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*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*

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3
4 **Running title:** Cerebral autoregulation in cervical SCI

5
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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
Jan W. van der Scheer	X	X	X	X		X
Yoshi-Ichiro Kamijo	X	X	X		X	X
Christof A. Leicht	X		X		X	X
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24
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26
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29
30 **Ethical approval:** The study was approved by the Medical Ethical Committee of Wakayama
31 Medical University (Wakayama, Japan)

34 **Abstract**

35 **Study design:** Experimental study.

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

39 **Setting:** Japan

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

47 **Results:** MAP increased in both groups during cold and post-cold recovery (mean differences:
48 5 to 10 mm Hg; main effect of time: $p=0.001$). Static CA was not different between the able-
49 bodied vs the cervical SCI group (mean [95% CI] of between-group difference: -4 [-11 to 3]
50 and -2 [-5 to 1] cm/s/mmHg for cold ($p=0.22$) and post-cold ($p=0.24$), respectively). At
51 baseline, transfer function phase was shorter in the cervical SCI group (mean [95% CI] of
52 between-group difference: 0.6 [0.2 to 1.0] rad; $p=0.006$), while between-group differences in
53 changes in phase were not different in response to the cold stress (interaction term: $p=0.06$).

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

57

58 **Sponsorship:** Financial support for this project was provided by Kyoten, Wakayama Medical
59 University (“Joint Research Project”) and The Peter Harrison Foundation (Grant# J13307).

60

61 **MeSH Keywords:** spinal cord injuries; tetraplegia; cerebrovascular circulation; arterial blood

62 pressure; sympathetic nervous system; cold

63 **Alphabetical list of abbreviations**

64 CA = cerebral autoregulation

65 CI = confidence interval

66 CBF = cerebral blood flow

67 SCI = spinal cord injury

68 MAP = mean arterial pressure

69

70 **INTRODUCTION**

71 The precise regulation of cerebral blood flow (CBF) is essential in preventing
72 unconsciousness and brain damage.^{1, 2} The capacity of the central vasculature to maintain
73 CBF by adjusting cerebrovascular resistance over a range of mean arterial pressure (MAP) is
74 referred to as cerebral autoregulation (CA).³⁻⁵ The physiological mechanisms responsible for
75 CA are not yet clear, but include myogenic (smooth muscle responding to changes in vascular
76 wall tension), cholinergic, and sympathetic mechanisms.^{3, 6-11} CA is typically evaluated by
77 measuring CBF changes in response to a steady-state change in MAP ('static' CA), or by
78 measuring CBF changes in response to transient fluctuations in MAP ('dynamic' CA). Static
79 CA has for example been determined by examining mean CBF changes relative to MAP
80 changes over two minutes in response to orthostatic stress,^{12, 13} while dynamic CA is
81 evaluated commonly using transfer function coherence, gain and phase of spontaneous
82 changes in MAP and CBF velocity.^{14, 15} Coherence reflects the linear correlation between
83 changes in MAP and changes in CBF velocity, gain reflects the magnitude in which a given
84 change in MAP alters CBF velocity, and phase reflects the time delay between changes in
85 MAP to be reflected in changes in CBF velocity.^{14, 15} A higher transfer function gain can be
86 interpreted as the primary indicator of less adequate dynamic CA, while a higher coherence
87 and shorter phase may also reflect less adequate dynamic CA.^{14, 15} Important to note is that
88 static and dynamic CA represent two experimental approaches for quantifying the relationship
89 between MAP and CBF velocity over different time scales⁶ and not necessarily distinct
90 physiological mechanisms.³

91 Whether disruption of central sympathetic control, present in individuals with cervical
92 spinal cord injury (SCI),¹⁶ leads to inadequate CA remains unclear.¹⁷⁻¹⁹ An inability to buffer
93 the frequently occurring periods of high and low MAP caused by impaired sympathetic
94 control¹⁶ may explain why the SCI population is at increased risk of stroke and

