Cerebrovascular reactivity and dynamic autoregulation in tetraplegia

Luke C. Wilson, James D. Cotter, Jui-Lin Fan, Rebekah A. I. Lucas, Kate N. Thomas, and Philip N. Ainslie

1Department of Physiology, Otago School of Medical Science and 2School of Physical Education, University of Otago, Dunedin, New Zealand; and 3Department of Human Kinetics, University of British Columbia-Okanagan, Kelowna, British Columbia, Canada

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Wilson LC, Cotter JD, Fan JL, Lucas RA, Thomas KN, Ainslie PN. Cerebrovascular reactivity and dynamic autoregulation in chronic tetraplegia (Tetra). After baseline, steady-state hypercapnia (5% CO2) and hypocapnia (controlled hyperventilation) were used to assess cerebrovascular reactivity in 6 men with Tetra (C5–C7 lesion) and 14 men without [able-bodied (AB)]. Middle cerebral artery blood flow velocity (MCAv), cerebral oxygenation, arterial blood pressure (BP), heart rate (HR), cardiac output (Q; model flow), partial pressure of end-tidal CO2 (PETCO2), and plasma catecholamines were measured. Dynamic CA was assessed by transfer function analysis of spontaneous fluctuations in BP and MCAv. MCAv pulsatility index (MCAv PI) was calculated as (MCAv systolic – MCAv diastolic)/MCAv mean and standardized by dividing by mean arterial pressure (MAP). Resting BP, total peripheral resistance, and catecholamines were lower in Tetra (P < 0.05), and standardized MCAv PI was ≈36% higher in Tetra (P = 0.003). Resting MCAv, cerebral oxygenation, HR, and PETCO2 were similar between groups (P > 0.05). Although phase and transfer function gain relationships in dynamic CA were maintained with Tetra (P > 0.05), coherence in the very low-frequency range (0.02–0.07 Hz) was ≈21% lower in Tetra (P = 0.006). Full (hypo- and hypercapnic) cerebrovascular reactivity to CO2 was unchanged with Tetra (P > 0.05). During hypercapnia, standardized MCAv PI reactivity was enhanced by ≈78% in Tetra (P = 0.016). Despite impaired cardiovascular function, chronic Tetra involves subtle changes in dynamic CA and cerebrovascular reactivity to CO2. Changes are evident in coherence at baseline and MCAv PI during baseline and hypercapnic states in chronic Tetra, which may be indicative of cerebrovascular adaptation.

spinal cord injury; cerebral autoregulation; reliability

HUMANS WITH SPINAL CORD INJURY (SCI) have major impairment in cardiovascular control that is dependent on the level and completeness of the lesion (27). The compromise in cardiovascular control is associated with loss of sympathetic nervous system control of the heart (38) and vasculature (42). Although the influence of SCI on the regulation of cerebral blood flow (CBF) is unclear, individuals with SCI are at higher risk of cerebrovascular disease such as stroke and transient ischemic attacks; additionally, those with tetraplegia (Tetra; lesion at or above C7) have a fivefold greater risk than those with paraplegia (Para; lesion at or below T1) (19, 33). Although recently challenged (29), CBF is traditionally thought to remain relatively constant within a range of blood pressures (BPs), at least in nonpathological situations. This unique characteristic of the mammalian brain is known as cerebral autoregulation (CA; Ref. 36). If CA fails, the brain is at risk of ischemic damage at low BP and of hemorrhage (stroke) at high BP (36). Such extremes of BP are common in SCI, especially during autonomic dysreflexia (26) and orthostatically induced hypotension (9).

