemic regulation of perfusion pressure, spontaneous baroreflex sensitivity in the low-frequency (0.04–0.15 Hz) alpha index (\( \alphaLF \)) was also calculated (42). Also, transfer function metrics for the PCA were not possible (owing to fragmenting of continuous data recordings) to calculate in an additional SCI file and two SCImido files.

### Statistical Analysis

Following confirmation of normal distribution (Shapiro-Wilk test), SCI and AB individuals were compared using parametric (i.e., independent-samples \( t \)-tests) or nonparametric comparisons (i.e., related-samples Wilcoxon signed rank test, independent-samples Mann-Whitney U-test). Also, paired-sample \( t \)-tests were used to compare SCI and SCImido groups and to compare the within-group MCAv and PCAv responses. Bivariate correlations were also performed. \( P < 0.05 \) was considered significant unless otherwise reported. Two-way repeated measures ANOVA was used to compare the effect of midodrine on symptoms orthostatic tolerance over the tilt-stages in
SCI. Data are reported as means ± SE. Previous data indicated a required sample size of 4–10 per group when comparing transfer function analysis between SCI and AB (49). Spontaneous transfer function analysis (TFA) metrics of dynamic pressure-flow relationships have been shown to have moderate to strong repeatability (i.e., intraclass correlation of 0.46–0.47) (49).

RESULTS

Able-Bodied Vs. Spinal Cord Injured

Homeostatic response to progressive tilt. Steady-state changes in systemic and cerebral hemodynamics are presented in Fig. 2. Briefly, although BP was significantly lower in SCI during both supine and upright positions (P < 0.05), MCAv and PCAv were similar, indicating effective static CA. Also, BP increased significantly in AB, but decreased in SCI in response to tilt. Both MCAv and PCAv decreased similarly in SCI compared with AB (Fig. 2). Conductance in MCA and PCA decreased in response to tilt in AB (P <0.05), but did not change in SCI. Heart rate increased and PETCO2 decreased to a similar extent in both SCI and AB.

Acute hemodynamic responses to orthostatic challenge. The acute hemodynamic response to tilt is presented in Fig. 3. Those with SCI had significantly lower MAP during the first 60 s of tilt. MCAv decreased from baseline in both AB and SCI (P < 0.001), but this response was not different between groups. MCAv was reduced during tilt in both SCI and AB (P < 0.001), but the magnitude of these reductions were not different between AB and SCI groups. PCAv was reduced in response to orthostatic challenge (both P < 0.001), but this was similar between AB and SCI. The tilt-induced decrease in MCA conductance was abolished in the SCI group throughout the 60 s after tilt. In SCI, MCA conductance was maintained at baseline levels in the 60 s after tilt, whereas in AB it consistently decreased over this time period. PCA conductance was also similar between SCI and AB throughout the first 30 s after tilt. On the other hand, from 30 to 60 s the tilt-induced decrease in PCA conductance was abolished in SCI. The heart rate response to tilt was similar in both SCI and AB. Pretilt PETCO2 was not significantly different between SCI and AB. PETCO2 decreased more in AB compared with SCI over the first 30 s but was similar from 30 to 60 s. Acute responses of MCAv and PCAv to upright tilt were not significantly different from each other within the SCI or AB groups.

Transfer function metrics of dynamic cerebral autoregulation. Transfer function metrics of the dynamic cerebral pressure-flow relationship in MCA and PCA are presented in Table 3. Power spectra for MAP and MCAv were lower in SCI compared with AB (P < 0.05). Also, upright low-frequency coherence for BP-MCAv and BP-PCAv was lower in SCI than in AB (both P < 0.001). Phase was not different between SCI and AB for MAP-MCAv or MAP-PCAv; however, SCI gain was increased for MAP-PCAv (P < 0.05; Table 3).

Spinal Cord Injured Individuals With and Without Midodrine

Homeostatic response to progressive tilt. The effect of midodrine on supine and upright steady-state measured hemodynamic variables are presented in Fig. 2. Supine and upright steady-state BPs were higher in SCI following midodrine; however, heart rate, PETCO2, MCAv, and PCAv values were unaltered.

