Autonomic monitoring

Marek Sykora
St. John’s Hospital
SFU Med Vienna, Austria
Agenda

• Meaning of ANS in acute brain injury

• Studies using ICM+ for autonomic assessment
Types of brain injury

Ischemic stroke | ICH +/- IVH | SAH | TBI
Stress and stress-reaction

- Stress is everything that disturbs or endangers *homeostasis*

- ANS, hypothalamic-pituitary-adrenal axis, cardiovascular, metabolic, and immune systems try to maintain “stability through change”

- Adaptive stress-reaction
- Maladaptive stress-reaction
Stress response: a major contributor to harm

_Fight-or-flight-or-freeze reaction_
- Adrenaline, Cortisole ↑
- Glycogenolysis
- Blood pressure centralisation
- BP, HF ↑
- Bronchodilation
- Leu, Tr ↑
- Thrombogenisity ↑

Arrhythmiae
- Myocardial necrosis
- Endothelial dysfunction
- Insulin resistance, hyperglycemia
- Immunodepression
- Catabolism, end-organ damage
- SIRS, MODS
Central autonomic network

Cortical

Subcortical

Brain stem

Medulla

INS

MPF

CING

INS

MPF

CING

INS

MPF

CING

INS

MPF

CING

INS

MPF

CING

INS

MPF

CING
Central autonomic network

Stressor

- INS
- MPF
- CING
- AMG
- HYP
- PAG
- PVN
- LHA
- NTS
- NA DVN
- IML
- CRH

Receptors
Parasympathetic
Sympathetic

X
IX
(-)

Central autonomic network diagram showing the interconnections between various brainstem and hypothalamic nuclei involved in the autonomic response to stress.
Central autonomic network

Brain injury

Receptors
Parasympathetic ≈ Sympathetic
Central autonomic disconnection syndrome

Brain injury → SNS - PNS imbalance → HPA activation

Acute-phase response

↑catecholamines, ↑cortisol, ↑TNFα, ↑NPY, ↑IL1, ↑IL6, ↑IL10, insuline resistency, ↑Glu

Ly-Apoptosis
Th1->Th2 cytokines
↓NK activity
↓Macrophage activity

Immunosupression

Contraction band necrosis
Myocytolysis
Cross-band formation
Subendocardial hemorrhage

Myocardial damage

IL 6, syst. immfl.
↑Vessel permeability
Second hit

NPE

Hypoperfusion
↑Permeability
Endotoxin
Loc. autonomic Dysreg.

Colon paralysis
Extracerebral effects

- **Brain injury**
  - Sympathetic nervous system
  - Catecholamine and hormone response
  - Systemic inflammatory response syndrome

- **Neurocardiogenic injury**
  - ECG changes, including T-wave inversions, ST depression, high R waves, and prolongation of QTc interval
  - Tako-tsubo syndrome
  - Myocardial enzymes changes

- **Neurogenic pulmonary injury**
  - Neurogenic pulmonary edema
  - Pneumonia
  - Aspiration

- **Neurogenic renal injury**
  - Hypomagnesemia
  - Hyponatremia
  - High glucose level

- **Hyperglycemia electrolyte imbalance**

- **Hematological failure**
  - Coagulative and fibrinolytic disorders
  - High D-dimer

Chen, BRI, 2014
Cerebral effects (secondary brain injury)

- Vasoconstriction
- ↑ Permeability
- Microthrombosis
- Hyperglycemia
- BBB breakdown

- Spleen Tr, systemic IL-1, IL-6, IL-12, TNFalpha
- Local inflammation

- Immunosupression
- Post-stroke autoimmune response
- Autoimmune inflammation

- Hypoperfusion
- Baroreflex failure
- Impaired autoregulation
- Impaired CBF
Surrogates of autonomic activity

cardiac derived
HRV
(SDNN, RMSSD
HF, LF, HF/LF, VLF powers)
BRS
Decelaration capacity
HR turbulence
QT-variability index

HPA derived
AVP, CRH
Cortisol
Catecholamines
Degradation products
Orexin, Urocortins
Copeptin

IS, ICH, IVH, SAB, TBI, GBS, SIRS, MODS, acute MI, HF

↓ Outcome and ↑ Mortality
90 days, 6 month, 1 year, 5 years
HRV and BRS in brain injury