CA adjusts cerebral arteriolar caliber, or cerebrovascular resistance (CVR), to ensure that CBF is matched to metabolic needs and comprises two main components: static and dynamic. Static CA acts to limit CBF changes over gradual changes in perfusion pressure (36). Dynamic CA refers to the rapid regulation of CBF in response to changes in arterial BP occurring within a few seconds (46). Dynamic CA may have different control mechanisms than static CA (12), including more effective neural control of CBF (46). Studies have indicated that static CA is maintained with SCI [Tetra chronic lesion C4–C7 (20, 34, 35)]. On the basis of a maintained CBF velocity during profound orthostatic stress, Gonzalez et al. (18) interpreted this finding to indicate that static CA was actually improved after acute Para and Tetra SCI (C5–T6); however, since no comparison was made with noninjured control subjects [preinjury or an able-bodied (AB) control group], this interpretation should be treated with caution. Furthermore, no study has examined whether dynamic CA is altered in Para or Tetra SCI. In view of the frequency and latency of severe BP changes in SCI and the lack of sympathetic cerebrovascular control in Tetra, assessment of dynamic CA is of particular relevance.

Absolute CBF and its distribution are also highly sensitive to changes in the partial pressure of arterial CO2 (PACO2; Ref. 2). This local control process—termed cerebrovascular CO2 reactivity—is a vital homeostatic function that helps regulate central pH, and therefore maintains breathing stability (2). Impairment in cerebrovascular CO2 reactivity has also been linked to an increased risk of certain cerebrovascular diseases [e.g., ischemic stroke (44)]. Experimental studies assessing cerebrovascular reactivity to CO2 in SCI individuals (14, 34, 35) have produced conflicting findings. One early study, conducted in Tetra [C5–C7 (14)], reported that hypercapnic CBF reactivity is maintained, although the control group in the study were high-level Para (T2–T4); thus these findings do not reveal whether CBF reactivity is maintained in SCI. However, the same group reported an abolished CBF hypocapnic reactivity and concluded that cerebral vasconstrictor response to hypocapnia was dependent on intact sympathetic nervous outflow from the spinal cord (14). In contrast, other studies (34, 35) found that hypocapnic reactivity is maintained with Tetra SCI (C4–8) compared with AB control subjects, indicating that cerebrovascular reactivity to hypocapnia is independent of
sympathetic control. These scant and divergent findings are difficult to interpret and warrant clarification for reasons of clinical importance (dampening CBF fluctuations) and physiological importance (CBF control mechanisms).

Therefore the purpose of this study was to examine whether the integrity of dynamic CA and the cerebrovascular responsiveness to changes in CO$_2$ are altered in chronic Tetra SCI. We tested the hypothesis that cerebrovascular function would be unchanged in chronic Tetra SCI. To test this hypothesis, we combined transcranial Doppler to assess middle cerebral artery blood velocity (MCAV) and near-infrared spectroscopy (NIRS) for the monitoring of local cerebral oxygenation during step changes in Pa$_{CO_2}$. Transcranial Doppler provides a direct measure of blood flow velocity, whereas NIRS provides activation-dependent information. Moreover, dynamic CA was assessed by transfer function analysis between BP and MCAV (46). The combination of NIRS and MCAV and assessment of cerebrovascular reactivity and dynamic CA provides complementary information for the evaluation of cerebral hemodynamic function.

METHODS

Subjects

Subjects included six men with cervical transection (Tetra; mass 81 ± 9 kg, stature 189 ± 8 cm, and age 33 ± 5 yr) and fourteen healthy able-bodied men (AB; mass 79 ± 8 kg, stature 181 ± 9 cm, and age 27 ± 7 yr; all P > 0.05 relative to Tetra). The Tetra group had a transection level of C5–C7, with a time since injury of 14 yr. The study was approved by the Lower South Island Regional Ethics Committee and complies with the Declaration of Helsinki. Subjects were informed of the experimental procedures and possible risks involved before their written consent was obtained. All subjects were nonsmokers; none had any history of cardiovascular, cerebrovascular, or respiratory disease. With the exception of one Tetra subject (baclofen), none was taking any medication.