Acute hemodynamic responses to tilt. Midodrine did not influence the MAP response to tilt from 0 to 30 s. In contrast, from 0 to 60 s, the decline in MAP was mitigated with midodrine (Fig. 3). The MCAv response to tilt was not significantly different with or without midodrine. PCAv did not decline as much 30 – 60 s after tilt when SCI were administered midodrine (P < 0.05). Conductance of the MCA and PCA we not influenced by midodrine administration, and neither was...
Pretilt PETCO2 (Fig. 3). Pretilt PETCO2 was not significantly different in SCI with or without midodrine. The acute responses of MCAv and PCAv to upright tilt were not significantly different from each other in SCI with or without midodrine. Rate pressure product was not related to PETCO2 in SCI before or after midodrine.

Transfer function metrics of cerebral pressure-flow relationships. Midodrine did not substantially alter the dynamic cerebral pressure-flow relationships in the MCA and PCA (Table 3). Supine MAP-MCAv phase was increased with midodrine in SCI, whereas PCA metrics were unchanged. No upright-tilt transfer function metrics differed with or without midodrine.

Orthostatic Tolerance

Symptoms of presyncope were significantly improved at 45° and 60° tilt with midodrine (Fig. 4). Those with SCI had an average 59% improvement in OTi (P = 0.003) during the midodrine tilt trial. There was no relationships between OTi with any transfer function metrics or static hemodynamic variables, (i.e., BP, MCAv/PCAv; mean values, absolute

In participants with SCI, αLF was significantly higher than it was in AB participants (30.0 ± 15.6 vs. 15.7 ± 10.7 ms/mmHg; P = 0.03). Midodrine did not result in significant changes in αLF in either the supine or upright position. In the SCI group, there was a positive relationship between upright mean BP with the MCA low-frequency gain at the last stage of fully tolerated tilt (r = 0.64, P < 0.05). In AB individuals only, there was a strong relationship between αLF and MCA low-frequency gain (r = 0.75, P = 0.01) and normalized gain (r = 0.68, P = 0.03).
In SCI participants, there was a negative relationship between dynamic cerebral pressure-flow relationships in AB and the organotypic equivalent of Ohm's law, known as Darcy's law: \( Q = R \cdot \Delta P / \Delta x \). The main findings are as follows: 1) the steady-state cerebral hemodynamics, as well as orthostatic tolerance in those with SCI, and the influence of midodrine administration, underwent such autoregulatory-caliber adjustments in response to orthostatic exposure, preserving CBF and BP (12, 13, 21). Such reflex adjustments in vascular resistance were evident in the AB group, whereas orthostatic exposure in SCI is similar to that in AB, whereas orthostatic exposure in SCI is similar to that in AB. As such, orthostatic exposure to BP (12, 13, 21). Such reflex adjustments in vascular resistance were evident in the AB group, whereas orthostatic exposure to AB, indicating effective CA, although midodrine does not diminish the acute cerebral pressure-flow response to tilt, it improved between-supine, percent changes from supine) related to those with SCI, and the influence of midodrine administration. This study showed that although the BP response to tilt was maintained at supine levels in SCI, whereas orthostatic exposure in SCI is similar to that in AB, whereas orthostatic exposure in SCI is similar to that in AB. As such, orthostatic exposure to AB, indicating effective CA, although midodrine does not diminish the acute cerebral pressure-flow response to tilt, it improved.
>30 s results in reduced BP and PCAv. BP dropped similarly between AB and SCI over the first 20 s after tilt; however, only in AB did it return back to baseline levels before 30 s. In SCI, BP continued to gradually drop in the 60 s after tilt. The failure of sympathetic vasomotor control to maintain BP and hence cerebral perfusion pressure in SCI appears to be partially mitigated by increased cerebrovascular conductance in both the MCA and PCA. As a result of the increased conductance, velocity is preserved in the MCA and PCA. It appears that time-domain cerebral pressure-flow relationships in SCI allow for maintained MCA and PCAv during orthostatic challenges. Maintained cerebral perfusion in response to acute orthostatic challenge in SCI is remarkable considering recent work showing impaired MCAv in the 30 s after standing up with alpha-1 adrenoreceptor blockade (24). Although the BP response was blunted after alpha-1 adrenoreceptor blockade, Lewis et al. showed that mean MCAv was also reduced (24). As such, it may be that SCI-induced chronic sympathetic vasomotor decentralization leads to enhanced capacity to dynamically alter cerebrovascular conductance, compared with acute sympathetic vasomotor antagonism. Together, the steady-state and dynamic cerebral perfusion-pressure findings show that both MCAv and PCAv regulation is effective in those with SCI.

