Title: A comparison of static and dynamic cerebral autoregulation during mild whole-body cold stress in individuals with and without cervical spinal cord injury: a pilot study

Running title: Cerebral autoregulation in cervical SCI

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	Study concept and design	Acquisition of data	Analysis and interpretation of data	Drafting the manuscript	Critical revision of manuscript for intellectual content	Approved the final version of the manuscript
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Yoshi-Ichiro Kamijo	X	X	X		X	X
Christof A. Leicht	X		X		X	X
Philip Millar			X		X	X
Manabu Shibasaki	X	X	X		X	X
Victoria Goosey-Tolfrey	X		X		X	X
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Ethical approval: The study was approved by the Medical Ethical Committee of Wakayama Medical University (Wakayama, Japan)

Abstract

Study design: Experimental study.

Objectives: To characterize static and dynamic cerebral autoregulation (CA) of individuals with cervical spinal cord injury (SCI) compared to able-bodied controls in response to moderate increases in mean arterial pressure (MAP) caused by mild whole-body cold stress.

Setting: Japan

Methods: Five men with complete autonomic cervical SCI (sustained>5y) and six age-matched able-bodied men participated in hemodynamic, temperature, catecholamine and respiratory measurements for 60 min during three consecutive stages: baseline (10 min; 33^0C water through a thin-tubed whole-body suit), mild cold stress (20 min; 25^0C water) and post-cold recovery (30 min; 33^0C water). Static CA was determined as the ratio between mean changes in middle cerebral artery blood velocity and MAP, dynamic CA as transfer function coherence, gain and phase between spontaneous changes in MAP to middle cerebral artery blood velocity.

Results: MAP increased in both groups during cold and post-cold recovery (mean differences: 5 to 10 mm Hg; main effect of time: p=0.001). Static CA was not different between the able-bodied vs the cervical SCI group (mean [95% CI] of between-group difference: -4 [-11 to 3] and -2 [-5 to 1] cm/s/mmHg for cold (p=0.22) and post-cold (p=0.24), respectively). At baseline, transfer function phase was shorter in the cervical SCI group (mean [95% CI] of between-group difference: 0.6 [0.2 to 1.0] rad; p=0.006), while between-group differences in changes in phase were not different in response to the cold stress (interaction term: p=0.06).

Conclusions: This pilot study suggests that static CA is similar between individuals with cervical SCI and able-bodied controls in response to moderate increases in MAP, while dynamic CA may be impaired in cervical SCI due to disturbed sympathetic control.

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MeSH Keywords: spinal cord injuries; tetraplegia; cerebrovascular circulation; arterial blood pressure; sympathetic nervous system; cold

Alphabetical list of abbreviations

CA = cerebral autoregulation

CI = confidence interval

CBF = cerebral blood flow

SCI = spinal cord injury

MAP = mean arterial pressure

INTRODUCTION

The precise regulation of cerebral blood flow (CBF) is essential in preventing unconsciousness and brain damage.[1, 2] The capacity of the central vasculature to maintain CBF by adjusting cerebrovascular resistance over a range of mean arterial pressure (MAP) is referred to as cerebral autoregulation (CA).[3-5] The physiological mechanisms responsible for CA are not yet clear, but include myogenic (smooth muscle responding to changes in vascular wall tension), cholinergic, and sympathetic mechanisms.[3, 6-11] CA is typically evaluated by measuring CBF changes in response to a steady-state change in MAP ('static' CA), or by measuring CBF changes in response to transient fluctuations in MAP ('dynamic' CA). Static CA has for example been determined by examining mean CBF changes relative to MAP changes over two minutes in response to orthostatic stress,[12, 13] while dynamic CA is evaluated commonly using transfer function coherence, gain and phase of spontaneous changes in MAP and CBF velocity.[14, 15] Coherence reflects the linear correlation between changes in MAP and changes in CBF velocity, gain reflects the magnitude in which a given change in MAP alters CBF velocity, and phase reflects the time delay between changes in MAP to be reflected in changes in CBF velocity.[14, 15] A higher transfer function gain can be interpreted as the primary indicator of less adequate dynamic CA, while a higher coherence and shorter phase may also reflect less adequate dynamic CA.[14, 15] Important to note is that static and dynamic CA represent two experimental approaches for quantifying the relationship between MAP and CBF velocity over different time scales[6] and not necessarily distinct physiological mechanisms.[3]

Whether disruption of central sympathetic control, present in individuals with cervical spinal cord injury (SCI),[16] leads to inadequate CA remains unclear.[17-19] An inability to buffer the frequently occurring periods of high and low MAP caused by impaired sympathetic control[16] may explain why the SCI population is at increased risk of stroke and

cerebrovascular disease.[18, 20, 21] Prior studies indicate that static CA is not different in participants with chronic cervical SCI compared to able-bodied controls (see [17] for an overview), while data from able-bodied participants indicates that pharmaceutically-induced sympathetic blockade has little or no effect on static CA.[6, 22] However, each of these studies tested the capacity to maintain CBF during reductions in MAP, which in able-bodied individuals exhibits less effective buffering than increases in MAP, a phenomenon called CA hysteresis.[3, 4, 23, 24] Static CA has also been reported to be similar between participants with SCI and able-bodied controls in response to increases in MAP evoked via the cold pressor test.[25, 26] However, it remains unclear whether this stress elicited peripherally-mediated sympathetic outflow secondary to autonomic dysreflexia.[27-29] Furthermore, prior studies have largely failed to measure respiratory rate, P_{aO2} and P_{aCO2}, which can influence interpretation of CA.[15, 30, 31] As such, it has yet to be tested whether static CA is also similar between individuals with cervical SCI and able-bodied controls in response to moderate increases in MAP without peripherally-mediated sympathetic outflow and changes in respiratory rate, P_{aO2} and P_{aCO2}.