Procedures

Subjects were fully familiarized with the experimental procedures and measurements during an initial visit to the laboratory. Subjects arrived at the laboratory on experimentation days at 7:00 AM after a standardized breakfast, having abstained from alcohol, caffeine, and exercise in the 12 h before experimentation. Twelve of the subjects were required to report to the laboratory on multiple days for experimentation, which allowed assessments of reliability (see Data Analysis). Eight subjects reported for 2 days, two subjects for 3 days, and two subjects for 4 days. Instrumentation occurred in the supine posture, ~45 min before any data collection began, in a temperate room (~23°C). Quantification of dynamic CA (see Data Analysis) occurred during a 5-min baseline period in which subjects breathed room air. Tests of cerebrovascular reactivity comprised 3 min of hypercapnia induced by inspiring gas of 5% CO$_2$ (in 21% O$_2$ and N$_2$ balance) followed by 3 min of hypocapnia [partial pressure of end-tidal CO$_2$ (PET$_{CO_2}$); AB 19 ± 2 vs. Tetra 20 ± 3 mmHg, P = 0.258] achieved by controlled hyperventilation. Verbal feedback was provided to assist subjects to reach and maintain the target levels of hypocapnia. Hypercapnic reactivity was always assessed first because prior hypocapnia (but not hypercapnia) may cause persistent cerebral vasoconstriction, thus influencing the normal MCAV-CO$_2$ reactivity to hypercapnia (23). Previous work from our laboratory (37) has established that 3-min steps of two changes in PET$_{CO_2}$ produce cerebrovascular results comparable to those obtained from longer periods even when obtained over four or five progressive changes in PET$_{CO_2}$.

Cerebrovascular measurements. CBF was indexed by measuring the right middle cerebral artery blood flow velocity (MCAV) with a 2-MHz pulsed Doppler ultrasound system (DVL Doppler, Sterling, VA) using the searching techniques described elsewhere (1) and fixed in place by a headband. Beat-to-beat arterial BP was measured by finger photoplethysmography (Finometer; TPD Biomedical Instruments) on the middle finger of the left hand between the middle and distal digital creases. Mean arterial pressure (MAP) and mean MCAV (MCAVmean) were calculated as one-third systolic value + two-thirds diastolic value. Stroke volume (SV) and cardiac output (Q) were calculated from the BP waveform by the Model Flow method, which incorporates the subject’s age, sex, stature, and body mass (Beatscope 1.0 software; TNO TPD; Biomedical Instruments). Although these noninvasive measures of SV and Q have been clinically validated with invasive studies at rest (5), it should be noted that they have not been validated in Tetra. Nevertheless, a previous study, which used echocardiographic estimates of stroke volume and Q, found similar SV and Q values for Tetra subjects and matched control subjects (13). Heart rate was determined by three-lead electrocardiogram (ECG).

Frontal cortical oxygenation was monitored noninvasively by NIRS [NIRO-200; Hamamatsu Photonics; Hamamatsu, Japan]. A probe holder housing an emission and detection probe was attached to the right side of the forehead with a distance of ~5 cm between the probes. The methodology of this system has been discussed previously (3). The optodes were housed in an optically dense plastic holder secured on the skin with cloth tape to minimize extraneous light. Local frontal cerebral oxygenation and the changes in deoxygenated (deoxy-Hb), oxygenated (oxy-Hb), and total (t-Hb) hemoglobin were measured at 1 Hz throughout data collection.

Respiratory gas exchange. Pulmonary ventilation (VT) and its components of tidal volume (VT) and breathing frequency (f) were measured with a heated pneumotach (Hans-Rudolph HR800, Kansas City, MO) and expressed in units adjusted to BTPS. The fractional changes in inspired and expired O$_2$ and CO$_2$ were used to calculate partial pressure of end-tidal O$_2$ (PET$_{O_2}$) and PET$_{CO_2}$, with fast-responding gas analyzers [model CD-3A (CO$_2$) and S-3A/1 (O$_2$) AEI Technologies, Pittsburgh, PA]. The pneumotach was calibrated with a 3-liter syringe (Hans-Rudolph 2700), and the gas analyzers were calibrated with known concentrations of O$_2$ and CO$_2$ before each testing session.

All measurements described above were sampled at 200 Hz via an analog-to-digital converter (Powerlab/16SP ML795; ADInstruments, Colorado Springs, CO) with commercially available software (Chart version 5.5.6, ADInstruments) and stored on a computer for later analysis.

