Systemic and Cerebral Hemodynamics in Persons with SCI:
Presentation, Consequences, Treatments

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Background

Autonomic Nervous System (ANS)

“As we approach the centennial of the use of the term “autonomic nervous system,” which was coined by Langley in 1898, we should ask whether autonomic disorders are being sufficiently considered, suitably investigated, and appropriately managed in clinical practice”.


Hemodynamic (in)stability in persons with spinal cord injury (SCI) may reflect segmental differences in ANS cardiovascular and cerebrovascular control.
Cardiovascular-Autonomic Innervation

C  Cholinergic synapses PARASYMPATHETIC (Vagal)

A  Adrenergic synapses SYMPATHETIC

Tetraplegia (Tetra) C1-T1

High Paraplegia (HP) T2-T5

Low Paraplegia (LP) T6 and below
ANS Impairment leads to Blood Pressure Dysregulation (BPD)

Autonomic dysreflexia (AD)
  • Increase in SBP +20 mmHg over baseline SBP

Chronic hypotension (HYPO)
  • SBP males ≤ 110 mmHg; females ≤ 100 mmHg

Orthostatic hypotension (OH)
  • Fall in BP ≥ 20/10 mmHg with upright positioning

However, many, if not most, individuals with SCI remain asymptomatic and therefore are not diagnosed or treated.
A retrospective chart review of heart rate and blood pressure abnormalities in veterans with spinal cord injury

Carolyn Zhu, Marinella Galea, Elayne Livote, Dan Signor & Jill M. Wecht

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Diagnosis Rates in Veterans with Chronic (18±15 years) SCI

ICD-9 codes:

**AD:** 337.3  
**OH:** 458.0  
**Hypertension:** 401.0; 401.1; 401.9;  
**Hypotension:** 458.1; 458.2; 796.3
Blood Pressures & Medication Use

A. Clinical values reflecting:
- Systolic hypertension (≥ 140 mmHg)
- Systolic hypotension (≤ 110 mmHg)

B. & C. Prescription medication use:
- Hypertension
- Hypotension
So what:

Are there adverse effects of BPD on the cerebral circulation?
Stroke & Impaired Cerebrovascular Buffering of Blood Pressure

• Reports of a 3-4 fold increased stroke risk in the SCI population may relate to the diminished ability to buffer BP (Wu et al. Neurology, 2012; Cragg et al. Neurology, 2013).

• Recent evidence indicates impaired cerebrovascular buffering of BP in hypotensive persons with chronic cervical SCI.
  o The authors suggest may be due to loss of supraspinal sympathetic control over the cerebral circulation (Saleem et al. AJP Heart, 2018).
Cerebral Hemodynamics: Autonomic Dysreflexia (AD)

Transient increases in cerebral blood flow velocity (CBFv) were recently noted in patients with SCI during AD

- Linear relationship between ΔBP & ΔCBFv in males with SCI during sperm retrieval and urodynamics
- Similar findings in an animal model (T3) of chronic AD (colorectal distension 6x/day for 10 minutes; 5x/week; 4 weeks).
- Transient hyper-perfusion was associated with:
  - Stiffening of the MCA
  - Reduced distensibility
  - Increased collagen expression.
  - Reduced sympathetic nerve fiber density

Phillips et al. Journal of Neurotrauma 35: 573-581, 2018
Comparison of 24-hour cardiovascular and autonomic function in paraplegia, tetraplegia, and control groups: Implications for cardiovascular risk

Dwindally Rosado-Rivera¹, M. Radulovic¹-⁴, John P. Handrakis¹-⁶, Christopher M. Cirnigliaro¹-⁵, A. Marley Jensen¹-⁵, Steve Kirshblum⁵, William A. Bauman¹-⁴, Jill Maria Wecht¹-⁴

Daytime SBP
TETRA vs. other groups; p<0.05
Cerebral Hemodynamics: Chronic Hypotension

We reported significantly reduced CBFv in hypotensive individuals with SCI [C3-T4] who were asymptomatic compared to matched able-bodied (AB) controls.