The effects of cervical SCI and the role of disturbed sympathetic control of the cerebrovasculature on dynamic CA are also unclear. A recent study reported that participants with SCI at or above the 4th thoracic segment had a shorter transfer function phase compared to able-bodied controls during supine conditions, suggesting that dynamic CA is impaired in cervical SCI.[32] Earlier studies also demonstrated a higher transfer function gain or shorter phase in participants with cervical SCI compared to able-bodied controls during an orthostatic challenge that decreased MAP.[19, 33] However, transfer function coherence, gain and phase during a stress that moderately increases MAP has never been studied in individuals with cervical SCI.

Therefore, the objective of this pilot study was to characterize static and dynamic CA of individuals with cervical SCI compared to able-bodied controls in response to a moderate increase in MAP caused by mild whole-body cold stress, in order to provide insight into the effect of disturbed central sympathetic control of the cerebrovasculature on CA. We hypothesized that in response to a moderate increase in MAP 1) static CA would be similar between the cervical SCI and able-bodied group; and 2) dynamic CA, operationalized by transfer function coherence, gain and phase, would be different between the cervical SCI and able-bodied group.

METHODS

Participants

Five otherwise healthy men with C5/C6 lesions (5-26 y post-injury; AIS A: n=4; AIS B: n=1) participated in the study, along with six healthy age-matched able-bodied men who served as a control group (Table 1). Resting levels of plasma noradrenaline < 94 pg/mL indicated autonomic completeness[19, 35] (Table 1). In addition, the drop of 19 to 30 mmHg in systolic blood pressure measured during a sit-up test[36] was also suggestive of autonomic completeness. Two additional participants (SCI: n=1, aged 25 y; able-bodied: n=1, aged 28 y) were excluded from the study given an unanticipated decrease in MAP during the cold stress stage (SCI: -7 mmHg; able-bodied: -11 mmHg).

Procedures

All participants fasted for ≥4 hours before the trial and emptied their bladder upon arrival at the testing facilities. Participants were tested in a supine position wearing a thin-tubed whole-

144 body suit (Allen-Vanguard Technologies Inc, Ottawa, Canada) in a laboratory with an
145 ambient temperature of 27.5-28.6^{0}C and 40-45% relative humidity. The water-perfused suit
146 covered the entire skin surface except for the feet, hands and head.[37] Standardized whole-
147 body normothermic conditions at the start of trial were achieved by perfusing 33^{0}C water
148 through the suit for approximately 30 min during instrumentation.[37] After this, the total time
149 of the trial was 60 min, consisting of three consecutive stages: baseline normothermic
150 conditions (10 min with 33^{0}C water through the suit), mild cold stress (20 min with 25^{0}C
151 water) and post-cold recovery (30 min with 33^{0}C water). Previous data indicated that 20 min
152 of cold is the minimal duration to evoke a drop in skin temperature and that 30 min is the
153 minimum duration required to return skin temperature to normothermic levels.[37] The use of
154 previously established minimum durations was also used to reduce the risk of pressure sores.
155 To further reduce the risk of pressure sores, participants with cervical SCI were manually
156 lifted from the table for one minute after each of the instrumentation, baseline, and cold stress
157 stages. Hemodynamic, body temperature, and respiratory measurements were conducted
158 continuously throughout the trial, while blood samples for catecholamines were taken three
159 minutes before the end of each stage.
160
161 **Hemodynamic outcomes**
162 Discrete systolic and diastolic blood pressure were measured each minute using an upper-arm
163 cuff on the right arm (Tango$^+$, SunTech Medical Inc., Morrisville, NC, USA). MAP was
164 calculated by: diastolic blood pressure plus one-third multiplied by pulse pressure.[38] CBF
165 velocity was measured in the middle carotid artery at 200 Hz using a 2-MHz probe (WAKI,
166 Atys Médical, Soucieu-en-Jarrest, France) placed over the participant's temporal window.
167 The probe was fixed at a constant angle with a custom-made probe holder. The transcranial
168 Doppler ultrasound sample volume was adjusted to capture the proximal segment of the

middle carotid artery, after which an optimal signal was obtained by trying different angles and positions of the probe.[22] Beat-by-beat blood pressure was measured at 200 Hz using finger photoplethysmography (MUB101-50, MediSense Inc., Tokyo, Japan) from a long or ring finger digit on the left hand. Heart rate was determined using the peak-to-peak intervals of the beat-by-beat blood pressure signal. Impedance cardiography was used to measure stroke volume and cardiac output at a sample frequency of 1 Hz (PhysioFlow Lab-1, Manatec Biomedical, Paris, France).