Catecholamine analysis. A venous blood sample was taken from an indwelling catheter located in a forearm antecubital vein, inserted during initial instrumentation. Blood samples (~5 ml) were procured into a chilled EDTA tube after discard of the dead space within the catheter (~1 ml) and centrifuged immediately for 15 min at 4°C (IEC refrigerated centrifuge, Needham Heights, MA). The plasma was then extracted and frozen at ~80°C for later analysis. Plasma norepinephrine and epinephrine were measured by high-performance liquid chromatography with electrochemical detection (17). The limit for detection for both epinephrine and norepinephrine was <100 pmol/l.

Data Analysis

Steady-state data from baseline, hypercapnia, and hypocapnia were analyzed in 15-s bins to allow for identification and removal of artifacts (e.g., sighs, coughs) and were averaged for the last minute in each condition for each dependent variable (e.g., MCAVmean, MAP). The data from subjects who attended multiple testing sessions were averaged for quantification of dynamic CA and reactivity testing. Tests of reliability were conducted for baseline, dynamic CA, and full (hyper- and hyper-
capnic) reactivity measures. Coefficient of variation (%) was calculated as the total unbiased error divided by grand mean multiplied by 100. Intraclass correlation was also used to determine reliability (Table 2 as detailed in Ref. 22). Absolute hypercapnic, hypocapnic, and full reactivity were assessed for each dependent variable of interest [e.g., MCAvmean, MCAv PI (see Fig. 2), as a response to a change in PETCO2, for each subject, by linear regression analysis.

Calculations. Total peripheral resistance was calculated as MAP/Q. CVR was calculated as MAP/MCAvmean, and cerebral blood flow (CBF, CVC; MCAvmean/MAP) was similarly calculated to normalize for the prevailing BP and as an index of static autoregulation. Middle cerebral artery pulsatility index was calculated as MCAv PI = (MCAv systolic - MCAv diastolic)/MCAv mean. To account for differences in perfusion pressure, the standardized MCAv pulsatility index was also calculated [MCAv PI/MAP (11)].

Dynamic cerebral autoregulation. Dynamic CA was quantified by transfer function analysis (45) of the 3-min steady-state data during the reactivity testing baseline. The BP and MCAV waveforms were simultaneously sampled and analyzed at 200 Hz, and beat-to-beat MAP and MCAvmean were obtained for each by integrating the analog signals within each cardiac cycle (24). The beat-to-beat signals were then linearly interpolated and resampled at 2 Hz for spectral analysis (see Ref. 45 for more detail). Briefly, the transfer function H(f) between the two signals was calculated as

\[ H(f) = \frac{S_{xy}(f)}{S_{xx}(f)} \]

where \( S_{xy}(f) \) is the cross-spectrum between the two signals and \( S_{xx}(f) \) is the autospectrum of input signal (45). The transfer-function magnitude \( |H(f)| \) and phase spectrum \( \Phi(f) \) were obtained (45) from the real part \( [HR(f)] \) and imaginary part \( [HR(f)] \) of the complex transfer function and

\[ \Phi(f) = \tan^{-1} \left( \frac{H(f)}{HR(f)} \right) \]

The squared coherence function MSC(f) was estimated as MSC(f) = \( (S_{xy}(f))^2/[S_{xx}(f)S_{yy}(f)] \), where \( S_{yy}(f) \) is the autospectrum of changes in MCAV (45). Relative amplitude and time relationship between BP and MCAV are reflected as transfer gain and phase shifts over a specific frequency range. However, the coherence function reflects the fraction of output power that is linearly related to input power at each frequency. The coherence function varies between 0 and 1, and is similar to a correlation coefficient in that values approximating 0 may indicate a nonlinear relationship, severe extraneous noise in the signals, or no relationship between signals. A coherence value approaching 1 reflects a correlation coefficient in that values approximating 0 may indicate a lack of correlation between signals. A coherence value approaching 1 reflects a nonlinear relationship, severe extraneous noise in the signals, or no relationship (45).

Between-group differences (AB vs. Tetra) were assessed with parametric and nonparametric equivalents of independent samples t-tests (SPSS 17.0.0, Chicago, IL). Values are presented as means ± SD.