**IS**  Colivicchi 2005
Hilz 2011

**ICH**  Sykora 2008
Sykora 2018

**SAH**  Chiu 2012
Chen 2016
Nasr 2018

**TBI**  Sykora 2016
Henden 2014
Biswa 2000

↓ Outcome and ↑ Mortality
Autonomic impairment influences outcome

- Cardiac complications und susceptibility to sudden death
- Boost of brain edema und BBB damage
- Blood pressure derrangements und cerebral hypoperfusion
- Stress hyperglycemia
- Immunosupression / Infections
Sympathetic activity in ICP

Schmidt, Fro Physiol, 2018
Baroreflex sensitivity in ICP

Tymko, CAN, 2018
Autonomic assessment

ICM+ peak detection
ectopics removal
spectral analysis
cross-correlation
moving window

HRV variability
HF, LF, VLF powers
LF/HF ratio

xBRS
Baroreceptors (carotids, aortic arch)

Baroreflex - physiology

NTS

VLM

NA

DVN

INS

PF

CING

AMG

TAL

HYP

baroreceptors

BP elevation

neg. chronotropy
neg. dromotropy
neg. inotropy
vasodilatation
↓ vasopressin

(-> HR decrease)
The slope of the linear regression between 10s series of RR intervals and 10s series of systolic BP is calculated. The RR window is shifted against the systolic BP in stepwise manner and the highest correlation is reported, if it fulfills the criteria outlined below. Valid BRS value is returned only if the correlation coefficient is significant at p<0.01, and if no irregular beats (ectopics) are detected by the software. The BRS is updated every 10s and expressed in ms/mmHg.
Baroreflex sensitivity (xBRS) im ICM+®
Baroreflex sensitivity (xBRS) im ICM+®
Baroreflex sensitivity (xBRS) im ICM+®
Autonomic Impairment in Severe Traumatic Brain Injury: A Multimodal Neuromonitoring Study

Marek Sykora, MD, PhD, MSc1,2; Marek Czosnyka, PhD1; Xiuyun Liu1; Joseph Donnelly, MBChB1; Nathalie Nasr, MD, PhD1,3; Jennifer Diedler, MD, MSc4; Francois Okoroafor, MD1; Peter Hutchinson, BSc (hons), MBBS, PhD, FRCS (Surg Neurol)1; David Menon, MBBS, MD, PhD, FRCP, FRCA, FmedSci6; Peter Smielewski, PhD1

Baroreflex Impairment After Subarachnoid Hemorrhage Is Associated With Unfavorable Outcome

Nathalie Nasr, MD, PhD; Rita Gaio, PhD; Marek Czosnyka, PhD; Karol Budohoski, PhD; Xiuyun Liu, PhD; Joseph Donnelly, PhD; Marek Sykora, MD, PhD; Peter Kirkpatrick, MD, FMedSci; Anne Pavy-Le Traon, MD, PhD; Christina Haubrich, MD, PhD; Vincent Larrue, MD; Peter Smielewski, PhD

Heart rate variability is associated with outcome in spontaneous intracerebral hemorrhage

Jozef Szabo a, Peter Smielewski b, Marek Czosnyka b, Stanislava Jakubicek c, Stefan Krebs d, Pavel Siarmik a, Marek Sykora d,e,*
Autonomic Impairment in Severe Traumatic Brain Injury: A Multimodal Neuromonitoring Study

- Monocentric, non-randomised comparison
- Cambridge TBI database, n=327, 2003-2009
- Severe TBI, sedated, with ICP monitoring
- xBRS every 10s and HRV every 300s with ICM+
- Adjustment for ICP, CPP und autoregulation (PRx)
- Mortality und Outcome GOS at 6 months

Sykora, CCM, 2016
# Autonomic Impairment in Severe Traumatic Brain Injury: A Multimodal Neuromonitoring Study