95 cerebrovascular disease.^{18, 20, 21} Prior studies indicate that static CA is not different in
96 participants with chronic cervical SCI compared to able-bodied controls (see ¹⁷ for an
97 overview), while data from able-bodied participants indicates that pharmaceutically-induced
98 sympathetic blockade has little or no effect on static CA.^{6, 22} However, each of these studies
99 tested the capacity to maintain CBF during reductions in MAP, which in able-bodied
100 individuals exhibits less effective buffering than increases in MAP, a phenomenon called CA
101 hysteresis.^{3, 4, 23, 24} Static CA has also been reported to be similar between participants with
102 SCI and able-bodied controls in response to increases in MAP evoked via the cold pressor
103 test.^{25, 26} However, it remains unclear whether this stress elicited peripherally-mediated
104 sympathetic outflow secondary to autonomic dysreflexia.²⁷⁻²⁹ Furthermore, prior studies have
105 largely failed to measure respiratory rate, P_{aO_2} and P_{aCO_2} , which can influence interpretation of
106 CA.^{15, 30, 31} As such, it has yet to be tested whether static CA is also similar between
107 individuals with cervical SCI and able-bodied controls in response to moderate increases in
108 MAP without peripherally-mediated sympathetic outflow and changes in respiratory rate, P_{aO_2}
109 and P_{aCO_2} .

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

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

127

128

129 **METHODS**

130

131 **Participants**

132 Five otherwise healthy men with C5/C6 lesions (5-26 y post-injury; AIS A: n=4; AIS B: n=1)
133 participated in the study, along with six healthy age-matched able-bodied men who served as
134 a control group (Table 1). Resting levels of plasma noradrenaline < 94 pg/mL indicated
135 autonomic completeness^{19, 35} (Table 1). In addition, the drop of 19 to 30 mmHg in systolic
136 blood pressure measured during a sit-up test³⁶ was also suggestive of autonomic
137 completeness. Two additional participants (SCI: n=1, aged 25 y; able-bodied: n=1, aged 28 y)
138 were excluded from the study given an unanticipated decrease in MAP during the cold stress
139 stage (SCI: -7 mmHg; able-bodied: -11 mmHg).

140

141 **Procedures**

142 All participants fasted for ≥ 4 hours before the trial and emptied their bladder upon arrival at
143 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 27.5-28.6⁰C 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 33⁰C 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 33⁰C water through the suit), mild cold stress (20 min with 25⁰C
151 water) and post-cold recovery (30 min with 33⁰C 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

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

176

177 **Body temperature**

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

184

185 **Respiratory outcomes**

186 Open-circuit spirometry and mass spectrometry (ARCO-2000, Arco System Inc., Kashiwa,
187 Japan) were used to measure respiratory rate, P_{ETCO_2} and P_{ETO_2} , which have been shown to be
188 valid estimators of P_{aO_2} and P_{aCO_2} .³⁰

189

190 **Catecholamines**

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

194

195 **Data analysis**

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

202

203 **Static and dynamic CA**

204 Static CA was determined as the ratio between mean changes in CBF velocity and MAP
205 (cm/s/mmHg)⁴ from baseline to the mild cold stress, and from baseline to the post-cold
206 recovery. For the spectral power and transfer function outcomes underpinning dynamic CA,
207 beat-to-beat MAP and CBF velocity were obtained by integrating the respective signals
208 within each cardiac cycle. Cardiac cycles were determined based on the diastolic (nadir-to-
209 nadir) intervals of the beat-by-beat blood pressure signal. Beat-to-beat MAP and CBF velocity
210 were first linearly interpolated and resampled at 2 Hz and then detrended by subtracting their
211 3rd order polynomial.^{15, 22} Subsequently, the beat-to-beat time series were used for spectral and
212 transfer function analyses based on the Welch algorithm.¹⁵ Each time series was subdivided
213 into successive 256-point Hann windows that overlapped by 50% before fast Fourier
214 transform analysis.^{14, 15} This resulted in a spectral resolution of 0.0020 Hz in all but two
215 participants (0.0039 Hz). The cross-spectrum between MAP (input) and CBF velocity
216 (output) was determined and divided by the MAP autospectrum to derive the transfer function
217 coherence, gain and phase.¹⁵ Spectral power of MAP and CBF velocity as well as coherence,
218 gain and phase were averaged over the previously established 0.07-0.20 Hz low-frequency