RESULTS

Measurements were obtained in all participants throughout all procedures except that MCAv data were unable to be obtained from one Tetra subject and NIRS data were unable to be obtained in another. Therefore cerebrovascular data for our Tetra group are reported for n = 5. Also, assessment of dynamic CA was completed on only 13 AB subjects because of unstable MCAv and BP waveforms in one subject.

Baseline

Baseline data are summarized in Table 1. Tetra subjects had lower resting systolic, mean, and diastolic arterial BP compared with AB subjects (P < 0.01); total peripheral resistance and epinephrine and norepinephrine concentrations were also reduced (P < 0.05). All other cardiovascular resting values were similar between groups (P < 0.05). MCAV values trended to be ~16% lower with Tetra (P = ~0.10). However, there were no differences in CVR, CVC, or cerebral oxygenation between AB and Tetra (P < 0.05). Although MCAV PI was not different between AB and Tetra (P = 0.444), standardized MCAV PI was higher (~36%) in Tetra (P = 0.003). Resting PETCO2, PETO2, V˙E, VT, and f were similar between the groups (P > 0.05). For each variable the coefficient of variation ranged between 0.1% and 16.9% and the intraclass correlation ranged between 0.24 and 0.99 (Table 2).

Dynamic Cerebral Autoregulation

There were no differences evident between groups in frequency-domain profiles of BP variability, MCAV variability, and transfer function gain or phase (P > 0.05). However, the area under the curve for VLF coherence was significantly lower (~21%) in Tetra (P = 0.006; Fig. 1, Table 3). Reliability is presented in Table 2.

CO2 Reactivity

The groups had equivalent (P > 0.05) hypercapnia-induced absolute changes in MCAV mean, CVR, cerebral oxygenation and its components (deoxygen-Hb, oxy-Hb, and t-Hb), Ve, and MAP (data not presented) (Fig. 2). However, the MCAV PI hypercapnic reactivity was higher in Tetra subjects, by ~65% as an absolute measure (P = 0.012) and by ~78% for standardized MCAV PI (P = 0.016). Responses to hypocapnia were also equivalent between groups for all measures except that CVR absolute reactivity response was ~35% lower in Tetra than in AB subjects (P = 0.039). CO2 reactivity across the full range (hypocapnia to hypercapnia) was equivalent between groups for all measures (Fig. 2, P > 0.05). Reliability data are presented in Table 2.

DISCUSSION

This is the first study to examine whether chronic Tetra involves an altered cerebral perfusion response to spontaneous fluctuations in perfusion pressure (dynamic CA) or to increases and decreases in arterial Pco2 (cerebrovascular CO2 reactivity). The new findings were that 1) although transfer function gain and phase in all frequency ranges were maintained, indicative of normal dynamic CA, coherence in the VLF range was ~21% lower in Tetra; 2) full cerebrovascular reactivity to CO2 is maintained with chronic Tetra; and 3) there is a selective...
enhancement in MCAv PI in Tetra, both during baseline (when standardized) and during hypercapnia (both unstandardized and standardized). Collectively, changes are evident in coherence at baseline and MCAv PI during both baseline and hypercapnic states following chronic Tetra, which may be indicative of cerebrovascular adaptation.

Cerebrovascular Function at Rest in Tetra

No studies have previously reported cerebrovascular function in Tetra in conjunction with comprehensive assessment of the influencing cardiovascular factors. Cerebral perfusion (as indexed by MCAv) was, on average, ~16% lower in Tetra than AB subjects, but not significantly so (P ~0.10; see Technological Considerations below), which agrees with some (6, 20) but not all (7, 8) previous studies. Reports from Catz et al. (6–8) are conflicting, showing significant differences (7, 8) and no differences (6) in resting MCAvmean between AB, Para, and Tetra subjects. In these studies (6–8) the same subjects were tested during the same day, and the prior experimentation may have confounded their data. Furthermore, interpretation is difficult in those studies as the SCI group included both acutely and chronically injured subjects. In conjunction with the trend
for lower MCAv, we observed lower BPs (systolic, diastolic, and mean) and total peripheral resistance in Tetra subjects consistent with previous reports (31, 42), although SV and \( Q \) were similar. The lower total peripheral resistance is a consequence of impaired sympathetic control of the vasculature below the lesion (42). Resting heart rate was similar between groups, which is consistent with a previous study (20). Since parasympathetic tone to the heart is mediated via the 10th cranial (vagus) nerve (15), it is unlikely to be influenced by SCI. Epinephrine and norepinephrine concentrations generally below the detection threshold at rest support the existence of sympathetic dysfunction in our Tetra subjects in agreement with previous investigations (10, 30). Despite the observed alterations in resting cardiovascular function with Tetra, systolic, mean, and diastolic MCAv were similar.