Body temperature

Oesophageal temperature was measured at a sample frequency of 2 Hz using a copper-constantan thermocouple (LT6A, Gram Corporation, Saitama, Japan).[37] Skin temperature was collected using a similar sensor at 7 sites: forehead, chest, abdomen, upper arm, lower arm, thigh and calf.[37] Mean skin temperature was calculated based on weighting of each site: forehead (0.07), chest (0.175), abdomen (0.175), upper arm (0.1), lower arm (0.1), thigh (0.2) and calf (0.16).[39]

Respiratory outcomes

Open-circuit spirometry and mass spectrometry (ARCO-2000, Arco System Inc., Kashiwa, Japan) were used to measure respiratory rate, P_{ETCO2} and P_{ETO2}, which have been shown to be valid estimators of P_{aO2} and P_{aCO2}.[30]

Catecholamines

Blood samples were analyzed for noradrenaline and adrenaline plasma concentrations using high-performance liquid chromatography (coefficients of variation computed by analysis of standards: 8.8% and 7.0%, respectively).

Data analysis

Data processing was conducted using Matlab 2015b (Mathworks, Natick, USA). Data over the last 5 minutes of each condition were selected for further analyses. A different time window with steady-state body temperature was selected if CBF data contained artifacts.[40] Only 4 or 4.5 minutes of artifact-free CBF velocity data was available in some participants (baseline: n=2; cold: n=1; post-cold: n=1), but this was still considered sufficient.[41] The mean over the selected window was calculated for all outcomes.

Static and dynamic CA

Static CA was determined as the ratio between mean changes in CBF velocity and MAP (cm/s/mmHg)[4] from baseline to the mild cold stress, and from baseline to the post-cold recovery. For the spectral power and transfer function outcomes underpinning dynamic CA, beat-to-beat MAP and CBF velocity were obtained by integrating the respective signals within each cardiac cycle. Cardiac cycles were determined based on the diastolic (nadir-to-nadir) intervals of the beat-by-beat blood pressure signal. Beat-to-beat MAP and CBF velocity were first linearly interpolated and resampled at 2 Hz and then detrended by subtracting their 3rd order polynomial.[15, 22] Subsequently, the beat-to-beat time series were used for spectral and transfer function analyses based on the Welch algorithm.[15] Each time series was subdivided into successive 256-point Hann windows that overlapped by 50% before fast Fourier transform analysis.[14, 15] This resulted in a spectral resolution of 0.0020 Hz in all but two participants (0.0039 Hz). The cross-spectrum between MAP (input) and CBF velocity (output) was determined and divided by the MAP autospectrum to derive the transfer function coherence, gain and phase.[15] Spectral power of MAP and CBF velocity as well as coherence, gain and phase were averaged over the previously established 0.07-0.20 Hz low-frequency

bandwidth,[15] which is considered to be the primary bandwidth representing sympathetic influences on the vasculature.[42] The contribution of gain and phase toward the band average was weighted according to their individual precision, which depended on coherence at each spectral frequency.[14]

Statistical analyses

A previous study found significant differences between an able-bodied (n=7) vs a cervical SCI group (n=4) in transfer function gain during supine conditions (1.1±0.1 vs. 1.5±0.1 mm/s/mmHg, respectively).[19] These data were used in G*Power 3.1.9.3 for Mac OS X[43] to estimate that sample sizes of N≥5 (able-bodied) and N≥3 (cervical SCI), based on 95% power, are required to detect mean differences in transfer function gain of 0.4 cm/s/mm Hg, using a two-tailed test with $\alpha=0.05$. The mean and 95% confidence interval (CI) of the difference was calculated for each within and between-group comparison. In addition, parametric statistics were applied to all outcome measures with a normal distribution, which was assessed using Shapiro-Wilks tests ($p<0.05$). Data were log-transformed if the Shapiro-Wilk test indicated a non-normal distribution. Comparison of baseline characteristics between the able-bodied and cervical SCI group were conducted using unpaired two-tailed Student *t*-tests. Hemodynamic, body temperature, respiratory and catecholamine responses from baseline to mild cold stress and post-cold recovery within and between the able-bodied and cervical SCI group were assessed using 2 x 3 repeated measures ANOVA. Between-group comparisons of static and dynamic CA outcomes were conducted using unpaired two-tailed Student *t*-tests. The interaction term of 2 x 3 ANOVA was used to assess whether responses in transfer function coherence, gain and phase to mild cold stress and post-cold recovery were different between the able-bodied and cervical SCI group. The significance level was set at $p<0.05$. Analyses were conducted using SPSS Statistics v22 (SPSS Inc., Chicago, USA).

Statement of ethics

The authors certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research. The study was approved by the Medical Ethical Committee of Wakayama Medical University (Wakayama, Japan) and all participants provided written informed consent.

RESULTS

Baseline characteristics

Table 1 presents all between-group comparisons of baseline characteristics. Lower heart rate ($p=0.03$), noradrenaline ($p=0.001$) and adrenaline ($p<.001$) outcomes were found in the cervical SCI compared to the able-bodied group. No between-group differences were observed in the other hemodynamic ($p=0.20$-0.99), body temperature ($p=0.37$-0.98), respiratory ($p=0.19$-0.66), and spectral power outcomes ($p=0.07$-0.61) at baseline.