Cerebral Hemodynamics: Chronic Hypotension

- Comparable CBFv was reported in 10 hypotensive individuals with SCI and matched AB controls; however 8 of the 10 subjects with SCI were acutely injured [5-11 weeks post injury]. Phillips et. al., J. of Applied Physiology, 116: 645-653, 2014

- Our preliminary data in individuals with chronic SCI (2-31 years) again suggests significantly lower seated CBFv in hypotensive individuals with SCI compared to age-matched normotensive controls.
Orthostatic Hypotension (OH)

CBFv changes during the sit-up test (supine to head at 90°) were not different among individuals with cervical and thoracic lesions compared to uninjured controls. However, orthostatic diastolic CBFv was significantly lower in those with autonomic complete (plasma NE ≤ 0.56 nmoL/L) compared to those with incomplete lesions and controls.

Importantly, 6 of the 7 participants with tetraplegia had a fall in CBFv greater than 25% of their resting levels; whereas only 1 control had a fall that met this criteria (and this subject was symptomatic).

This finding underscores the asymptomatic nature of hypotension and OH in the SCI population.
Cerebral Hypo-perfusion

• Because most hypotensive individuals with SCI do not complain of symptoms associated with low CBFv:
  o Dizziness, lightheadedness, nausea, blurred vision, ringing in the ears, syncope.

• Most are not diagnosed or treated as previously described.

• We have sought to determine the impact of hypotension and cerebral hypo-perfusion on cognitive function.
## Hypotension: Cognitive Function

<table>
<thead>
<tr>
<th></th>
<th>Hypotensive ($n = 11$)</th>
<th>Normotensive ($n = 9$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h SBP</td>
<td>102 ± 7</td>
<td>115 ± 10</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>24-h DBP</td>
<td>63 ± 6</td>
<td>71 ± 4</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>24-h HR</td>
<td>69 ± 10</td>
<td>79 ± 8</td>
<td>$&lt;0.05$</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39 ± 8</td>
<td>46 ± 10</td>
<td>0.1006</td>
</tr>
<tr>
<td>Female # (%)</td>
<td>0</td>
<td>1 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>DOI (years)</td>
<td>16 ± 10</td>
<td>18 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Lesion level</td>
<td>C4–T4</td>
<td>C4–T11</td>
<td>NS</td>
</tr>
<tr>
<td>Tetraplegia # (%)</td>
<td>9 (82)*</td>
<td>4 (44)</td>
<td>NS</td>
</tr>
<tr>
<td>Lesion level (continuous)</td>
<td>6.09 ± 2.74</td>
<td>10.33 ± 5.29</td>
<td>$&lt;0.05$</td>
</tr>
<tr>
<td>AIS A # (%)</td>
<td>9 (82)</td>
<td>9 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>BDI</td>
<td>5.46 ± 5.47</td>
<td>0.64 ± 3.67</td>
<td>0.0878</td>
</tr>
<tr>
<td>Level of education (years)</td>
<td>15 ± 3</td>
<td>15 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-morbid IQ</td>
<td>103 ± 14</td>
<td>103 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Measured IQ</td>
<td>91 ± 20</td>
<td>98 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Positive history of TBI # (%)</td>
<td>5 (45)</td>
<td>4 (44)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Jegede et. al., *Clinical Autonomic Research* 20: 3-9, 2010
24-hour Systolic Blood Pressure: Memory (t-scores)

Fig. 1 The relationship between 24-h SBP and the average normalized T-score on the CVLT memory test; open squares are subjects with tetraplegia, closed circles are subjects with paraplegia. The relationship between average normalized CVLT T-score and 24-SBP was significant after controlling for age, level of lesion (continuous) and BDI depression score.
Systemic & Cerebral Hemodynamics: Cognitive Performance

The Symbol Digit Modalities Test (SDMT) assessment of information processing speed, sustained attention and visual working memory is significantly lower in individuals with tetraplegia compared to healthy controls.
Systemic & Cerebral Hemodynamics: Cognitive Performance

Change in SBP and change in CBFv contributed significantly to the prediction of SDMT performance in participants with tetraplegia.

![Graphs showing correlation between SBP change and SDMT score, and CBFv change and SDMT score.](image)
Cognitive Functioning and Experimental Treatment of Hypotension

The authors speculate:

“This study highlights the potential for an inverted-U shape with respect to BP and cerebral function, where in addition to hypertension, low BP leads to cerebrovascular and cognitive decline. As too high a BP damages the microvasculature, low BP may impair cerebral metabolic status and cerebrovascular responsiveness to cognition”.

