Cognitive Consequences of Autonomic Dysfunction:
Possible implication for Persons with SCI & MS

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At the conclusion of this activity, the participant will be able to:

- A. Autonomic impairment in spinal cord injury and multiple sclerosis
- B. Cognitive impairments in spinal cord injury and multiple sclerosis
- C. Possible association between autonomic impairment and cognitive impairments spinal cord injury and multiple sclerosis
Obtaining CME Credit

• If you would like to receive CME credit for this activity, please visit:

http://www.pesgce.com/PVAsummit2011/

• This information can also be found in the Summit 2011 Program on page 8.
Components of the Autonomic Nervous System & Cognition

1. Sympathetic component
2. Vagal component
3. Baroreceptor reflex
Sympathetic Nervous System:

- **Animal data:**
  - enhanced memory during activation of \( \beta \)-adrenergic systems (Cahill et al. 1998, 1994)

- **Clinical data:**
  - significantly impaired verbal memory in elderly (Solomon 1983) and cognitively impaired (Gliebus 2007) individuals prescribed beta-blockers.

- **Experimental evidence:**
  - Impaired memory with beta-blocker compared to placebo (Maheu, 2004; Cahill 1994).
  - Epinephrine improves memory (Cahill 2003).

Cross-sectional studies have consistently documented improved cognitive performance in individuals with higher levels of vagal tone. 

- **Infants** (14-26 weeks of age) with higher heart rate variability (HRV) displayed increased attentional capacity compared to infants with low HRV.

- **School age children** (3rd-5th grade) with higher vagal tone performed better on a sustained attention task.

- **Adults** (18-34 years) Higher resting HRV was associated with better executive function.

1. *Resting* baroreceptor reflex sensitivity (BRS) is associated with improvements in cognitive task performance.

2. Cognitive elaboration is associated with reliable reductions in BRS.

3. The relationship between BRS and cognition may be in part modulated by tonic BP: the relationship between success ratio and BRS appears to be *inverse* in relatively higher BP and *positive* in persons with relatively lower BP.

Yasumasu et al. Psychophysiology; 2006; Duschek et al. Biological Psychology; 2009; Del Paso et al. Psychophysiology; 2009.
Clinical signs and symptoms of autonomic cardiovascular impairment:

Spinal Cord Injury
Although AIS level and completeness of SCI may not relate to the *degree of autonomic impairment*, we distinguish the model of tetraplegia from paraplegia to document the degree of autonomic dysfunction.

Alexander et al., 2009; Claydon & Krassioukov et al., 2006; Krassioukov 2007 & 2009.
Sympathetic Control: Spinal Cord Injury

TETRAPLEGIA C1-C8
- Absolute low levels of plasma catecholamine concentrations:
  - Resting
  - Head-up tilt
  - Maximal exercise
- Absent or diminished sympathetic skin responses (SSR):
  - Palmer
  - Plantar

PARAPLEGIA T1 & BELOW
- Plasma catecholamine concentrations vary by level of lesion:
  - T1-T5 – low NE
  - T6 & below – high NE
- Variable SSR in hand
- Diminished or absent SSR in the foot

Several recent papers have made a strong argument that the LF component of heart rate variability reflects baroreflex function and not cardiac sympathetic activity.

Vagal Withdrawal and HR Increase

Wecht et al. Clinical Auto Res. 2006
Vagal Cardiovascular Control: Spinal Cord Injury

Wecht et al. Clinical Auto Res. 2009
Impact of Autonomic Dysfunction on Cardiovascular and Cerebral Vascular Function

Spinal Cord Injury
Cardiovascular Consequences of Autonomic Dysfunction: Tetraplegia

- **Bradycardia** - ≤ 50 bpm
  - Diagnosis ?
  - Empirical evidence 15%
- **Persistent hypotension** W.H.O. definition SBP males ≤ 110 mmHg & females ≤ 100 mmHg
  - Diagnosis 30%
  - Empirical evidence 70%
- **Orthostatic hypotension** - AAS and AAN definition ≥ 20 mmHg ↓ SBP and/or ≥ 10 mmHg ↓ DBP
  - Diagnosis 3%
  - Empirical evidence 21%
- **Autonomic dysreflexia** - ≥ 20 mmHg ↑ in SBP and/or ≥ 10 mmHg ↑ in DBP
  - Diagnosis 10%
  - Empirical evidence (urodynamic testing) 79%
- **Hypertension** - SBP ≥ 139 and/or DBP ≥ 90 mmHg
  - Diagnosis 29%
  - Empirical evidence 24% (systolic hypertension)
Cardiovascular Consequences of Autonomic Dysfunction: Paraplegia

- **Elevated heart rate** - ≥ 90 bpm
  - Diagnosis?
  - Empirical evidence 53% *(more than 50% of the day above 90 bpm)*
- **Persistent hypotension**
  - Diagnosis 42%
  - Empirical evidence 21%
- **Orthostatic hypotension**
  - Diagnosis 1%
  - Empirical evidence *(HP-21%)*
- **Autonomic dysreflexia**
  - Diagnosis 1%
  - Empirical evidence *(urodynamic testing) 58%*
- **Hypertension**
  - Diagnosis 42%
  - Empirical evidence 43% *(systolic hypertension)*
Mean Arterial Pressure (MAP) during Head-up Tilt (HUT)

Orthostatic hypotension?