Responses to mild whole-body cold stress

Table 2 presents all within-group responses during and following exposure to the mild cold stress. Hemodynamic responses were similar in both groups (interaction terms: $p=0.12$-0.91). An increase in MAP was found in the groups from baseline to cold and post-cold (main effect of time: $p=0.001$). Heart rate decreased in both groups from baseline to cold (main effect of time: $p=0.02$), leading to a decrease in cardiac output (main effect of time: $p=0.02$). Body temperature responses were also similar in both groups (interaction terms: $p=0.21$-0.27). Mean skin temperature decreased during the cold stage (main effect of time: $p<.001$) and returned to baseline levels during the post-cold stage. Oesophageal temperature was stable

from baseline to cold, but decreased during the post-cold stage (main effect of time: p<.001). Respiratory outcomes were stable in both groups (main effects of time: p=0.57-0.97; interaction terms: p=0.33-0.91), indicating that these outcomes did not confound the interpretation of static or dynamic CA results (see below). For catecholamines, the increases in noradrenaline in the able-bodied group during cold and post-cold recovery differed from the stable noradrenaline levels observed in the cervical SCI group (main effect of time: p<.001; interaction term: p<.001), in contrast to the responses observed in adrenaline (main effect of time: p=0.06; interaction term: p=0.09). In the spectral outcomes, no differences were observed in the groups for low-frequency power of MAP or CBF velocity (main effect of time: p=0.15 and 0.80; interaction terms: p=0.10 and 0.15, respectively).

Static CA

In both groups, only small or no changes in CBF velocity were observed during and following exposure to the mild cold stress when faced with the increases in MAP (Table 2). As such, no differences in static CA were observed for the cold stress when the able-bodied group (mean±SD: 0±2 cm/s/mmHg) and cervical SCI group (mean±SD: 4±8 cm/s/mmHg) were compared (mean [95% CI] of between-group difference: -4 [-11 to 3] cm/s/mmHg; p=0.24). Also for the post-cold recovery, no differences in static CA were observed when the able-bodied group (mean±SD: 0±1 cm/s/mmHg) and cervical SCI group (mean±SD: 2±3 cm/s/mmHg) were compared (mean [95% CI] of between-group difference: -2 [-5 to 1] cm/s/mmHg; p=0.22).

Dynamic CA

Table 3 presents the between-group comparisons of transfer function outcomes at baseline. For dynamic CA at baseline, transfer function in the cervical SCI group demonstrated a

shorter phase (p=0.006) but no difference in coherence (p=0.40) or gain (p=0.08) when compared to the able-bodied group. Figure 1 presents the responses in transfer function outcomes during and following exposure to the mild cold stress. When compared to baseline, smaller or no between-group differences in phase were observed during cold (mean [95% CI]: 0.4 [0.0 to 0.7] rad; p=0.04) and post-cold recovery (mean [95% CI]: 0.2 [-0.1 to 0.5] rad; p=0.15). However, the responses in phase were not different between the groups when analyzed using 2 x 3 ANOVA (interaction term: p=0.06). Responses between the groups were also not different for coherence (interaction term: p=0.07) or gain (interaction term: p=0.41).

DISCUSSION

This pilot study is the first to characterize static and dynamic CA in individuals with cervical SCI using a moderate increase in MAP caused by mild-whole body cold stress. Importantly, this intervention evoked a moderate increase in MAP without signs of peripherally-mediated sympathetic outflow or changes in respiratory rate, P_{aO2} and P_{aCO2}. These preliminary data suggest that static CA in response to moderate increases in MAP was similar between the cervical SCI and able-bodied group. In contrast, the shorter transfer function phase between spontaneous changes in CBF velocity and MAP in the cervical SCI group suggests that dynamic CA was impaired in the cervical SCI group. Furthermore, smaller between-group differences in transfer function phase were observed when MAP was increased in response to the mild cold stress.

The findings on static CA in response to an increase in MAP are similar to other studies that showed adequate static CA in individuals with chronic cervical SCI compared to able-bodied controls using an orthostatic challenge to decrease MAP (see [17] for an overview). Comparable measures of static CA were also observed in SCI and able-bodied individuals during cold pressor tests and periods of autonomic dysreflexia.[25, 26, 29] Our pilot data extend

those findings by showing similar static CA during moderate MAP increases without signs of peripherally-mediated increases in sympathetic outflow or changes in respiratory rate, P_{aO2} and P_{aCO2}. Taken together, these results suggest that central sympathetic control is not a prerequisite for static CA, in line with findings of the largely unaffected static CA after pharmaceutically-induced sympathetic blockade in able-bodied participants.[6, 22]