Frequency domain metrics derived through transfer function analysis of cerebral pressure-flow relationships showed a reduced MCA and PCA coherence, and increased PCAv gain in the SCI group in the upright position. This finding is broadly consistent with a similar report in tetraplegic SCI (49), whereas these findings extend previous work (examining only the MCA) by showing increased gain in the PCA as well (37). However, it should be noted that transfer function analysis can be interpreted in two distinct manners. The traditional interpretation is to assume that these metrics reflect dynamic CA (see METHODS for a specific interpretation of coherence, phase, and gain) (49, 53). Interpreted in this way, reduced coherence in the MCA/PCAv would indicate more effective dynamic CA in those with SCI. However, by the other interpretation (i.e., the one we favor), reported impairments in the dynamic cerebral pressure-flow relationship may be due simply to a poor signal-to-noise ratio, which is a limitation of using TFA under spontaneous conditions (20, 28). Consistent with this view, reduced coherence in SCI as shown in two other studies (37, 49), may not indicate enhanced dynamic CA, as altered input power secondary to varying oscillation amplitude in given frequencies [as noted in mean BP power in SCI (Table 3)] is sufficient to alter coherence (5). Caution in the meaningful interpretation of select TFA metrics has been documented (40).

Effect of midodrine on static CA. In agreement with two previous studies, the present investigation found that midodrine did not alter steady-state MCAv in those with SCI (44, 45). However, for the first time, this study has also illustrated that steady-state PCAv is not altered by midodrine administration in SCI. Although the steady-state BP response to the last tolerable stage of tilt was improved by midodrine, the MCAv, heart rate, and PetCO2 responses were not different. Interestingly, midodrine effectively mitigated the decline in PCAv that occurs in SCI after tilt (Fig. 3). Maintenance of posterior cerebral perfusion (as indexed by PCAv) after midodrine may explain two prior studies that reported marked improvements in orthostatic tolerance but limited influence on MCAv after midodrine administration in SCI (44, 45).

Effect of midodrine on dynamic cerebral pressure-flow relationships. Our data suggest that PCA dynamic time-domain pressure-flow relationships in SCI became more similar to those of AB with when individuals with SCI were administered midodrine (i.e., the PCAv response improved), whereas MCA regulation was unchanged (Fig. 3). From a functional perspective, the current study largely supports recent work showing that posterior regional CBF control plays a crucial role in the development of syncope by showing that vertebral artery blood flow was better maintained compared with the internal carotid artery during orthostatic challenge (38). Transfer function analysis-derived metrics of dynamic cerebral pressure-flow velocity relationships in the MCA and PCAv were largely not influenced by midodrine in SCI, however, MCA phase increased in SCI with midodrine (Table 3). Traditionally interpreted, increased PCA phase may indicate an improved dynamic cerebral pressure-flow regulation.

Orthostatic tolerance. This study clearly showed for the first time, using both self-reported symptoms of presyncope and a calculated OTi, that orthostatic tolerance is markedly improved by midodrine in those with high-level SCI. One double-blind placebo-controlled study in AB individuals with neurally mediated syncope convincingly showed a reduction in episodes of syncope when using midodrine (43). Two studies, albeit using only self-reported symptoms of presyncope and not reporting any statistical analysis, also reported reductions in symptoms during head-up tilt with midodrine in individuals with SCI (44, 45). The current data indicate that in those with SCI, steady-state metrics do not relate to the development of presyncope symptoms, which is not surprising given the marked heterogeneity with regard to the human hemodynamic response to orthostatic challenges (27).

In terms of orthostatic tolerance, it is reasonable to suggest a greater relative importance of CBF maintenance in the posterior cortex, because reductions in blood flow in the posterior region may cause an interruption of the blood supply to the medulla oblongata, which contains autonomic control centers, and discrete regions responsible for consciousness (39). Indeed, early work using the 133Xenon inhalation technique showed a relative redistribution of CBF away from the frontal lobe and toward the occipital lobe in response to orthostatic challenge (31). In those with SCI and orthostatic hypotension in general, PCA blood flow disruption likely plays a key role in the development of syncope, which appears to be mitigated by midodrine administration.

