Brain the Forgotten Organ in Resuscitation

Brian J. O’Neil, MD, FACEP, FAHA

Professor and Chair
Department of Emergency Medicine
Wayne State University
Detroit, Michigan

EVENTS LEADING TO NEURONAL DEATH DURING POST-ISCHEMIC BRAIN REPERFUSION

- Ischemia
- ATP Depolarization
- Cytosol Ca++
- Activated P’lipases
- Proteolysis of eIF4G by Calpain
- Depletion ER Ca++
- Epinephrine cAMP
- ATP PP1 inhibited
- PP2A PKA activation
- PERK Autophosphorylation
- eIF-2α(P)
- Inhibition of Protein Synthesis
- Caspase 3
- Apoptosis
- Cells unable to respond to injury and DIE
- Membrane Damage
- Lipid Peroxidation Fe²⁺
- Free Arachidonate O₂⁻
- Inhibited Growth Factor Signaling
- Bad, Bax, Mito caspase 9 & cyt c release to APAF1
- Activation
Cerebral Metabolism: High Octane

- Human brain:
  - 2% of body weight
  - 25% of total body energy expenditure
  - 20% oxygen consumption

- Excellent to monitor because it is the canary in the coal mine.
- Early warning system for ischemia

Figure 1. Some of the pathological cascades contributing to aggravate neuronal injury after acute brain injury. Initial mechanisms, such as excitotoxicity and mitochondrial dysfunction, initiate damage in the very early minutes/hours; other factors, such as energy dysfunction, edema, and inflammation come into play later in the process. CBF, cerebral blood flow.
HOW DO YOU MONITOR THE BRAIN??

- ADMIT IT
  - YOU DON’T
- IT IS JUST ALONG FOR THE RIDE
- WE FLY BLIND AND HOPE FOR THE BEST
- IS THIS OUR TACT FOR UNDENIABLY OUR MOST IMPORTANT ORGAN ??

Overall Aims of Neuromonitoring:

1. Identify worsening neurological function and secondary cerebral insults that may benefit from specific treatment(s)
2. Improve pathophysiological understanding of cerebral disease in critical illness
3. Provide clear physiological data to guide and individualize therapy
4. Assist with prognostication
Current Monitoring Choices:

- **Non-invasive:**
  - Trans-cranial Doppler (TCD)-derived pulsatility index
  - optic nerve sonography
- **Intra-ventricular devices:**
  - considered the “gold standard”
  - intra-parenchymal pressure monitoring provides particularly useful when CSF drainage is desirable.
Transcranial Doppler

- Flow velocity (rather than flow itself)
- TCD combines ultrasound and the Doppler principle to represent erythrocyte flow in the basal cerebral arteries.
- In some 10% of patients, transtemporal insonation is not feasible
- Cerebral vascular resistance increases
  - Systolic velocity increases
  - Diastolic velocity decreases

Cerebral Blood Flow Monitoring

- Continuous measurement of regional CBF is now feasible using a thermal diffusion probe (TDP)
- TDP technique showed good agreement with CBF measured by xenon-CT
Jugular venous bulb oximetry

- Arterio-jugular difference in oxygen content (AJDO$_2$):
  - proportional to CBF
  - inversely proportional to oxygen consumption (cerebral metabolic rate for oxygen, CMRO$_2$)
- Normal values for SjO$_2$ are about 57%
  - (95% CI 52% to 62%)
- Global measure
  - Insensitive to small regional changes

Direct PbtO$_2$ Measurement

- PbtO$_2$ probe is in white matter
- Provides a reasonable estimate of global brain oxygenation
- It varies not only with CBF but also with changes in arterial oxygen tension
- values <20mmHg are considered worth treating
- any PbtO$_2$ values ≤5 mmHG are associated with poor outcome after TBI
Near infra-red spectroscopy

- Oxyhemoglobin, deoxyhemoglobin, and oxidized cytochrome oxidase absorb specific portions of the light spectra
- Correlated to the relative proportions of oxyhemoglobin and deoxyhemoglobin (HbO$_2$/Hb) and oxidized cytochrome oxidase in the tissue
- Non-invasive and continuous
- Baseline normal values vary widely
  - Extracranial contamination is a problem
  - Hair absorbs the light

Cerebral Oximetry (CereOx)

- Regional Oxygen saturation (rSO$_2$)
- Reflects cellular $O_2$ extraction
- Does not require a pulse
- Strong correlation with cerebral blood flow and jugular vein bulb saturation
Oximetry Trends in the ED Cardiac Arrest:

<table>
<thead>
<tr>
<th>rso2 Trend</th>
<th>Good CPC</th>
<th>Poor CPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABN -&gt; ABN</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>ABN -&gt; NL</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>NL -&gt; ABN</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>NL -&gt; NL</td>
<td>16</td>
<td>21</td>
</tr>
</tbody>
</table>