In contrast to static CA, differences between the SCI and able-bodied group were found in transfer function phase based on spontaneous changes in MAP and CBF velocity during normothermic supine baseline conditions, suggesting that sympathetic control is required for optimal dynamic CA.[6] The focus on static CA in older studies could explain why it was traditionally thought that sympathetic mechanisms had no role in CA.[6, 9, 11, 44] A shortened transfer function phase in participants with cervical SCI compared to able-bodied controls, along with an absence of differences in transfer function coherence and gain, were also found in a recent, larger study during supine baseline conditions.[32] The mean between-group difference in phase in that study of 0.2 rad (95% CI of the difference not reported) was somewhat smaller than the mean of 0.6 rad (95% CI: 0.2 to 1.0) in our study. This size difference may be attributed to the inclusion in the prior study of participants with lesions at or the 4th thoracic segment,[32] who may have had more sympathetic control than the participants with cervical SCI included in our study.[16] Our findings are strengthened by rigorous artifact checking,[40] and the use of weighting based on coherence level when averaging phase and gain over a spectral frequency bandwidth.[14] This method is considered to minimize risk of bias inherent to low coherence.[14] Not using this method might explain why previous studies found no significant differences in phase between able-bodied and cervical SCI groups during supine conditions.[19, 33, 34] Taken together, the shortened transfer function phase found in the recent larger study,[32] along with ours, suggest that intact central sympathetic control is a prerequisite for optimal dynamic CA, providing insights that can inform the ongoing debate about the role of sympathetic control for CA.[3, 9, 11]

Besides disturbed central sympathetic control, another explanation for suboptimal CA could be the low resting blood pressure commonly occurring in individuals with cervical SCI.[16, 32] Recent data indicate that CA of healthy, able-bodied men is better adapted to compensate for transient hypertension than transient hypotension.[3, 4, 23, 24] It could be that human CA is also less effective at compensating for chronic hypotension than chronic hypertension due to reduced cerebral perfusion pressure caused by lower resting blood pressure.[32] A role of low resting blood pressures influencing dynamic CA in cervical SCI may also explain the smaller between-group difference in transfer function phase observed during the moderate increase in MAP caused by the mild cold stress, although this remains speculative given that responses in dynamic CA were not significantly different between the groups (Figure 1). A longer phase could imply that the cerebrovasculature has more time to respond to transient changes in MAP using mechanisms other than sympathetic control, such as myogenic factors.[3, 6, 7]

Given the absence of signs of peripherally-mediated sympathetic outflow or changes in respiratory rate, P_{aO2} and P_{aCO2}, mild whole-body mild cold stress seems an appropriate intervention for studying the role of the disturbed central sympathetic control in cervical SCI. Not anticipated was that MAP was still significantly increased in both groups during the post-cold stage. Even though mean skin temperature returned to baseline levels during the post-cold stage, MAP was still significantly increased in the cervical SCI as well as the able-bodied group. It seems the stressor was sufficient to maintain MAP at levels similar to the cold stage, even 30 minutes after cessation of the stressor.

Study limitations

The assumption of indexing CBF using transcranial Doppler ultrasound is that the cross-sectional diameter of the insonated vessel is unchanged; CBF velocity is then proportional to

CBF.[3] Although this assumption can be violated,[46] various studies have shown that changes in middle cerebral artery diameter are unlikely during resting conditions without extreme changes in MAP.[47] The moderate changes in MAP independent of a change in respiratory outcomes observed in our study further strengthen the likelihood against a change in vessel diameter. The goal of the present study was to compare each participant against their own normothermic baseline. However, in this design, we cannot exclude the possibility that the observed changes in the cervical SCI group were influenced by normal variations over time or measurement error. These risks were reduced in our study by the post-cold measurements demonstrating a return to baseline values in most outcomes, along with the previously reported reliability of dynamic CA metrics during supine conditions,[48, 49] which was further enhanced by the use of rigorous artifact checking[40] and use of weighting based on coherence level.[14] Finally, unconscious bias due to the unblind nature of the present protocol cannot be excluded. To reduce such risk, all data analyses were conducted by one author (JWvdS) and independently verified by another author (YK).

Recommendations for future research

Our data suggest the need for better understanding if and how inadequate dynamic CA is influencing the increased risk of stroke and other cerebrovascular conditions of individuals with CSCI.[18, 20, 21] Longitudinal studies are needed to understand if and what adaptations in static and dynamic CA[13, 17] occur from the acute to chronic post-injury stages. Mild whole-body mild cold stress seems an appropriate intervention for further studying the role of the disturbed central sympathetic control in cervical SCI. An intervention with a longer post-cold recovery could provide further insight into the responses of CA outcomes when MAP returns to baseline after mild cold stress. Measurement of the posterior carotid artery, in addition the middle carotid artery, may elucidate if these vessels respond differently to increases in MAP

caused by mild cold stress.[30, 33] Future research on quantification of dynamic CA in individuals with cervical SCI should ideally be expanded to non-linear relationships in addition to the linear relationships examined using transfer function analyses.[50, 51] Finally, individual data of this study should be used in a future meta-analysis regarding transfer function in cervical SCI compared to able-bodied groups. Not only can these research angles further elucidate the still debated role of the sympathetic nervous system as a mechanism contributing to CA in humans,[3, 9, 11] but they may also help reduce the risk of stroke and cerebrovascular disease of individuals with cervical SCI.[18, 20, 21]

Conclusions

This pilot study suggests that in response to a moderate increase in MAP using mild cold stress, static CA is similar in individuals with cervical SCI compared to able-bodied controls. In contrast, our preliminary data suggest that dynamic CA may be impaired in individuals with cervical SCI compared to able-bodied controls due to disturbed central sympathetic control over the cerebrovasculature and/or due to the indirect result of reduced cerebral perfusion pressure caused by lower resting blood pressure.