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

223

224 **Statistical analyses**

225 A previous study found significant differences between an able-bodied (n=7) vs a cervical
226 SCI group (n=4) in transfer function gain during supine conditions (1.1±0.1 vs. 1.5±0.1
227 mm/s/mmHg, respectively).¹⁹ These data were used in G*Power 3.1.9.3 for Mac OS X⁴³ to
228 estimate that sample sizes of $N \geq 5$ (able-bodied) and $N \geq 3$ (cervical SCI), based on 95%
229 power, are required to detect mean differences in transfer function gain of 0.4 cm/s/mm Hg,
230 using a two-tailed test with $\alpha=0.05$. The mean and 95% confidence interval (CI) of the
231 difference was calculated for each within and between-group comparison. In addition,
232 parametric statistics were applied to all outcome measures with a normal distribution, which
233 was assessed using Shapiro-Wilks tests ($p < 0.05$). Data were log-transformed if the Shapiro-
234 Wilk test indicated a non-normal distribution. Comparison of baseline characteristics between
235 the able-bodied and cervical SCI group were conducted using unpaired two-tailed Student *t*-
236 tests. Hemodynamic, body temperature, respiratory and catecholamine responses from
237 baseline to mild cold stress and post-cold recovery within and between the able-bodied and
238 cervical SCI group were assessed using 2 x 3 repeated measures ANOVA. Between-group
239 comparisons of static and dynamic CA outcomes were conducted using unpaired two-tailed
240 Student *t*-tests. The interaction term of 2 x 3 ANOVA was used to assess whether responses
241 in transfer function coherence, gain and phase to mild cold stress and post-cold recovery were
242 different between the able-bodied and cervical SCI group. The significance level was set at
243 $p < 0.05$. Analyses were conducted using SPSS Statistics v22 (SPSS Inc., Chicago, USA).

244

245 **Statement of ethics**

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

250

251 **RESULTS**

252

253 **Baseline characteristics**

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

259

260 **Responses to mild whole-body cold stress**

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

269 from baseline to cold, but decreased during the post-cold stage (main effect of time: $p < .001$).
270 Respiratory outcomes were stable in both groups (main effects of time: $p = 0.57-0.97$;
271 interaction terms: $p = 0.33-0.91$), indicating that these outcomes did not confound the
272 interpretation of static or dynamic CA results (see below). For catecholamines, the increases
273 in noradrenaline in the able-bodied group during cold and post-cold recovery differed from
274 the stable noradrenaline levels observed in the cervical SCI group (main effect of time:
275 $p < .001$; interaction term: $p < .001$), in contrast to the responses observed in adrenaline (main
276 effect of time: $p = 0.06$; interaction term: $p = 0.09$). In the spectral outcomes, no differences
277 were observed in the groups for low-frequency power of MAP or CBF velocity (main effect
278 of time: $p = 0.15$ and 0.80 ; interaction terms: $p = 0.10$ and 0.15 , respectively).

279

280 **Static CA**

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

286 Also for the post-cold recovery, no differences in static CA were observed when the able-
287 bodied group (mean \pm SD: 0 ± 1 cm/s/mmHg) and cervical SCI group (mean \pm SD: 2 ± 3
288 cm/s/mmHg) were compared (mean [95% CI] of between-group difference: -2 [-5 to 1]
289 cm/s/mmHg; $p = 0.22$).

