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RESEARCH ARTICLE

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Effect of hypotensive challenge on systemic hemodynamics and cerebral blood flow in persons with tetraplegia

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Abstract *Introduction* Individuals with tetraplegia have impaired central control of sympathetic vascular modulation and blood pressure (BP); how this impairment affects cerebral blood flow (CBF) is unclear. *Objectives* To determine if persons with tetraplegia maintain CBF similarly to able-bodied controls after a hypotensive challenge. *Methods* Seven individuals with chronic tetraplegia and seven age-matched, non-SCI control subjects underwent a hypotensive challenge consisting of angiotensin-converting enzyme (ACE) inhibition (1.25 mg enalaprilat) and 45° head-up tilt (HUT). Heart rate (HR), low frequency systolic BP variability (LFsbp), brachial mean arterial pressure (MAP) and middle cerebral artery CBF were measured before and after the challenge. Group differences for the baseline (BL) to post-challenge response were determined by repeated measures ANOVA. *Results* HR did not differ between the groups in response to the hypotensive challenge. LFsbp response was significantly reduced in the tetra compared to the control group (−38 ± 51 vs. 72 ± 93%, respectively). MAP did not differ between the groups at BL but was significantly lower in the tetra compared to the control group post-challenge (55 ± 13 vs. 71 ± 9 mmHg, respectively); the percent change in MAP was significantly greater in the tetra than in the control group (−29 ± 14.1 vs. −13 ± 9%, respectively). However, CBF did not differ between the groups at baseline or post-challenge; the percent change in CBF post-challenge was not different between the tetra and control groups (−29 ± 13.2 vs. −23 ± 10.3%, respectively). *Interpretation* Despite impaired sympathetic vasomotor and BP control, CBF in persons with tetraplegia was comparable to that of control subjects during a hypotensive challenge.

Key words spinal cord injury · autonomic nervous system disorder · orthostatic hypotension · angiotensin-converting enzyme inhibitor · tilt-table test

Introduction

Persons with tetraplegia, due to disruption of descending spinal pathways to sympathetic pre-ganglionic neurons manifest altered cardiovascular control [1, 5, 6]. Therefore, persons with tetraplegia have a diminished capacity to increase sympathetic activity with upright posture [1, 2, 5, 6, 21, 28]. As a consequence of interrupted supraspinal control of sympa-

thetic activity, persons with tetraplegia are frequently reported to have MAP values below the lower limit for effective cerebral autoregulation reported in healthy controls (60 mmHg) [3, 16]. However, the hypotension in this population is often asymptomatic and, as such, may not be associated with cerebral hypoperfusion [1, 5, 10, 15]. The mechanism for this increased tolerance to hypotension in those with tetraplegia is unclear, and current data are inconclusive regarding the absolute systemic pressure below which persons with tetraplegia have cerebral hypoperfusion.

There is limited literature on the relationship between change in BP and the concurrent change in CBF in persons with SCI. The objective of this investigation was to determine CBF and MAP responses to a pharmacologic and mechanical hypotensive challenge in individuals with tetraplegia and able-bodied controls to gain insight into the relationship between systemic blood pressure and CBF. We hypothesized that due to chronic hypotension, persons with tetraplegia would maintain CBF comparable to controls, despite significantly lower MAP.

Methods

Subjects

All subjects (tetraplegia = 7; able-bodied = 7) were between 19 and 60 years old and had no known history of cardiovascular disease, pulmonary disease or diabetes mellitus. Subjects were current non-smokers for a minimum of one year prior to the investigation, were not taking medications known to effect autonomic cardiovascular function, and were free from acute illness; none were pregnant. Subjects with tetraplegia were at least one year post-injury. Using the American Spinal Injury Association (AIS) standards for neurological impairment [17], four individuals were diagnosed with complete injury (AIS A) and the other three with incomplete injury (AIS B and C); none were ambulatory. The able-bodied subjects were matched for age, height and weight to those with tetraplegia. All subjects were on an unrestricted sodium diet and were not taking medications known to interfere with salt and water homeostasis. The Institutional Review Board for Human Studies of the James J. Peters Veterans Affairs Medical Center granted approval for this investigation and informed consent was obtained prior to commencing the study.