Oximetry v ETCO2 in Cardiac Arrest
Oximetry v ETCO2 in Cardiac Arrest

Low brain tissue oxygenation contributes to the development of delirium in critically ill patients: A prospective observational study
Biomarkers

- Not touching this too many, too late and too variable
- Not a Real Time, Continuous Marker
- Best used as a prognosticator

Electro-physiological measurements

- EEG:
  - to detect and manage seizures
  - Neuroprognostication
- Seizures are often non-convulsive
  - aggravate brain injury
- Need Contentious monitoring:
  - Alarms are problematic
  - Need the ability to interpret output
Electro-physiological measurements

- qEEG may also be used to monitor the depth of sedation in the ICU.
- The most commonly used modality is the ‘bispectral index’ (BIS)
- 0 (brain dead) to 100 (normal brain function); a value of <60 indicates general anesthesia, and <30 indicates burst suppression

Continuous EEG Monitoring

![Graph showing Good Percent Alpha Variability and Poor Percent Alpha Variability over post-injury days.](image)

*Figure 5: Lack of variability over time of the percent alpha trend (PAV) is associated with poor clinical outcomes. The daily PAV scores are graphed for those brain injured patients who eventually had a good outcome (top panel) and those that had a poor outcome (bottom panel). The PAV scores tend to remain good or improve day by day in those patients with a good outcome, whereas they remain poor or worsen day by day in those patients with a bad outcome.*
Magnetic resonance spectroscopy
- Measures tissue levels of selected neurometabolites
- N-acetyl aspartate, a marker of neuronal integrity, is decreased in TBI, often in brain
- Brain N-acetyl aspartate levels are associated with worse clinical conditions and are predictive of functional outcome following TBI

Functional MRI
- Demonstrates cortical-subcortical networks governing motor activity are significantly impaired following TBI
Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage

**Figure 1.** Mean Hourly Minimum Systolic Blood Pressure during the First 24 Hours after Randomization, According to Treatment Group. The dashed vertical line indicates 2 hours, and I bars 95% confidence intervals.

**ATTACH-2**

**Score on the Modified Rankin Scale**

- Standard Treatment (N=480)
  - 7.1: 19.6%
  - 17.3: 17.3%
  - 18.3: 18.3%
  - 26.5: 26.5%

- Intensive Treatment (N=481)
  - 5.0: 19.8%
  - 19.1: 19.1%
  - 17.5: 17.5%
  - 26.0: 26.0%
ATTACH-2

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Relative Risk (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glasgow Coma Scale score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–11</td>
<td>143</td>
<td>0.90 (0.71–1.14)</td>
<td>0.62</td>
</tr>
<tr>
<td>12–14</td>
<td>278</td>
<td>1.16 (0.90–1.49)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>540</td>
<td>0.97 (0.73–1.38)</td>
<td></td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>253</td>
<td>1.14 (0.95–1.37)</td>
<td>0.53</td>
</tr>
<tr>
<td>No</td>
<td>697</td>
<td>1.00 (0.79–1.26)</td>
<td></td>
</tr>
<tr>
<td>Baseline hematoma volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30 cm³</td>
<td>91</td>
<td>0.95 (0.73–1.22)</td>
<td>0.73</td>
</tr>
<tr>
<td>&lt;30 cm³</td>
<td>859</td>
<td>1.04 (0.86–1.25)</td>
<td></td>
</tr>
<tr>
<td>Hematoma location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>486</td>
<td>1.06 (0.83–1.35)</td>
<td>0.75</td>
</tr>
<tr>
<td>Cerebral lobe</td>
<td>104</td>
<td>1.16 (0.85–2.06)</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>359</td>
<td>0.92 (0.74–1.15)</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>166</td>
<td>1.09 (0.75–1.59)</td>
<td>0.75</td>
</tr>
<tr>
<td>No</td>
<td>778</td>
<td>1.00 (0.84–1.20)</td>
<td></td>
</tr>
<tr>
<td>Met systolic blood pressure target</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>within 2 hr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>901</td>
<td>1.02 (0.87–1.21)</td>
<td>0.51</td>
</tr>
<tr>
<td>No</td>
<td>60</td>
<td>0.63 (0.26–1.63)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>595</td>
<td>1.15 (0.92–1.44)</td>
<td>0.20</td>
</tr>
<tr>
<td>Female</td>
<td>366</td>
<td>0.88 (0.67–1.16)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>555</td>
<td>0.92 (0.73–1.17)</td>
<td>0.60</td>
</tr>
<tr>
<td>Black</td>
<td>117</td>
<td>1.22 (0.81–1.86)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>269</td>
<td>1.09 (0.84–1.42)</td>
<td></td>
</tr>
<tr>
<td>Hispanic, ethnic group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>74</td>
<td>0.96 (0.54–1.70)</td>
<td>0.84</td>
</tr>
<tr>
<td>No</td>
<td>887</td>
<td>1.03 (0.67–1.57)</td>
<td></td>
</tr>
<tr>
<td>Enrolled at Asian site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>532</td>
<td>0.95 (0.74–1.21)</td>
<td>0.49</td>
</tr>
<tr>
<td>No</td>
<td>429</td>
<td>1.09 (0.85–1.34)</td>
<td></td>
</tr>
</tbody>
</table>