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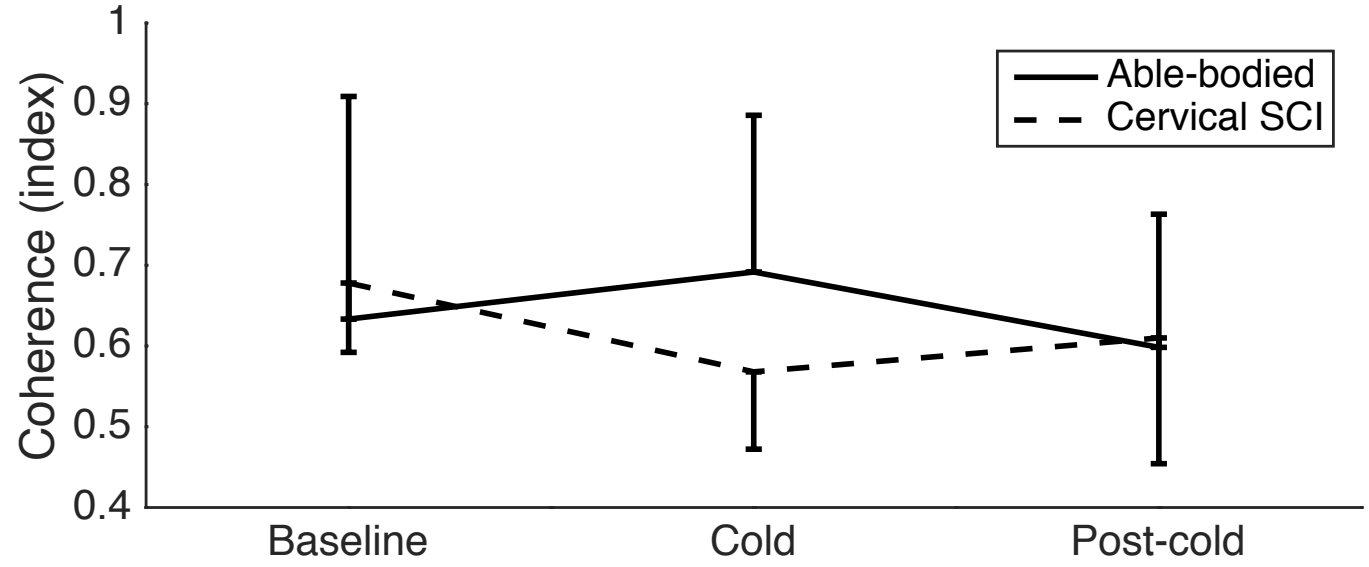
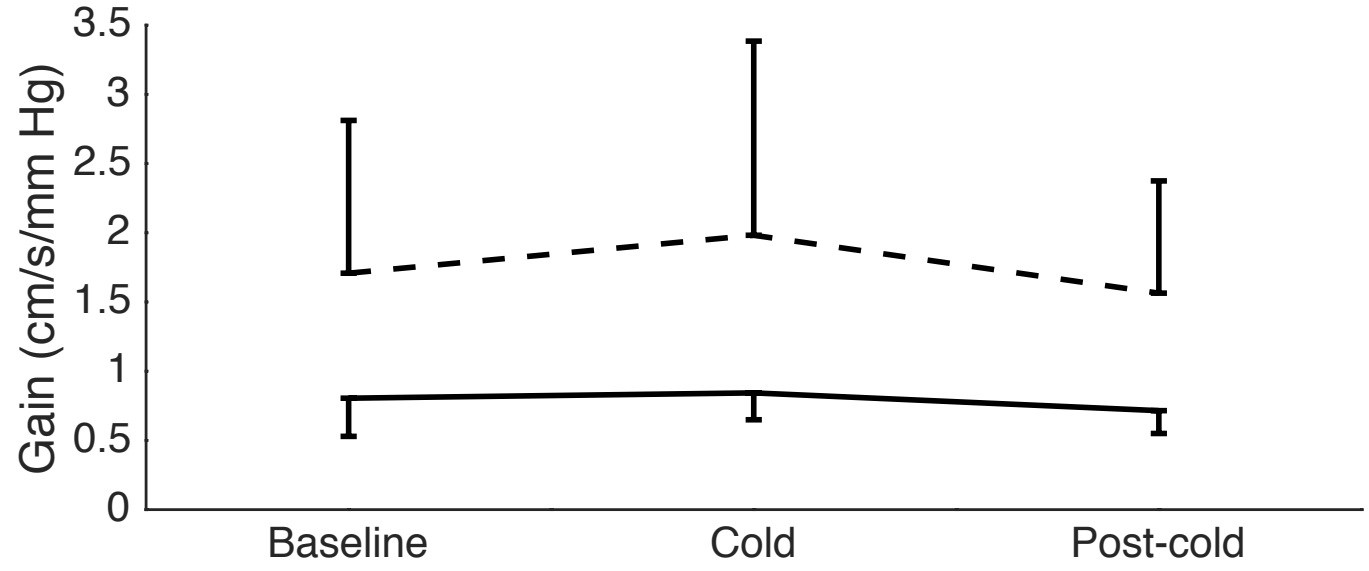
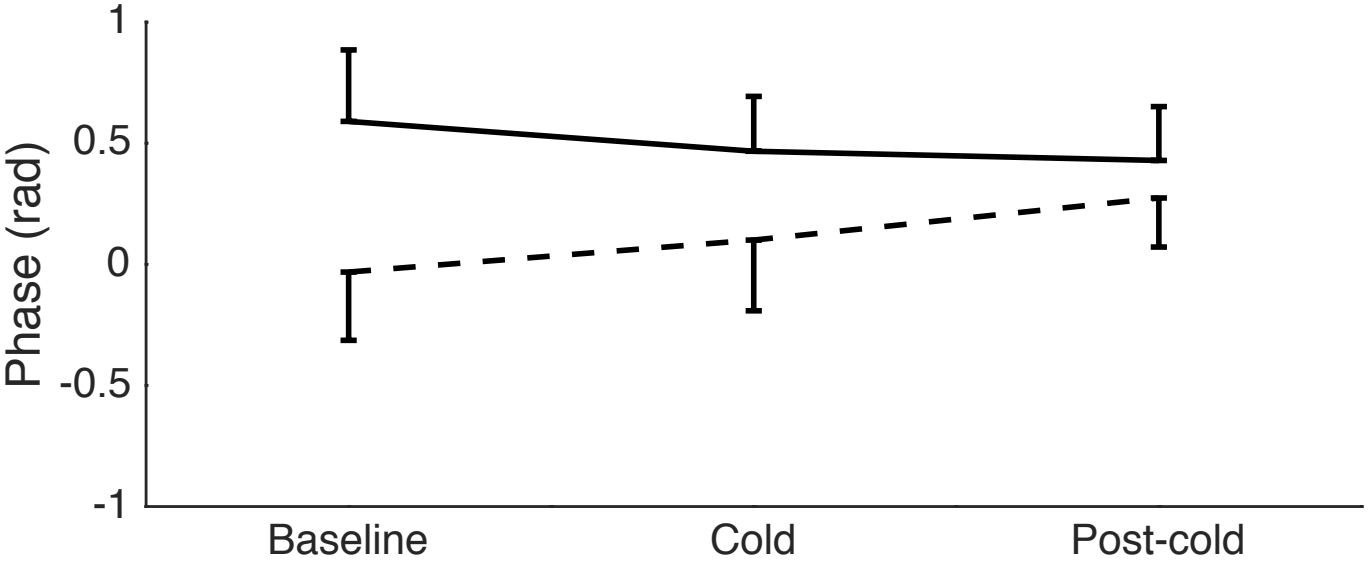
Conflicts of interests: None declared