Protocol procedures

This study was designed to compare the pre- and post-challenge values for heart rate (HR), systemic blood pressure (MAP) and cerebral blood flow (CBF) between individuals with tetraplegia compared to matched controls. The mechanisms of BP control were also compared between the groups; specifically, sympathetic vascular control (LFsbp) and the vasoactive hormone concentrations (active plasma renin and serum aldosterone). In addition, responses to the BP challenge for MAP, CBF, LFsbp, renin and aldosterone were compared between the groups.

HR data represent the average of three 5-minute continuous ECG recordings in the baseline position and a single 5-minute recording in the 45° HUT position. MAP data is reported as the average of three brachial pressure recordings at baseline (0, 20 and 40 minutes) and one measurement taken within the first 5 minutes at 45° HUT. A 60-second continuous recording of transcranial Doppler (TCD) ultrasound of the middle cerebral artery was used to determine CBF [16, 24, 27]. The baseline value for CBF is reported as the average of three 60-second recordings; the 45° HUT value is a single 60-second continuous recording taken within the first five minutes of tilt. Sympathetic vasomotor activity was quantified from the low frequency (0.04–0.15 Hz) portion of the spectral analysis of beat-to-beat systolic blood pressure (LFsbp) [8, 14, 22, 25]. Baseline LFsbp is reported as the average of three continuous 5-minute recordings and 45° HUT LFsbp is a single 5-minute recording taken within the first five minutes of tilt. Baseline aldo and renin data are the average of two blood draws (0 and 40 minutes); the 45° HUT levels are reported from a single blood sample taken within the first five minutes of tilt.

Fourteen subjects reported to the laboratory between 10 AM and 1 PM, at least four hours post-prandial, instructed to be well hydrated, and to have avoided caffeine and alcohol for at least 24 hours prior to testing. Supine BP was obtained prior to study initiation, and if MAP was less than 55 mmHg, the study would be postponed. During the visit, HR, MAP, CBF, LFsbp and the vasoactive hormonal responses to the BP challenge were evaluated. The hypotensive challenge included the combined intravenous infusion of an angiotensin-converting enzyme (ACE) inhibitor [1.25 mg of Vasotec (enalaprilat: Biovail, Morrisville, NC)] and a subsequent progressive head-up tilt (HUT) maneuver to 45º. This challenge was selected to exaggerate the hypotensive response in persons with tetraplegia who are reported to have an increased dependence on the renin-angiotensin-aldosterone system for orthostatic BP maintenance [19, 20, 28].

Upon arrival to the laboratory, subjects were transferred or were instructed to lie on the tilt table in the supine position for a minimum of 20 minutes. While resting quietly, ECG electrodes were applied to the chest for continuous HR monitoring (742 Mennen Medical ECG Monitor, Bio-Medical Equipment Service Co. Louisville, KY, USA). A TCD probe was positioned and stabilized over the temporal area for assessment of middle cerebral artery blood flow velocity. A BP cuff was placed around the left upper arm for periodic manual BP recordings (W.A. Baum Co. Inc., Copiague, NY) and beat-to-beat BP was continuously monitored at the third and fourth fingers of the right hand using a Portapres Model-2 (Finapres Medical Systems BV, Arnhem, The Netherlands). The tilt table was then adjusted to the 15° HUT position and baseline (BL) data were collected at 0, 20, 40 minutes; the average of these three data collection segments was used as the BL value.

Tilt table testing

The tilt-table was padded and motorized. Restraining straps were used on the lower extremities and trunk to insure subject safety during higher inclinations of HUT and to avoid lower extremity muscle contractions in the control subjects. The straps were wide and padded for subject comfort and to insure that stimulation of sympathetic spinal reflexes was not evoked in subjects with tetraplegia. The orthostatic provocation involved a progressive HUT maneuver from a baseline of 15° to 25°, 35° and 45° for five minutes at each angle. Adjustment of the tilt table was accomplished in less than five-seconds and subjects were questioned at each angle of inclination regarding symptoms of cerebral hypoperfusion (i.e., blurry vision, dizziness, light-headedness or nausea).

ACE inhibitor administration

IV infusion of the ACE inhibitor Vasotec (enalaprilat; 1.25 mg) was administered over a five-minute period. This dose of enalaprilat is the standard recommended dose. In a prior report in subjects with

tetraplegia severe hypotensive effects did not occur after the administration of 0.625 mg enalaprilat [26, 28]. A clinical response to enalaprilat is usually reported within 15 minutes of administration, and although peak responses have been documented for up to 4 hours, the hemodynamic effect is generally apparent within the first hour of administration [26]. To ensure near peak hemodynamic effects of the ACE inhibitor, the HUT maneuver was initiated 20 minutes after beginning the drug infusion and continued for 15 minutes thereafter. Enalaprilat does not readily cross the blood-brain barrier [9, 26].