290

291 **Dynamic CA**

292 Table 3 presents the between-group comparisons of transfer function outcomes at baseline.

293 For dynamic CA at baseline, transfer function in the cervical SCI group demonstrated a

294 shorter phase ($p=0.006$) but no difference in coherence ($p=0.40$) or gain ($p=0.08$) when
295 compared to the able-bodied group. Figure 1 presents the responses in transfer function
296 outcomes during and following exposure to the mild cold stress. When compared to baseline,
297 smaller or no between-group differences in phase were observed during cold (mean [95% CI]:
298 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;
299 $p=0.15$). However, the responses in phase were not different between the groups when
300 analyzed using 2 x 3 ANOVA (interaction term: $p=0.06$). Responses between the groups were
301 also not different for coherence (interaction term: $p=0.07$) or gain (interaction term: $p=0.41$).

302

303 **DISCUSSION**

304 This pilot study is the first to characterize static and dynamic CA in individuals with cervical
305 SCI using a moderate increase in MAP caused by mild-whole body cold stress. Importantly,
306 this intervention evoked a moderate increase in MAP without signs of peripherally-mediated
307 sympathetic outflow or changes in respiratory rate, P_{aO_2} and P_{aCO_2} . These preliminary data
308 suggest that static CA in response to moderate increases in MAP was similar between the
309 cervical SCI and able-bodied group. In contrast, the shorter transfer function phase between
310 spontaneous changes in CBF velocity and MAP in the cervical SCI group suggests that
311 dynamic CA was impaired in the cervical SCI group. Furthermore, smaller between-group
312 differences in transfer function phase were observed when MAP was increased in response to
313 the mild cold stress.

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

319 those findings by showing similar static CA during moderate MAP increases without signs of
320 peripherally-mediated increases in sympathetic outflow or changes in respiratory rate, P_{aO_2} and
321 P_{aCO_2} . Taken together, these results suggest that central sympathetic control is not a
322 prerequisite for static CA, in line with findings of the largely unaffected static CA after
323 pharmaceutically-induced sympathetic blockade in able-bodied participants.^{6, 22}

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

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

357 Given the absence of signs of peripherally-mediated sympathetic outflow or changes
358 in respiratory rate, P_{aO_2} and P_{aCO_2} , mild whole-body mild cold stress seems an appropriate
359 intervention for studying the role of the disturbed central sympathetic control in cervical SCI.
360 Not anticipated was that MAP was still significantly increased in both groups during the post-
361 cold stage. Even though mean skin temperature returned to baseline levels during the post-
362 cold stage, MAP was still significantly increased in the cervical SCI as well as the able-
363 bodied group. It seems the stressor was sufficient to maintain MAP at levels similar to the
364 cold stage, even 30 minutes after cessation of the stressor.

365

366 **Study limitations**

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

369 CBF.³ Although this assumption can be violated,⁴⁶ various studies have shown that changes in
370 middle cerebral artery diameter are unlikely during resting conditions without extreme
371 changes in MAP.⁴⁷ The moderate changes in MAP independent of a change in respiratory
372 outcomes observed in our study further strengthen the likelihood against a change in vessel
373 diameter. The goal of the present study was to compare each participant against their own
374 normothermic baseline. However, in this design, we cannot exclude the possibility that the
375 observed changes in the cervical SCI group were influenced by normal variations over time or
376 measurement error. These risks were reduced in our study by the post-cold measurements
377 demonstrating a return to baseline values in most outcomes, along with the previously
378 reported reliability of dynamic CA metrics during supine conditions,^{48, 49} which was further
379 enhanced by the use of rigorous artifact checking⁴⁰ and use of weighting based on coherence
380 level.¹⁴ Finally, unconscious bias due to the unblind nature of the present protocol cannot be
381 excluded. To reduce such risk, all data analyses were conducted by one author (JWvdS) and
382 independently verified by another author (YK).