## TABLE 1. Comparison of Clinical and Autonomic Variables Between Traumatic Brain Injury Survivors and Nonsurvivors at 6 Months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors, n = 201</th>
<th>Nonsurvivors, n = 61</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), median (range; IQR)</td>
<td>33 (16–76; 23)</td>
<td>44 (18–76; 32)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Glasgow Coma Scale, median (range; IQR)</td>
<td>7 (3–15)</td>
<td>5 (3–14)</td>
<td>0.072</td>
</tr>
<tr>
<td>Intracranial pressure, mm Hg, median (range; IQR)</td>
<td>15.8 (4.5–29.0; 5.6)</td>
<td>17.6 (3.0–50.9; 9.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cerebral perfusion pressure, mmHg, median (range; IQR)</td>
<td>77.7 (57.7–100.1; 6.6)</td>
<td>74.2 (56.2–102.1; 11.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pressure reactivity index, median (range; IQR)</td>
<td>0.05 (−0.29–0.70; 0.20)</td>
<td>0.14 (−0.30–0.70; 0.23)</td>
<td>0.002</td>
</tr>
<tr>
<td>Baroreflex sensitivity, ms/mm Hg, median (range; IQR)</td>
<td>6.6 (1.6–18.8; 4.2)</td>
<td>5.1 (1.3–18.7; 4.0)</td>
<td>0.026</td>
</tr>
<tr>
<td>HF power, ms², median (range; IQR)</td>
<td>160.0 (9.9–1853.9; 285.4)</td>
<td>115.0 (6.2–1840.3; 212.1)</td>
<td>0.024</td>
</tr>
<tr>
<td>HF relative power, median (range; IQR)</td>
<td>25.8 (5.0–65.4; 175)</td>
<td>33.4 (6.6–81.8; 22.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LF-to-HF ratio, median (range; IQR)</td>
<td>1.6 (0.2–8.3; 1.3)</td>
<td>1.0 (0.0–8.8; 1.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LF power, ms², median (range; IQR)</td>
<td>598 (9–133; 927, 1,883)</td>
<td>748 (1–41; 628, 2,291)</td>
<td>0.833</td>
</tr>
<tr>
<td>LF relative power, median (range; IQR)</td>
<td>22.1 (7.7–39.5; 7.5)</td>
<td>19.9 (2.6–45.7; 12.1)</td>
<td>0.137</td>
</tr>
<tr>
<td>Heart rate variability total power, ms², median (range; IQR)</td>
<td>2,551 (90–250; 617, 3,802)</td>
<td>2,169 (56–66; 197; 4,228)</td>
<td>0.701</td>
</tr>
</tbody>
</table>

IQR = interquartile range, HF = high frequency, LF = low frequency.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Adj OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model for mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRS, ms/mm Hg</td>
<td>0.888</td>
<td>0.801–0.984</td>
<td>0.024</td>
</tr>
<tr>
<td>HF relative power, ms²</td>
<td>1.046</td>
<td>1.019–1.074</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>1.073</td>
<td>1.046–1.101</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Admission GCS</td>
<td>0.800</td>
<td>0.713–0.899</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICP, mm Hg</td>
<td>1.140</td>
<td>1.062–1.225</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PRx</td>
<td>11.927</td>
<td>1.559–91.254</td>
<td>0.017</td>
</tr>
<tr>
<td>Model for poor outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRS, ms/mm Hg</td>
<td>0.887</td>
<td>0.804–0.978</td>
<td>0.016</td>
</tr>
<tr>
<td>HF relative power, ms²</td>
<td>1.041</td>
<td>1.015–1.068</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>1.068</td>
<td>1.043–1.095</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Admission GCS</td>
<td>0.802</td>
<td>0.718–0.897</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICP, mm Hg</td>
<td>1.132</td>
<td>1.058–1.211</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PRx</td>
<td>7.317</td>
<td>1.041–51.420</td>
<td>0.045</td>
</tr>
<tr>
<td>Model for unfavorable outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRS, ms/mm Hg</td>
<td>1.027</td>
<td>1.003–1.051</td>
<td>0.030</td>
</tr>
<tr>
<td>HF relative power, ms²</td>
<td>0.999</td>
<td>0.998–1.000</td>
<td>0.061</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>1.058</td>
<td>1.037–1.080</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Admission GCS</td>
<td>0.811</td>
<td>0.741–0.888</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICP, mm Hg</td>
<td>1.079</td>
<td>1.017–1.144</td>
<td>0.012</td>
</tr>
</tbody>
</table>
Baroreflex Impairment After Subarachnoid Hemorrhage Is Associated With Unfavorable Outcome

AUC(BRS)=0.835 (dotted line)
AUC(WFNS)=0.853 (solid line)
AUC(BRS & WFNS)=0.900 (dashed line)
Heart rate variability is associated with outcome in spontaneous intracerebral hemorrhage