Manual blood pressure

Blood pressure was measured and recorded every 10 minutes during the baseline period and one time at each angle of HUT by auscultation at the brachial artery using a manual mercury sphygmomanometer (W.A. Baum Co. Inc., Copiague, NY). BP was monitored during recovery in all subjects until MAP returned to pre-tilt levels (±5%) to ensure subject safety, especially in persons with tetraplegia.

Cerebral blood flow

A TCD probe operating at 2.0 MHz (PMD 100, Spencer Technologies, Terumo Cardiovascular Systems, Tustin CA) was positioned and stabilized over the temporal area for sonographic measurement of middle cerebral artery blood flow velocity. Mean flow velocity (MFV) of the middle cerebral artery has been reported to be a valid index of CBF [16, 24, 27]. The middle cerebral artery is a conductance vessel and under normal physiologic conditions its diameter was shown to vary little [27]. Thus, changes in MFV of the middle cerebral artery correlate with changes in CBF. All data were saved to a hard disc for storage and subsequent analysis of the Doppler waveforms to determine MFV (MFV $= [V_{\text{systolic}} + (V_{\text{diastolic}} \times 2)]/3$).

Low frequency systolic blood pressure variability

Beat-to-beat SBP was measured at the third and fourth fingers by photoplethysmography (Portapres Model-2, Finapres Medical Systems BV, Arnhem, the Netherlands). Variability of systolic blood pressure peaks was converted into the frequency domain by fast Fourier transform algorithms. The low frequency portion (0.04–0.15 Hz) of that frequency spectrum has been shown to be a valid index of sympathetic vasomotor activity in persons with SCI, as well as control subjects [8, 25]. An increase in sympathetic vasomotor activity elicited during an orthostatic challenge will be reflected by increased spectral power centered around 0.1 Hz (Mayer waves) [22]. Low frequency systolic blood pressure variability (LFsbp) was used to compare the sympathetic nervous system response to the hypotensive challenge between the two groups. Respiratory rates were not controlled but were continuously monitored during the study using an impedance pneumographer (RESP 1: UFI; Morro Bay, California).

Vasoactive hormonal assessments

Active plasma renin and serum aldosterone concentrations were assessed by radioimmunoassay (Renin IRMA, DSL-25100, Aldosterone RIA, DSL-8600; the mean intra-assay CV for plasma renin and serum aldosterone is 1.29 and 3.9%, respectively; Diagnostic Systems Laboratories, Inc., Webster, Texas). Antecubital venous blood samples were collected at 0 and 40 minutes during the BL period (15° HUT) and once at the 45° HUT position.

Heart rate

A continuous ECG signal recorded from a three lead configuration was used to continuously monitor HR (742 Mennen Medical ECG Monitor, Bio-Medical Equipment Service Co. Louisville, Kentucky). Electrodes were placed at the distal right and left clavicle and in the left lateral fifth intercostal space (V-5) using standard skin-abrading and hair-shaving methods. Data were recorded from the V-5 electrode to be used for possible future analysis.

Symptomatic assessment

The presence of symptoms of orthostatic hypotension (OH) was assessed every 10 minutes during the baseline period, and once at each angle of HUT using a 9-point subjective questionnaire based on the common symptoms of cerebral hypoperfusion [18]. The questionnaire determined the presence and severity of symptoms, including dizziness, light-headedness, sweating, blurred vision, nausea, fatigue, faintness (symptoms of syncope) and chest discomfort. If presyncopal symptoms were evident, the test was immediately terminated and the subject was returned to the supine, or if necessary, the Trendelenburg position, with the feet elevated above the head. During all experimental procedures, advanced life support measures were available in case emergent care was needed.

Data analysis

Data were analyzed using a statistical analysis program (StatView, SAS Institute). Unpaired *t* tests were used to assess group differences for demographic, BL and post-challenge data. Group differences for the response from baseline to post-challenge of HR, MAP, CBF, LFsbp, aldosterone and renin, were assessed using repeated measures ANOVA. Statistical significance was set at an alpha level of $P < 0.05$.