383

384 **Recommendations for future research**

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

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

402

403 **Conclusions**

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

410

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417

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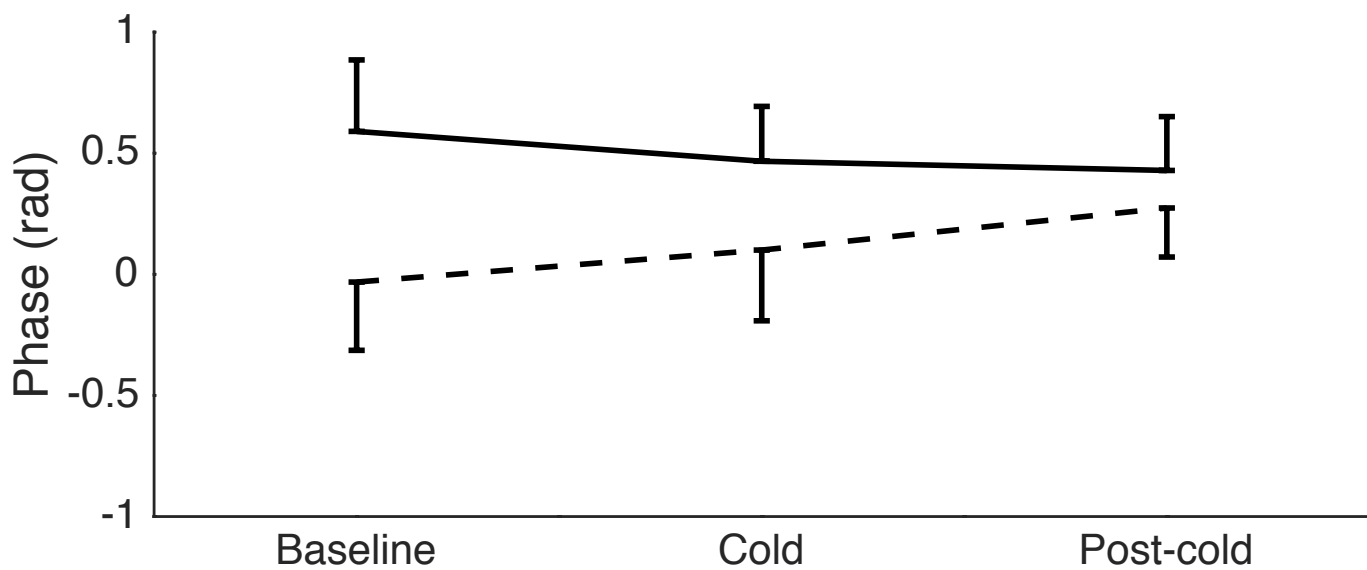
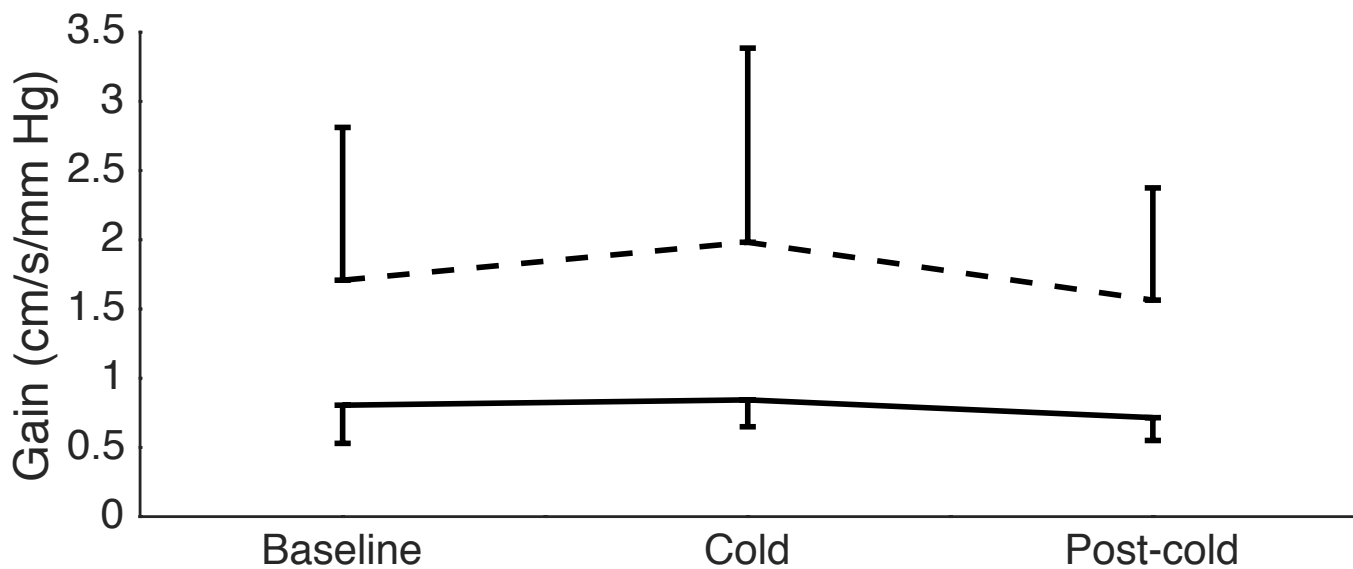
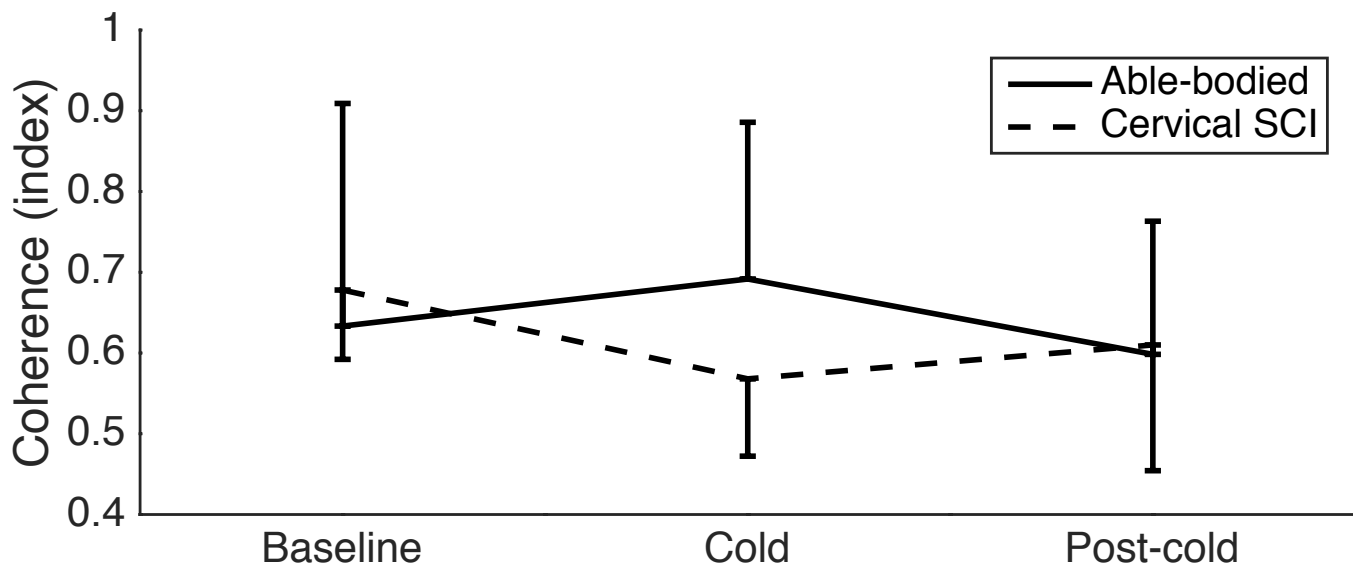
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420 **Titles and legends to Figures**