Titles and legends to Figures

Figure 1. Mean and SD of transfer function coherence, gain and phase at baseline during and following exposure to mild whole-body cold stress in the cervical SCI (n=5) and able-bodied group (n=6). P-values represent the interaction terms of 2 x 3 repeated measures ANOVA.


Able-bodied
Cervical SCI
Coherence (index)
1
0.9
0.8
0.7
0.6
0.5
0.4
Baseline
Cold
Post-cold


Gain (cm/s/mm Hg)
3.5
3
2.5
2
1.5
1
0.5
0
Baseline
Cold
Post-cold


Phase (rad)
1
0.5
0
-0.5
-1
Baseline
Cold
Post-cold

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611 **Table 1.** Baseline participant characteristics in the able-bodied compared to the cervical spinal cord injury
612 group.

	Able-bodied (n=6)	**Cervical SCI (n=5)**	**Able-bodied vs. cervical SCI**
	Mean±SD	**Mean±SD**	**Mean (95% CI) difference**
Demographics/anthropometrics			
Age (y)	40±15	36±9	4 (-13 to 21)
Height (m)	174±6	178±9	-5 (-15 to 5)
Body weight (kg)	67±6	63±15	4 (-12 to 19)
Hemodynamic			
MAP (mm Hg)	85±8	79±9	6 (-6 to 17)
CBF velocity (cm/s)	63±12	67±20	-4 (-25 to 18)
Heart rate (b/min)	70±11	56±6	15 (2 to 27)*
Stroke volume (mL)	77±8	77±17	0 (-17 to 17)
Cardiac output (L/min)	5.5±1.0	4.6±1.3	0.9 (-0.6 to 2.5)
Body temperature			
Mean skin temperature (^{0}C)	34.9±0.6	34.6±0.6	0.3 (-0.5 to 1.1)
Oesophageal temperature (^{0}C)	36.7±0.2	36.7±0.6	0.0 (-0.6 to 0.5)
Respiratory			
End-tidal P_{CO2} (mm Hg)	39±3	38±2	-2 (-2 to 6)
End-tidal P_{O2} (mm Hg)	106±2	109±5	-3 (-8 to 2)
Respiratory rate (Hz)	0.25±0.07	0.27±0.09	-0.02 (-0.13 to 0.09)
Catecholamines			
Noradrenaline	228±80	56±30	172 (85 to 258)**
Adrenaline	37±11	7±4	30 (18 to 42)***
Spectral power			
Power MAP (mm Hg^2/Hz)	21±20	2±1	-18 (-1 to -34)
Power CBF velocity ([cm/sec]^2/Hz)[a]	17±27	10±13	-7 (-31 to 18)

613 MAP = mean arterial pressure; SCI = spinal cord injury; CBF = cerebral blood flow
614 *p<0.05; **p<0.01; ***p<0.001 in unpaired two-tailed Student *t*-tests
615 [a] Tested after log transform, as data were not normally distributed.