Results

Demographic characteristics of each group were similar for age, height, weight and body mass index (BMI) (Table 1). The individual characteristics of the subjects with tetraplegia are shown (Table 2); four of the seven individuals had a complete lesion, no subject was ambulatory, and all were chronically injured. Of the seven individuals with tetraplegia, two became symptomatic during the challenge; both of these subjects had a complete lesion at C5. One individual with a higher (C4), complete and more recent lesion (one year post injury) did not have symptoms of cerebral hypoperfusion; the other asymptomatic

Table 1 The mean characteristics of subjects in each group

	Tetraplegia $n = 7$	Controls $n = 7$
Age (years)	41 ± 11.6	37 ± 14.4
Height (cm)	173 ± 5.9	169 ± 8.8
Weight (kg)	73 ± 7.1	71 ± 9.8
BMI (kg/m^2)	24 ± 2.4	25 ± 2.5
DOI (years)	17 ± 13.9	NA

Data are means ± SD
BMI body mass index, *DOI* duration of injury

Table 2 The individual characteristics of subjects with tetraplegia

Subject #	Age (years)	Gender	Ht (cm)	Wt (kg)	Neurological Level	DOI (years)	AIS	Symp/Asymp
15	40	M	168	73	C5	1	A	Asymptomatic
08	25	M	175	69	C5	6	A	Symptomatic
05	32	M	165	74	C6	8	A	Symptomatic
17	60	M	175	75	T1	30	A	Asymptomatic
02	41	M	178	66	C5	28	C	Asymptomatic
03	51	F	168	66	C7	35	B	Asymptomatic
09	38	M	180	86	C8	8	B	Asymptomatic

DOI duration of SCI, *AIS* American Spinal Injury Association standards for neurological impairment, *Symp/Asymp* symptomatic or asymptomatic response to hypotensive challenge

Table 3 The mean baseline data for tetraplegia and control groups

	Tetraplegia	Controls	Significance
Heart Rate (bpm)	67 ± 14	61 ± 7	NS
LFsbp ($mmHg^2/Hz$)	28.2 ± 21.2	35.0 ± 18.7	NS
Mean arterial pressure (mmHg)	78 ± 9	82 ± 9	NS
CBF (cm/sec)	53.2 ± 14.8	48.2 ± 15.0	NS
Active Plasma Renin (pg/mL)	31.6 ± 42.9	10.9 ± 4.3	NS
Range (pg/mL)	8.0–22.5	4.1–17.0	
Aldosterone (pg/mL)	65.0 ± 35.5	68.7 ± 17.4	NS
Range (pg/mL)	38.7–130.1	54.7–99.0	

LFsbp low frequency systolic blood pressure variability, *CBF* cerebral blood flow

subjects with tetraplegia had lower and/or incomplete lesions. Baseline cardiovascular, autonomic, respiratory and hormonal data were not significantly different between the groups (Table 3).

Post-challenge MAP and LFsbp were reduced in the tetraplegia compared to the control group ($P < 0.05$) (Table 4). However, mean values for CBF, HR and respiration rates did not differ between the two groups. The active plasma renin and serum aldosterone responses to the hypotensive challenge were increased in the group with tetraplegia compared to the control group, although this difference did not attain statistical significance.

Post-challenge data for MAP and CBF are presented by group and study subject (Figure 1). In five subjects with tetraplegia, post-challenge MAP was at or below the lower threshold measured in the control group (62 mmHg), but CBF remained within a similar range in both groups.

Discussion

These data suggest that in individuals with chronic tetraplegia, CBF is maintained within a range of values similar to that demonstrated in a matched control group, despite having lower absolute MAP.

There have been several reports on the effects of orthostatic maneuvers on CBF and MAP in persons with tetraplegia; the results are somewhat conflicting and none has identified a lower limit of MAP below which CBF is compromised [10–12, 23]. One study examined group differences for the change in MAP and CBF during a graded HUT maneuver among symptomatic and asymptomatic individuals with tetraplegia [10]. However, mean data were reported and no reference was made to the lower limit of systemic pressure, which may have distinguished these groups [10].