421

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

425



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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 (°C)	34.9±0.6	34.6±0.6	0.3 (-0.5 to 1.1)
Oesophageal temperature (°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.

616 **Table 2.** Within-group responses in hemodynamic, body temperature, respiratory, catecholamine, and spectral outcomes during and following exposure to
 617 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 \pm SD (95% CI)	Mean \pm SD (95% CI)	Mean \pm SD (95% CI)	Mean \pm SD (95% CI)
Hemodynamic				
MAP upper-arm cuff (mm Hg)**	5 \pm 3 (2 to 7)	6 \pm 4 (2 to 9)	7 \pm 7 (-2 to 16)	10 \pm 8 (1 to 20)
CBF velocity (cm/s)	1 \pm 6 (-6 to 7)	1 \pm 5 (-5 to 7)	1 \pm 7 (-7 to 10)	2 \pm 2 (0 to 5)
Heart rate (beats/min)*	-3 \pm 3 (-6 to 0)	0 \pm 3 (-3 to 4)	-1 \pm 1 (-3 to 0)	0 \pm 3 (-4 to 4)
Stroke volume (mL)	0 \pm 3 (-3 to 3)	0 \pm 5 (-4 to 4) ^a	1 \pm 3 (-3 to 4)	-3 \pm 7 (0 to -6)
Cardiac output (L/min)*	-0.4 \pm 0.3 (-0.7 to 0.0)	-0.1 \pm 0.3 (-0.5 to 0.2) ^a	-0.2 \pm 0.2 (-0.4 to 0.1)	-0.4 \pm 0.4 (-0.1 to -0.7)
Body temperature				
Mean skin temperature (^o C)***	-1.7 \pm 0.5 (-2.2 to -1.2)	-0.4 \pm 0.6 (-1.1 to 0.2)	-2.1 \pm 0.3 (-2.5 to -1.7)	-0.4 \pm 0.6 (-1.1 to 0.4)
Oesophageal temperature (^o C)***	0.0 \pm 0.1 (-0.1 to 0.1)	-0.2 \pm 0.1 (-0.3 to 0.0)	-0.1 \pm 0.1 (-0.2 to 0.0)	-0.3 \pm 0.2 (-0.5 to -0.1)
Respiratory				
End-tidal P _{CO2} (mm Hg)	1 \pm 1 (0 to 2)	0 \pm 1 (-1 to 0)	0 \pm 2 (-3 to 2)	0 \pm 0 (-2 to 1)
End-tidal P _{O2} (mm Hg)	0 \pm 2 (-2 to 2)	0 \pm 2 (-2 to 2)	0 \pm 5 (-5 to 6)	0 \pm 3 (-4 to 3)
Respiratory rate (Hz)	0.01 \pm 0.04 (-0.03 to 0.05)	0.02 \pm 0.03 (-0.02 to 0.05)	0.00 \pm 0.02 (-0.03 to 0.03)	-0.01 \pm 0.03 (-0.05 to 0.03)
Catecholamines				
Noradrenaline***#	47 \pm 81 (-38 to 133)	183 \pm 72 (108 to 258)	-1 \pm 21 (-27 to 25)	21 \pm 17 (-1 to 43)
Adrenaline	-5 \pm 9 (-14 to 4)	13 \pm 22 (-10 to 36)	0 \pm 0 (0 to 0)	1 \pm 2 (-1 to 3)
Spectral power				
Power MAP (mm Hg ² /Hz)	6.2 \pm 8.4 (-2.6 to 15.1)	1.4 \pm 3.6 (-2.5 to 5.2)	0.0 \pm 1.0 (-1.2 to 1.3)	1.2 \pm 1.0 (-0.1 to 2.4)
Power CBF velocity ([cm/sec] ² /Hz) ^b	0.7 \pm 5.8 (-5.3 to 6.8)	-2.3 \pm 10.0 (-12.8 to 8.2)	1.1 \pm 3.0 (-2.6 to 4.8)	4.7 \pm 4.4 (-0.8 to 10.2)

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

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

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

621 ^a Missing data for n=1

622 ^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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