Interestingly, when standardized to account for difference in MAP, MCAv PI was higher with Tetra, possibly indicating some adaptation in cerebrovascular function. While speculative, these elevations in MCAv PI may be a defensive cerebrovascular adaptation that protects CBF in the face of hypotension. Whether adaptation or not, it seems advantageous in providing a higher MCAv for a given MAP. Findings from highly controlled animal models (28) and head-injured patients (11) have shown that elevations in MCAv PI occur when cerebral perfusion pressure, or its surrogate MAP, approaches the lower limit of CA—an elevation in the MCAv PI is believed to be an effective way of maintaining CBF in the face of hypotension.

Table 1. Baseline cardiovascular, respiratory, and cerebrovascular data for able-bodied and tetraplegic groups

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>AB</th>
<th>Tetra</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP, mmHg</td>
<td>116 ± 10</td>
<td>98 ± 12</td>
<td>0.002</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>81 ± 6</td>
<td>68 ± 9</td>
<td>0.001</td>
</tr>
<tr>
<td>DAP, mmHg</td>
<td>64 ± 5</td>
<td>53 ± 7</td>
<td>0.001</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>61 ± 11</td>
<td>57 ± 7</td>
<td>0.461</td>
</tr>
<tr>
<td>SV, ml</td>
<td>108 ± 17</td>
<td>121 ± 26</td>
<td>0.191</td>
</tr>
<tr>
<td>Q, l/min</td>
<td>6 ± 1</td>
<td>7 ± 1</td>
<td>0.588</td>
</tr>
<tr>
<td>TPR, mmHg·l(^{-1})·min(^{-1})</td>
<td>13 ± 3</td>
<td>10 ± 1</td>
<td>0.014</td>
</tr>
</tbody>
</table>

| Respiratory       |      |        |              |
| \( \text{PETCO}_2, \) mmHg | 39 ± 3 | 38 ± 6 | 0.662 |
| \( \text{PETO}_2, \) mmHg | 111 ± 5 | 109 ± 8 | 0.426 |
| \( \text{Ve}, \) l/min | 8.3 ± 1.9 | 8.9 ± 2.6 | 0.558 |
| \( \text{VT}, \) l | 0.60 ± 0.20 | 0.67 ± 0.17 | 0.489 |
| \( f, \) beats/min | 15 ± 4 | 14 ± 2 | 0.426 |

| Cerebrovascular   |      |        |              |
| MCAv\(_{\text{sys}}\), cm/s | 111 ± 15 | 94 ± 26 | 0.095 |
| MCAv\(_{\text{mean}}\), cm/s | 69 ± 8 | 58 ± 18 | 0.089 |
| MCAv\(_{\text{Diatolic}}\), cm/s | 47 ± 6 | 40 ± 15 | 0.108 |
| CVC, cm\(^{-1}\)·mmHg\(^{-1}\) | 0.85 ± 0.12 | 0.85 ± 0.20 | 0.968 |
| CVR, mmHg·cm\(^{-1}\)·s\(^{-2}\) | 1.21 ± 0.16 | 1.24 ± 0.30 | 0.821 |
| MCAv PI, au/\(\mu\)Hg | 0.92 ± 0.10 | 0.97 ± 0.13 | 0.444 |
| Standardized MCAv PI, au/\(\mu\)Hg | 0.011 ± 0.001 | 0.015 ± 0.004 | 0.003 |
| Cerebral oxygenation, % | 73 ± 4 | 74 ± 4 | 0.544 |

| Catecholamines |      |        |              |
| Epinephrine, pmol/l | 157 ± 91 | 27 ± 32 | <0.001 |
| Norepinephrine, pmol/l | 1.558 ± 430 | 381 ± 202 | <0.001 |