Autoregulation Curve is Shifted in HTN

- CBF = cerebral blood flow
- MAP = mean arterial pressure
Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II: A Phase II Randomized Trial: BOOST 2

<table>
<thead>
<tr>
<th></th>
<th>ICP &lt; 20</th>
<th>ICP ≥ 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>pBT\text{O}_2 ≥ 20</td>
<td>Type A: No interventions directed at pBT\text{O}_2 or ICP needed</td>
<td>Type B: Interventions directed at lowering ICP</td>
</tr>
<tr>
<td>pBT\text{O}_2 &lt; 20</td>
<td>Type C: Interventions directed at increasing pBT\text{O}_2</td>
<td>Type D: Interventions directed at lowering ICP and increasing pBT\text{O}_2</td>
</tr>
</tbody>
</table>

BOOST-2
**BOOST 2 Outcomes**

**A**  
**GOS-E at 6 Months**

<table>
<thead>
<tr>
<th></th>
<th>8</th>
<th>7</th>
<th>6</th>
<th>5</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>PbtO2 + ICP</td>
<td>13%</td>
<td>11%</td>
<td>9%</td>
<td>8%</td>
<td>19%</td>
<td>13%</td>
<td>9%</td>
<td>25%</td>
</tr>
<tr>
<td>ICP Only</td>
<td>6%</td>
<td>8%</td>
<td>9%</td>
<td>8%</td>
<td>23%</td>
<td>9%</td>
<td>4%</td>
<td>34%</td>
</tr>
</tbody>
</table>

8 = Upper Good Recovery; 7 = Lower Good Recovery; 6 = Upper Moderate Disability; 5 = Lower Moderate Disability; 4 = Upper Severity Disability; 3 = Lower Severe Disability; 2 = Vegetative State; 1 = Dead

**B**  
**DRS at 6 Months**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1-11</th>
<th>12-29</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>PbtO2 + ICP</td>
<td>21%</td>
<td>45%</td>
<td>9%</td>
<td>25%</td>
</tr>
<tr>
<td>ICP Only</td>
<td>13%</td>
<td>45%</td>
<td>8%</td>
<td>34%</td>
</tr>
</tbody>
</table>

0 = no disability; 1-11 = Mild to Moderate Disability; 12-29 = Severe Disability to Vegetative State

---

**ATTACH-2**

**Score on the Modified Rankin Scale**

- **Standard Treatment (N=480)**
  - 7.1 19.6 17.3 18.3 26.5

- **Intensive Treatment (N=481)**
  - 5.0 19.8 19.1 17.5 26.0

Percent of Patients

---

School of Medicine
Consensus Summary Statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care

In broad terms, the preservation or absence of pressure autoregulation can influence blood pressure management following brain injury. Patients who show preserved autoregulation may benefit from higher mean arterial pressure and CPP as part of an integrated management scheme for ICP control, while those who show pressure passive responses may be better served by judicious blood pressure control.

2. We recommend that hemodynamic monitoring be used to establish goals that take into account cerebral blood flow (CBF) and oxygenation. These goals vary depending on diagnosis and disease stage. (Strong recommendation, moderate quality of evidence.)

Consensus Summary Statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care

2. We recommend monitoring brain oxygen in patients with or at risk of cerebral ischemia and/or hypoxia, using brain tissue (PbtO2) or/and jugular venous bulb oximetry (SjvO2)—the choice of which depends on patient pathology. (Strong recommendation, low quality of evidence.)

5. We suggest the use of brain oxygen monitoring to assist titration of medical and surgical therapies to guide ICP/CPP therapy, identify refractory intracranial hypertension and treatment thresholds, help manage delayed cerebral ischemia, and select patients for second-tier therapy. (Weak recommendation, low quality of evidence.)
Conclusions

- At present, there is no ‘ideal’ single brain monitor; a combination of monitoring techniques may provide better insight into brain function than a single monitor used alone
  - Supply and Demand
  - Trends over time and threshold values are both important when assessing brain function

That Is All Well and Good, But What the Hell Am I supposed to do in the ED?!

- First give be very cognizant of the brain:
  - Systemic effects
  - Potential effects of your therapy
- Second do no harm
  - No Hypoxia
  - No Hyperoxia- Sats at 95-98%
  - No Hypotension
That Is All Well and Good, But What the Hell Am I supposed to do in the ED??

- Second do no harm
  - No Fever
  - No Hypoglycemia
  - No Hyperglycemia:
    - Just an excuse to give insulin

That Is All Well and Good, But What the Hell Am I supposed to do in the ED??

- Be Smart about CPP
  - Autoregulation is shifted in chronic hypertension
  - Autoregulation may be lost: Therefore CPP is directly dependent on MAP
  - If and When you are able monitor, trend and treat oxygenation and flow