In the present study, two individuals with tetraplegia became symptomatic (MAP = 47 and 41 mmHg), and although three other subjects with tetraplegia were at or below the theorized lower limit of cerebral autoregulation (60 mmHg) cerebral hypoperfusion was not evident. In conjunction with significant falls in MAP in the two symptomatic subjects with tetraplegia, CBF fell by 32 and 50% to an absolute blood flow of 26 and 27 cm/second, respectively. These absolute CBF values in the two symptomatic subjects with tetraplegia remained within the range of scores for CBF documented in both groups of subjects herein, albeit they were just above values at the lower threshold. From these data, it seems that

Table 4 The mean post-challenge data for tetraplegia and control groups

	Tetraplegia	Controls	Significance
Heart Rate (bpm)	74 ± 13	72 ± 12	NS
(% change)	11 ± 14	19 ± 13	NS
LFsbp ($mmHg^2/Hz$)	13.3 ± 7.3	56.1 ± 35.9	*P = 0.02*
(% change)	−37.6 ± 50.6	71.5 ± 93.3	*P = 0.04*
Respiratory Rate (brths/min)	14 ± 3.4	14 ± 2.4	NS
(% change)	−8.9 ± 19.9%	−4.1 ± 14%	NS
Mean arterial pressure (mmHg)	55 ± 13	71 ± 9	*P = 0.02*
(% change)	−29 ± 14	−13 ± 9	*P = 0.02*
CBF (cm/sec)	37.9 ± 15.1	36.3 ± 7.5	NS
(% change)	−29.5 ± 13.2	−22.9 ± 10.4	NS
Active Plasma Renin (pg/mL)	96.7 ± 72.3	37.9 ± 26.5	NS
Range (pg/mL)	17–220	7–75	NS
Aldosterone (pg/mL)	131.7 ± 139.0	74.1 ± 17.0	NS
Range (pg/mL)	42–398	57–95	NS

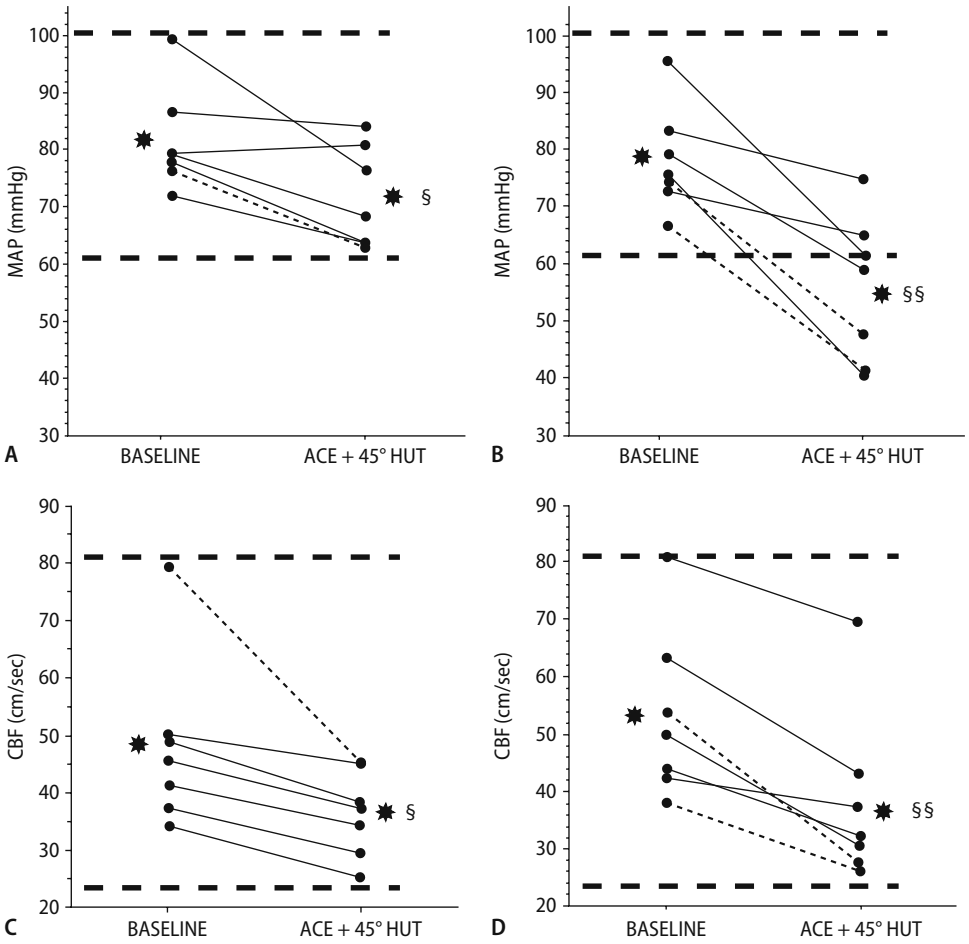

Fig. 1 The change in MAP and CBF from baseline to post-challenge. MAP: **a** controls and **b** tetraplegia; CBF: **c** controls and **d** tetraplegia. *Bold dashed lines* represent the upper and lower threshold as measured herein in the control group; *filled star* represents the group mean values; significant change from baseline § = $P<0.05$; §§ = $P < 0.01$. *Dashed lines* Symptomatic subjects