Table 2. Day-to-day variation and reliability of baseline, cerebral autoregulation, and reactivity measures

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>AB</th>
<th>Tetra</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP power spectrum, Hz·mmHg(^{-2})·Hz(^{-1})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLF</td>
<td>13.03 ± 6.86</td>
<td>11.26 ± 5.73</td>
<td>0.592</td>
</tr>
<tr>
<td>LF</td>
<td>16.41 ± 7.16</td>
<td>20.92 ± 13.47</td>
<td>0.468</td>
</tr>
<tr>
<td>HF</td>
<td>10.59 ± 4.98</td>
<td>8.37 ± 4.14</td>
<td>0.357</td>
</tr>
<tr>
<td>MCAv power spectrum, Hz(^{-1})·mmHg(^{-1})·s(^{-2})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLF</td>
<td>18.65 ± 10.96</td>
<td>12.36 ± 6.32</td>
<td>0.250</td>
</tr>
<tr>
<td>LF</td>
<td>22.34 ± 8.26</td>
<td>19.42 ± 9.67</td>
<td>0.530</td>
</tr>
<tr>
<td>HF</td>
<td>14.32 ± 7.17</td>
<td>10.04 ± 6.01</td>
<td>0.256</td>
</tr>
<tr>
<td>CA coherence, Hz·au</td>
<td>0.029 ± 0.003</td>
<td>0.023 ± 0.005</td>
<td>0.006</td>
</tr>
<tr>
<td>CA gain, Hz·cm(^{-1})·mmHg(^{-1})</td>
<td>0.051 ± 0.016</td>
<td>0.050 ± 0.034</td>
<td>0.967</td>
</tr>
<tr>
<td>CA phase, Hz·radian</td>
<td>0.041 ± 0.019</td>
<td>0.042 ± 0.013</td>
<td>0.909</td>
</tr>
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</table>

| Values are expressed as coefficient of variation and intraclass correlation (in parentheses), LF, low frequency (0.07–0.2 Hz). In the AB group, 5 subjects reported on 2 days, 2 subjects reported on 3 days, and 2 subjects reported on 4 days. In the Tetra group, 3 subjects reported on 2 days. |
of a reduction in MAP. We recommend that future studies consider this potential method of interpretation.

**Dynamic CA Is Maintained with Tetra**

This appears to be the first report on dynamic CA in Tetra subjects (Fig. 1 and Table 3). Although transfer function gain and phase were maintained in all frequency ranges, indicative of normal dynamic CA, coherence in the VLF range was ~21% lower in Tetra. A lack of correlation (low coherence) between MCAv and BP means a perfect state of autoregulation, whereas a high coherence indicates a close correlation between MCAv and BP [i.e., impairment in dynamic CA (16, 45)]. Thus the possibility that these changes are reflecting some cerebrovascular adaptation in Tetra warrants further research. However, because of the lack of elevations in phase and reductions in transfer function gain (24), the select changes in VLF coherence may be associated with reduced BP variability or reflect more nonlinearities between changes in BP and MCAv (46, 47) with Tetra. The ability to dynamically regulate CBF would seem advantageous in SCI, especially during periods of autonomic dysreflexia or orthostatically induced hypotension.

**Cerebrovascular Reactivity**

The present study was also novel in its comprehensive assessment of full cerebrovascular reactivity to CO₂, including separate analysis in the hypo- and hypercapnic ranges. Our data indicate that MCAv mean reactivity to CO₂ is unaffected by
Tetra. Nevertheless, some subtle differences with the modulation of MCAVmean were apparent within both the hypo- and hypercapnic ranges. MCAV PI (both normal and standardized) reactivity to hypercapnia was markedly (65–75%) enhanced in Tetra. Similarly, in the hypercapnic range, the CVR response was ~35% smaller in Tetra. The physiological implications of these differences are unclear and may warrant further study.