$p<0.01$

Controls

Low Paraplegia (T7-T12)

High Paraplegia (T2-T5)

Tetraplegia (C4-C8)
50% of the subjects with tetraplegia had a SBP at or BELOW 85 mmHg

Systolic Blood Pressure within 5 minutes of HUT to 45°
24-hour Systolic Blood Pressure

- Controls
- Low Paraplegia (T7-12)
- High Paraplegia (T2-5)
- Tetraplegia (C4-8)

Systolic Blood Pressure (mmHg)

24 time (hour)
24-Hour Systolic Blood Pressure by Gender in Tetraplegia

*S* Females with tetraplegia

* Males with tetraplegia

Male “hypotension”

Female “hypotension”
It must be appreciated that these individuals remain largely asymptomatic to these low blood pressures, and as such, hypotension attracts little focus from clinicians, pharmaceutical companies, or research scientists.

HOWEVER:
In several large population based studies in otherwise healthy non-SCI individuals, low blood pressure was associated with:

- Poorer reporting of general health
- Disturbance in mental state
- Increased reporting of tiredness, malaise, fatigue
- Impaired social wellbeing
- High incidence of depression reporting

In otherwise healthy non-SCI individuals, hypotension has been associated with:

- Slowed cognitive speed
- Fewer word recall
- Poor attentional flexibility
- Prolonged reaction times
- Lower concentration capacities

Cognitive Deficits in SCI

- It has been reported that between 10 & 60% of the SCI population have cognitive deficits in areas of **processing speed, attention, memory, and cognitive flexibility**

- Most reports suggest that the cognitive deficits are related to concomitant traumatic brain injury (TBI) and/or pre-morbid conditions

Can we associate hypotension with cognitive deficits in persons with SCI?
Cognitive Scores in Persons with SCI discordant for Hypotension

<table>
<thead>
<tr>
<th></th>
<th>Hypotensive</th>
<th>Normotensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=11)</td>
<td>(n=9)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>39 8</td>
<td>46 10</td>
</tr>
<tr>
<td>Female #(%),</td>
<td>0</td>
<td>1(11)</td>
</tr>
<tr>
<td>DOI (y)</td>
<td>16 10</td>
<td>18 13</td>
</tr>
<tr>
<td>Lesion Level</td>
<td>C₄ - T₄</td>
<td>C₄ - T₁₁</td>
</tr>
<tr>
<td>AIS A #(%),</td>
<td>9(82)</td>
<td>9(100)</td>
</tr>
<tr>
<td>BDI</td>
<td>5.46 5.47 *</td>
<td>0.64 3.67</td>
</tr>
<tr>
<td>Level of education (years)</td>
<td>15 3</td>
<td>15 4</td>
</tr>
<tr>
<td>pre-morbid IQ</td>
<td>103 14</td>
<td>103 13</td>
</tr>
<tr>
<td>measured IQ</td>
<td>91 20</td>
<td>98 8</td>
</tr>
<tr>
<td>Tetraplegia #(%),</td>
<td>9(82) χ²</td>
<td>4(44)</td>
</tr>
<tr>
<td>Positive History of TBI #(%)</td>
<td>5(45)</td>
<td>4(44)</td>
</tr>
</tbody>
</table>

Does the association between hypotension and cognitive deficits relate to cerebral blood flow in SCI?
Objectives:

Hypothesis:

Low blood pressure would contribute to cerebral hypoperfusion during testing and poor cognitive performance in the tetraplegic group compared to the non-SCI and paraplegic groups.
## Subject Demographics and Cognitive Performance

<table>
<thead>
<tr>
<th></th>
<th>non-SCI (n=16)</th>
<th>Paraplegia T2-10 (n=6)</th>
<th>Tetraplegia C4-8 (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQ measured</td>
<td>104 13</td>
<td>103 7</td>
<td>95 16</td>
</tr>
<tr>
<td>Level of education (y)</td>
<td>17 4</td>
<td>15 3</td>
<td>14 4</td>
</tr>
<tr>
<td>CVLT memory (t-score)</td>
<td>49 7</td>
<td>50 9</td>
<td>46 6</td>
</tr>
<tr>
<td>Beck’s Depression Inventory</td>
<td>4.8 4.7</td>
<td>4.5 3.5</td>
<td>3.7 4.8</td>
</tr>
</tbody>
</table>