Table 2. Within-group responses in hemodynamic, body temperature, respiratory, catecholamine, and spectral outcomes during and following exposure to mild whole-body cold stress.

	Able-bodied (n=6)		**Cervical SCI (n=5)**	
	Δ Baseline to cold	**Δ Baseline to post-cold**	**Δ Baseline to cold**	**Δ Baseline to post-cold**
	Mean±SD **(95% CI)**	**Mean**±SD **(95% CI)**	**Mean**±SD **(95% CI)**	**Mean**±SD **(95% CI)**
Hemodynamic				
MAP upper-arm cuff (mm Hg)**	5±3 (2 to 7)	6±4 (2 to 9)	7±7 (-2 to 16)	10±8 (1 to 20)
CBF velocity (cm/s)	1±6 (-6 to 7)	1±5 (-5 to 7)	1±7 (-7 to 10)	2±2 (0 to 5)
Heart rate (beats/min)*	-3±3 (-6 to 0)	0±3 (-3 to 4)	-1±1 (-3 to 0)	0±3 (-4 to 4)
Stroke volume (mL)	0±3 (-3 to 3)	0±5 (-4 to 4)[a]	1±3 (-3 to 4)	-3±7 (0 to -6)
Cardiac output (L/min)*	-0.4±0.3 (-0.7 to 0.0)	-0.1±0.3 (-0.5 to 0.2)[a]	-0.2±0.2 (-0.4 to 0.1)	-0.4±0.4 (-0.1 to -0.7)
Body temperature				
Mean skin temperature (^{0}C)***	-1.7±0.5 (-2.2 to -1.2)	-0.4±0.6 (-1.1 to 0.2)	-2.1±0.3 (-2.5 to -1.7)	-0.4±0.6 (-1.1 to 0.4)
Oesophageal temperature (^{0}C)***	0.0±0.1 (-0.1 to 0.1)	-0.2±0.1 (-0.3 to 0.0)	-0.1±0.1 (-0.2 to 0.0)	-0.3±0.2 (-0.5 to -0.1)
Respiratory				
End-tidal P_{CO2} (mm Hg)	1±1 (0 to 2)	0±1 (-1 to 0)	0±2 (-3 to 2)	0±0 (-2 to 1)
End-tidal P_{O2} (mm Hg)	0±2 (-2 to 2)	0±2 (-2 to 2)	0±5 (-5 to 6)	0±3 (-4 to 3)
Respiratory rate (Hz)	0.01±0.04 (-0.03 to 0.05)	0.02±0.03 (-0.02 to 0.05)	0.00±0.02 (-0.03 to 0.03)	-0.01±0.03 (-0.05 to 0.03)
Catecholamines				
Noradrenaline***#	47±81 (-38 to 133)	183±72 (108 to 258)	-1±21 (-27 to 25)	21±17 (-1 to 43)
Adrenaline	-5±9 (-14 to 4)	13±22 (-10 to 36)	0±0 (0 to 0)	1±2 (-1 to 3)
Spectral power				
Power MAP (mm Hg^2/Hz)	6.2±8.4 (-2.6 to 15.1)	1.4±3.6 (-2.5 to 5.2)	0.0±1.0 (-1.2 to 1.3)	1.2±1.0 (-0.1 to 2.4)
Power CBF velocity ([cm/sec]^2/Hz)[b]	0.7±5.8 (-5.3 to 6.8)	-2.3±10.0 (-12.8 to 8.2)	1.1±3.0 (-2.6 to 4.8)	4.7±4.4 (-0.8 to 10.2)

MAP = mean arterial pressure; CSCI = cervical spinal cord injury; CBF = cerebral blood flow; **Δ** Cold = cold – baseline; **Δ** Post-cold = post-cold – baseline

*p<0.05; **p<0.01; ***p<0.001 for main effect of time in 2 x 3 repeated measures ANOVA

# p<0.001 for the interaction term in 2 x 3 repeated measures ANOVA

[a] Missing data for n=1

[b] Tested after log transform, as data were not normally distributed

623 **Table 3.** Baseline transfer function outcomes of dynamic cerebral autoregulation in the able-bodied compared
624 to the cervical spinal cord injury group.

	Able-bodied (n=6)	**Cervical SCI (n=5)**	**Able-bodied vs. cervical SCI**
	Mean±SD	**Mean±SD**	**Mean (95% CI) difference**
Coherence (index of 0-1)	0.63±0.08	0.68±0.09	-0.05 (-0.16 to 0.07)
Gain (cm/s/mmHg)	0.8±0.3	1.7±1.1	-0.9 (-1.9 to 0.1)
Phase (rad)	0.6±0.3	0.0±0.3	0.6 (0.2-1.0)**

625 SCI = cervical spinal cord injury
626 **p<0.01
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