By including an AB group, our finding of unchanged MCAVmean reactivity to hypercapnia extends those of an early report (14). The effects of hypocapnia on MCAVmean are more controversial. For example, and in contrast with our findings, Eidelman et al. (14) reported that CBF hypocapnic reactivity was fully abolished with SCI, and therefore that such a response depends on intact sympathetic pathways. Consistent with our findings, however, Nanda et al. (34, 35) reported that hypocapnic reactivity is maintained with SCI, concluding that the mechanisms involved are independent of the sympathetic pathways. The discrepancies in the findings of Nanda et al. (34, 35) and Eidelman et al. (14) may be due to the differing methods used to assess CBF (modified and unmodified 133Xe inhalation), and/or by differences in the SCI groups. In support of our findings, a highly controlled anesthetized animal model of SCI, using α-adrenergic blockade, showed MCAVmean reactivity to hypocapnia to be maintained (21). Finally, our finding of unchanged MCAVmean full reactivity in Tetra is consistent with unchanged cerebral oxygenation (Fig. 2) and cardiorespiratory reactivity to CO2 (data not presented).

**Technological Considerations**

There are four main technological considerations that merit consideration.

First, transcranial Doppler is used to measure blood flow velocity in the middle cerebral artery, not CBF per se. However, MCAV is a reliable and valid index of CBF (reviewed in Ref. 2). Admittedly, the assessment of change in flow is preferred to an absolute flow value. Changes in MCAV are reported to be reflective of changes in CBF during CO2 testing (43). Furthermore, since determinations of cerebrovascular reactivity to CO2 are based on stimulus-response principles, reliable and repeatable recording with short time resolution is more important than absolute values (2).

Second, measurement of cerebral oxygenation with NIRS has both advantages and limitations. This technique provides noninvasive measurement of oxygenation and changes in deoxy-Hb, oxy-Hb, and t-Hb in tissues (25) and has been validated against multiple experimental and imaging modalities: PET scanning (39); 133Xe washout methods (40), and functional magnetic resonance imaging (41). Furthermore, the NIRS-derived tissue oxygenation index is sensitive to changes in hemispheric, intra-cerebral blood supply and seems minimally affected by extracranial contamination (3).

Third, after extensive recruitment of active and otherwise healthy Tetra subjects within New Zealand and Australia the sample size in our SCI (cervical injured) group is low (n = 6, and just 5 for several measures). To partly overcome this issue, we performed variability and reliability testing (2–4 occasions, Table 2) on each subject and then averaged the results to help improve reliability. Two-tailed priori test [independent means (2 groups)] of statistical power revealed a sample size of 394, 64, and 26 in each group for a small (0.2), medium (0.5) and large (0.8) effect size, respectively, to reach significance, for power level of 0.8. A two-tailed post hoc test of achieved power revealed that the standardized effect size obtained for baseline MCAVmean was 0.40 (small-medium effect).

Fourth, our Tetra subjects were not assessed with the American Spinal Injury Association (ASIA) classification of neurological impairment (32). However, the ASIA classification assesses only the neurological level and severity of injury to the motor and sensory pathways, with no quantification of autonomic nervous system integrity (4). In the present study, our Tetra subjects had lower norepinephrine and epinephrine (mostly undetectable) levels than AB subjects. Thus, because all our subjects also had medically confirmed transection levels between C5 and C7 and were chronically adapted to the injury (after 14 ± 4 yr), we contend that the lack of ASIA classification does not detract from our findings. Moreover, previous studies have reported that Tetra SCI results in much poorer prognosis and greater disability compared with Paral (26).

**Perspectives and Significance**

Our data indicate that dynamic CA may be altered whereas cerebrovascular reactivity to CO2 is maintained with Tetra. Moreover, changes are evident in coherence at baseline and MCAV PI during both baseline and hypercapnic states following chronic Tetra, which may be indicative of cerebrovascular adaptation. Thus, despite the incidence of cerebrovascular disease being higher in the SCI population (19, 33), on the basis of the present data such changes cannot be explained solely by alterations in cerebrovascular CO2 reactivity or dynamic CA.

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**DISCLOSURES**

No conflicts of interest are declared by the author(s).

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