The Stroop Task is a neuropsychological test of attention and cognitive flexibility; the cognitive mechanisms involved in this task is processing speed and directed attention.
Stroop t-scores in SCI and Controls

Paraplegia: 89% < non-SCI
Tetraplegia: 62% < non-SCI
Mean Arterial Pressure Change during Cognitive Testing
Left Middle Cerebral Artery Mean Flow Velocity Change during Cognitive Testing
Ratio of change in MAP to change in CBF: modulation of downstream cerebral vasculature
Relationship between Stroop color t-score and CVRi change during testing

Inadequate or inappropriate systemic and cerebral vascular responses to cognitive testing differs between individuals with tetraplegia and paraplegia:

However systemic and cerebral dysfunction may play a role; surprisingly, regardless of the level of lesion.
Persistently elevated heart rate may predispose individuals to increased arterial stiffening, with adverse cognitive consequences as reported in the non-SCI literature.

Two reports of increased arterial stiffness in persons with SCI compared to matched controls

In SCI: we & others have demonstrated:

↑ heart rate
↑ arterial stiffness &
↓ cognitive function

But we do not know if associations made in the non-SCI literature apply to the SCI population.

↑ heart rate → arterial stiffness → cognitive impairment ?
Clinical signs and symptoms of autonomic cardiovascular impairment:

Multiple Sclerosis
Autonomic Evaluation by means of standard tests and power spectral analysis in Multiple Sclerosis

- **Standard Tests**
  - Vagal: 25%
  - Sympathetic vasomotor: 5%
  - SSR: 75%

- **Spectral Analysis** - 13 of 20 (65%) patients presented with pathological response to at least 1 parameter; of those:
  - Vagal: 46%
  - Sympathetic vasomotor: 10%
  - Baroreceptor reflex: 35%
Autonomic Cardiovascular Dysfunction: Multiple Sclerosis

- Diminished or absent SSR
  - ↓ amplitudes 45-75%
  - Delayed responses 5-10%

- Impaired sympathetic vasomotor responses to head-up tilt
  - ↓ SBP frequency amplitudes 5-25%
  - ↓ cerebral blood flow velocities during tilt

- Vagal impairment
  - ↓ heart rate responses to deep breathing 18-40%

Cardiovascular Consequences of Autonomic Dysfunction: Multiple Sclerosis

- **Diminished heart rate responses (18-40%)**
  - Vagal impairment
    - Orthostasis
    - Deep breathing

- **Orthostatic intolerance (24-50%)**
  - Vasomotor pathology

- **Baroreceptor reflex dysfunction (28-42%)**
  - Cardio-vagal
  - Sympathetic vasomotor

Lesion site

- Autonomic dysfunction related to brainstem lesions by MRI (p<0.005)
- Lack of postural hypotension, normal responses to the Valsalva maneuver and abnormal BP response to mental stimulation suggest central autonomic impairment

Progression and severity of the disease varies among the studies.

Approximately 50-70% of individuals with MS are reported to have deficiencies in:

- Episodic memory
- Working memory
- Sustained attention
- Verbal fluency,
- Processing speed
- Information processing
- Executive function
- Visual spatial skills

Cognitive dysfunction in patients with relapsing-remitting multiple sclerosis (RRMS)

These authors concluded:
Clinical indices centered around motor disability (AI) may mirror cognitive impairments; however this may be due to the large sample size or selection bias.

EDSS = Expanded Disability Status Scale; AI = ambulation Index; FSS = Fatigue Severity Scale
Is there a connection between autonomic impairment and cognitive deficits in MS?
Examined heart rate reactivity during cognitive testing in 25 RRMS (EDSS=2.6 and duration of disease 10 years) compared to 25 matched control subjects. Sympathetic nervous system might mediate the stress response.
Evidence suggests that autonomic impairment of either sympathetic, vagal or baroreceptor reflex function may contribute to cognitive deficits. Our findings in SCI support a possible association between autonomic impairment and cognitive deficits. Associations specifically related to de-centralized cardiovascular autonomic control and hemodynamic changes in systemic and cerebral circulation.

IMPORTANT!
- Models of high paraplegia (T1-T6), low paraplegia (T7 and below) and tetraplegia (cervical) manifest different pathophysiological changes and should be examined as distinctly different groups.
Data are not available to support a possible link between autonomic impairment and cognitive deficits in the MS population. Although cognitive deficits in autonomic dysfunction and cardiovascular insufficiencies at rest and during provocations are evident. Findings in the SCI and general population linking autonomic impairment and cognitive deficits may apply to the MS population.
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