<table>
<thead>
<tr>
<th>Variable</th>
<th>mRS 0–3 at 3 months</th>
<th>mRS 4–6 at 3 months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean (range, SD)</td>
<td>59.5 (17–86, 20)</td>
<td>62.2 (34–84, 21)</td>
<td>0.8</td>
</tr>
<tr>
<td>Admission NIHSS, median (range, IQR)</td>
<td>5 (1–34, 13)</td>
<td>28 (6–34, 21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemorrhage volume median (range, IQR)</td>
<td>14 (1–102, 34)</td>
<td>50 (7–234, 84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intraventricular extension n (%)</td>
<td>8 (34.8)</td>
<td>18 (75)</td>
<td>0.008</td>
</tr>
<tr>
<td>Admission glucose mg/d, median (range, IQR)</td>
<td>113 (89–162, 26)</td>
<td>154 (95–327, 40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HF power, total, ms², median (range, IQR)</td>
<td>118 (16–22,588, 263)</td>
<td>55 (5–7458, 343)</td>
<td>0.04</td>
</tr>
<tr>
<td>HF power, normalized median (range, IQR)</td>
<td>21 (11–60, 16)</td>
<td>34 (15–83, 16)</td>
<td>0.01</td>
</tr>
<tr>
<td>LF power, total, ms² median (range, IQR)</td>
<td>162 (10–19,060, 262)</td>
<td>24 (2–4704, 178)</td>
<td>0.004</td>
</tr>
<tr>
<td>LF power, normalized median (range, IQR)</td>
<td>24 (10–52, 11)</td>
<td>16 (4–46, 14)</td>
<td>0.01</td>
</tr>
<tr>
<td>LF/HF ratio median (range, IQR)</td>
<td>1.2 (0.3–4.1, 1)</td>
<td>0.6 (0.05–3.0, 5)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alive at 3 months</th>
<th>Dead at 3 months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean (range, SD)</td>
<td>61.3 (17–86, 18)</td>
<td>60.2 (42–84, 13)</td>
<td>0.6</td>
</tr>
<tr>
<td>Admission NIHSS, median (range, IQR)</td>
<td>10 (1–34, 18)</td>
<td>34 (11–34, 21)</td>
<td>0.008</td>
</tr>
<tr>
<td>Hemorrhage volume median (range, IQR)</td>
<td>36 (1–202, 50)</td>
<td>50 (10–234, 94)</td>
<td>0.03</td>
</tr>
<tr>
<td>Intraventricular extension n (%)</td>
<td>15 (43)</td>
<td>11 (92)</td>
<td>0.006</td>
</tr>
<tr>
<td>Admission glucose mg/d, median (range, IQR)</td>
<td>124 (89–300, 45)</td>
<td>150 (95–327, 232)</td>
<td>0.04</td>
</tr>
<tr>
<td>HF power, total, ms², median (range, IQR)</td>
<td>118 (5–22,588, 338)</td>
<td>34 (6–923, 62)</td>
<td>0.01</td>
</tr>
<tr>
<td>HF power, normalized median (range, IQR)</td>
<td>27 (11–83, 19)</td>
<td>39 (20–80, 27)</td>
<td>0.04</td>
</tr>
<tr>
<td>LF power, total, ms² median (range, IQR)</td>
<td>153 (2–19,057, 314)</td>
<td>16 (2–283, 22)</td>
<td>0.001</td>
</tr>
<tr>
<td>LF power, normalized median (range, IQR)</td>
<td>22 (5–52, 12)</td>
<td>15 (4–37, 10)</td>
<td>0.006</td>
</tr>
<tr>
<td>LF/HF ratio median (range, IQR)</td>
<td>0.8 (0.1–4.1, 1)</td>
<td>0.4 (0.05–1.0, 6)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Future directions – monitoring time trends
Future directions – examining therapies

- BB reduce infarct size and mortality in stroke models (Savitz 2000)
- Pre-stroke BB may have positive outcome effects (n=111, Laowattana 2007)
- BB reduce edema in ICH (Sansing 2011)
- Pre-injury BB reduce stunned myocardium in SAH (Liang 2013)
- BB reduce tissue injury markers and inflammation in SAH (Kawaguchi 2010)
- BB reduce edema in TBI models (Liu 1995)
- Pre-injury BB have positive outcome effects in TBI (Mohseni 2014)
- Post-injury BB have positive outcome effects in TBI

(meta-analysis, n=4782, adjusted OR 0.35; 95 % CI 0.27-0.45, Alali 2014)
Thank you for your attention