Hypotension in the SCI Population: 

*Treatment Options*

- **Midodrine hydrochloride:**
  - Alpha-agonist

- **Pyridostigmine bromide:**
  - Acetylcholinesterase Inhibition

- **Mirabegron:**
  - Beta$_3$-agonist

- **Droxidopa:**
  - Norepinephrine precursor
Midodrine (10 mg) versus Placebo: Systolic Blood Pressure

Target SBP range 111-139 mmHg
# SBP Responses to Midodrine

<table>
<thead>
<tr>
<th></th>
<th>Hypotensive (n=17: 41%)</th>
<th>Normotensive (n=17: 41%)</th>
<th>Hypertensive (n=7: 17%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre SBP (mmHg)</td>
<td>91±14</td>
<td>101±11 **</td>
<td>101±8 *</td>
</tr>
<tr>
<td>SBP change (mmHg)</td>
<td>-1±15</td>
<td>21±16 ***</td>
<td>55±15 ***</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40±13</td>
<td>45±10</td>
<td>53±11 *</td>
</tr>
<tr>
<td>Level of Injury</td>
<td>C4-T4</td>
<td>C4-T6</td>
<td>C4-T2</td>
</tr>
<tr>
<td>Duration of Injury</td>
<td>13.6±10.0</td>
<td>14.2±12.3</td>
<td>24.4±14.6 *</td>
</tr>
<tr>
<td>Age at Injury (years)</td>
<td>26.3±12.0</td>
<td>30.9±11.0</td>
<td>28.4±16.4</td>
</tr>
<tr>
<td>AIS A/B</td>
<td>14 (44%)</td>
<td>12 (38%)</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>AIS C/D</td>
<td>3 (33%)</td>
<td>5 (56%)</td>
<td>1 (11%)</td>
</tr>
</tbody>
</table>

* p<0.05; ** p<0.01; *** p<0.0001 versus hypotensive group
Percent Change in SBP: Change in CBFv

![Graph showing percent change in SBP with CBFv]
Midodrine (10 mg) versus Placebo: 
Diastolic Blood Pressure

Regardless of condition: 82% of all observations indicate diastolic hypotension while at seated rest.
Research Article
Low Diastolic Blood Pressure as a Risk for All-Cause Mortality in VA Patients

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Figure 1: Interval likelihood ratios of all-cause mortality against a range of diastolic blood pressure. (Upper and lower 95% confidence intervals denoted by dotted lines.)

Conclusions. Reduction of DBP below 70 mmHg is associated with increased all-cause mortality. Hypertension guidelines should include a minimum blood pressure target.
Other anti-Hypotensive Medications

• We are currently testing the dose effects on SBP:
  o Pyridostigmine Bromide: 30, 60, 90, 120 mg
  o Mirabegron: 25, 50, 75, 100 mg
Change in SBP over 4 hours:  
Effect of Droxidopa
Pyridostigmine

- Hypotensive ≤ 110 mmHg
- Normal 111-139 mmHg
- Hypertensive ≥ 140 mmHg

Midodrine

Droxidopa

Mirabegron
Summary & Conclusions

• Blood pressure dysregulation (BPD) is under appreciated in persons with SCI due to the asymptomatic nature of the disorder.

• We and others have reported significant adverse effects of BPD on the cerebral circulation, cerebral blood flow and cognitive function.

• Current treatments for BPD are limited.

• Our goal is to increase the armamentarium of safe and effective pharmacologic treatment options for BPD, particularly hypotension, for use in the SCI population.
To a hammer everything looks like a nail.....

And while not all problems can be solved by addressing autonomic nervous system dysfunction & blood pressure dysregulation in individuals with SCI, understanding the potential adverse impacts on vital organ/system perfusion and function will have a beneficial effect on health and vitality.
In Appreciation

- **Study Participants**
- **Study Coordinators**
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  - Alex Lombard
  - Matt Maher
  - James LiMonta
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  - Dr. Glenn Wylie
  - Dr. Trevor Dyson-Hudson
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