although MAP is compromised to a greater degree in subjects with tetraplegia, CBF is maintained comparable to controls and that the lower limit of MAP may be expanded to compensate for chronic hypotension in this group.

One control subject became symptomatic when MAP fell to just above the theorized lower limit of cerebral autoregulation of blood flow (62 mmHg); CBF was reduced by 44% but still was maintained at a higher absolute CBF (45 cm/second) than the other asymptomatic or symptomatic subjects with tetraplegia. It is interesting to note that baseline CBF was much higher in the one symptomatic control subject (79 cm/second) compared to the mean of the other six controls (43 ± 6 cm/second). Whether this is a transient finding or a cerebral vascular adaptation to chronic hypotension/hypoperfusion it is not known, however this mechanism was not evident in the subjects with tetraplegia.

The control subjects in this study were able to minimize the fall in MAP during the hypotensive stressor by increasing sympathetic activity, as evidenced by a 72% increase in post-challenge LFsbp. In the group with tetraplegia, absence of an increase in LFsbp reflected decentralized sympathetic vasomotor control. The average reduction in MAP in the group with tetraplegia was 23 mmHg with an associated mean post-challenge MAP of 55 mmHg compared to an average reduction in MAP of 11 mmHg in the control group with an associated post-challenge MAP of 71 mmHg.

The active plasma renin and aldosterone responses to the hypotensive challenge were increased in the group with tetraplegia, albeit not significantly. However, there was an association between the change in plasma renin and the fall in MAP in the group with tetraplegia, which suggests increased reliance on this hormonal mechanism to maintain BP, as previously reported [19, 20, 28]. It may be speculated that group differences in this study did not attain statistical significance due to the brevity of the orthostatic challenge (5 minutes), the large variation in subject data, and the relatively small sample size.

Study limitations

End-tidal CO_2 was not measured in this study and, therefore, the influence of chemoreceptor sensitivity and CO_2 retention on CBF dynamics was not assessed. We appreciate that changes in PCO_2 may influence CBF independent of systemic blood pressure and there is evidence suggesting hyperventilation during HUT alters PCO_2 and TCD recordings of MFV in normal subjects [4]. However, a recent report suggests that during standing postures end-tidal CO_2 overestimates changes in arterial blood CO_2 and, therefore, postural changes in MFV of the MCA can not be accounted for by CO_2 reactivity alone [13]. Another limitation of the study is the lack of significant differences in baseline blood pressures and LFsbp among the groups. Although there is some evidence in the literature of similar supine resting BP values among subjects with tetraplegia and controls [1, 7], it is likely that the individuals with tetraplegia had predominantly incomplete autonomic spinal lesions, which may have contributed findings and renders extrapolation of the results to individuals with more complete lesions questionable. Finally, the change in MAP differed among the groups; the absolute post-challenge pressures were significantly lower in the group with tetraplegia than the control group. Thus, the group response of CBF to similar absolute post-challenge MAP could not be compared.

The ambitious goal of this study was to determine if the lower limit of cerebral autoregulation is expanded in persons with long standing tetraplegia. While this objective could not be definitively determined from these data due to the small sample of subjects with tetraplegia who became presyncopal, the evidence suggests that CBF is maintained in persons with tetraplegia within a range of scores comparable to the controls at systemic pressures which fall outside the theorized lower limit of autoregulation. This study has provided suggestive evidence that persons with chronic tetraplegia may be able to maintain CBF within a similar range as an age-matched control group despite having lower MAP. As expected, the renin-angiotensin system was shown to be more active in the maintenance of blood pressure during orthostatic challenge in subjects with tetraplegia than in controls. Future research aimed at defining the lower limit of systemic pressure below which CBF is compromised in persons with chronic SCI would be of physiological interest and clinical importance.

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Conflict of interest The authors have no involvement in any organization with a direct financial interest in the subject of this manuscript.

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