Cerebral pressure-flow relationships and baroreflex function. Previous work has shown an inverse relationship between metrics of dynamic cerebral pressure-flow relationships and cardiac vagal baroreflex sensitivity, suggesting that at least in young people, individuals with the lowest capacity to autoregulate CBF were also those who mounted the greatest heart rate response to sudden changes in BP (and vice versa) (42). The present study replicated this relationship in young AB, but not SCI. Such relationships between cerebral pressure-flow metrics and baroreflex sensitivity are believed to be intrinsic, as supported by the intimately coupled cerebral regulatory centers for both cerebral autoregulation and baroreflex integration, and the clear evolutionary advantage of redundant hemodynamic control systems for the brain (18, 26). An uncoupling of these functions in those with SCI may be due to a variety of issues in SCI, including the drastically reduced BP.
 decentralized sympathetic control cerebrovasculature (6, 23), and upregulation of vagal tone (7), all of which could alter transfer function metrics (1, 16, 36) (Table 3). Individuals with SCI and the lowest BP during tilt had the highest transfer function-derived metrics of cerebrovascular control, and the greatest regulatory capacity (i.e., lowest gain) was found in those with BP below the theorized autoregulatory threshold (i.e., mean BP <60 mmHg) (29). This unexpected finding of the highest autoregulation occurring in those with the lowest perfusion pressure generates additional skepticism that transfer function metrics of cerebral pressure and flow velocity validly measure dynamic CA (40).

Limitations

Transcranial Doppler was used for the assessment of CBF in this study, which required a consistent diameter to accurately reflect changes in flow. Indeed, two studies have shown that administration of similar alpha-1 agonists have not led to reductions in intracranial vessel diameter (14, 19), allowing the fair assumption of maintained MCA and PCA diameter with midodrine. Also, if vasoconstriction did occur with midodrine administration, it would be expected that MCAv and PCAv would increase greatly, which did not occur. With respect to vessels downstream of the MCA and PCA, the blood-brain barrier usually prevents intravascular catecholamines from binding to adrenergic receptors located in cerebral arterioles (25). Nevertheless, volumetric measured flow in the internal carotid artery, vertebral artery, and/or MCA is needed to further investigations of clinical cerebrovascular regulation. Because PCAv and MCAv were similar between groups, and this was the primary comparison being made in the present study (i.e., SCI vs. AB, not PCA vs. MCA), the choice to present either absolute or baseline values would not influence results from the present study. As such, we reported absolute values when comparing supine to baseline, and used relative changes when illustrating the dynamic response, because the use of absolute data would have precluded the summation of BP tilt contours. Because two of the individuals with SCI were injured >1 yr before testing, we correlated time since SCI with primary outcome metrics (i.e., orthostatic tolerance, change in BP/MCAv/PCAv during tilt). No metrics were related to time since injury. This was not a blinded, placebo-controlled trial. Although subjects were randomized with respect to the order of when they had the medication vs. control trial, participants were aware of the medications being provided. The participants were, however, completely blinded to the purpose of the study. The limitations of spontaneous linear TFA have been noted, including the well reported high variability in outcome measures (49). Future examination of dynamic pressure-flow relationships in SCI should consider the use of oscillatory lower body negative pressure to increase coherence between input and output and hence reliance on linear interpretation, and/or the use of nonlinear models (40). Although our group has shown that MCAv cerebrovascular reactivity is preserved in those with SCI, it was noted that the cerebrovascular resistance response was slightly reduced in response to hypocapnia in this population (49). Taking into consideration the similar decrease in PETCO2 noted in the present study, interpretation of our results should consider the fact that CBF is controlled by a number of factors outside of CA, including arterial CO2 concentration, and hence could have been influenced by a mitigated hypocapnic response. Similar caution should be employed when interpreting the midodrine results, because it in unknown whether midodrine administration influences cerebrovascular reactivity in those with SCI.

Conclusion

Independent of changes in transfer function metrics, midodrine led to improved PCAv responses after tilt and a 59% improvement in orthostatic tolerance. The vertebrobasilar region may be particularly susceptible to hypoperfusion in SCI, leading to increased orthostatic intolerance.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


