Assessing Cerebral Oxygenation and Intracranial Pressure Using Noninvasive Methods

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We will discuss noninvasive techniques to assess intracranial pressure and cerebral blood flow

– Potential adjuncts to more established clinical methods

– Interesting areas of discovery

– NOT a substitute for standard-of-care invasive intracranial monitoring
Bedside Assessment

What is going on in this patient’s head?

Roadmap

• **Intracranial pressure (ICP) assessment**
  – Physical examination and imaging
  – Pupillometry
  – Optic nerve ultrasound

• **Blood flow, autoregulation, and oxygenation**
  – Transcranial doppler (TCD)
  – Near Infrared Spectroscopy (NIRS)
  – Computed indices
    • Extra data from existing invasive sources

• **Multimodal Monitoring**
  – EEG
  – New technology
Cerebrovascular Physiology: Basic Review

Pinto et al, Intracranial Hypertension, Fundamentals of Neurosurgery, 2019

https://basicmedicalkey.com/neurosurgical-and-neurological-emergencies-for-surgeons
Cerebrovascular Physiology: Basic Review

Noninvasive Assessment of Intracranial Pressure
Physical Examination: Still Relevant

Fernando et al, *Diagnosis of elevated intracranial pressure in critically ill adults: systematic review and meta-analysis*. BMJ, 2019

### Results

<table>
<thead>
<tr>
<th>Physical examination signs</th>
<th>Sensitivity (percent, 95% CI)</th>
<th>Specificity (50, 100)</th>
<th>Evidence quality (GRADE score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any pupillary dilation</td>
<td></td>
<td></td>
<td>★★★★ Moderate</td>
</tr>
<tr>
<td>Motor posturing</td>
<td></td>
<td></td>
<td>★★★☆ Low</td>
</tr>
<tr>
<td>Glasgow coma scale ≤8</td>
<td></td>
<td></td>
<td>★★★☆ Low</td>
</tr>
</tbody>
</table>

### Computed tomography signs

<table>
<thead>
<tr>
<th>Computed tomography signs</th>
<th>Sensitivity (percent, 95% CI)</th>
<th>Specificity (50, 100)</th>
<th>Evidence quality (GRADE score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cisterns absent or compressed</td>
<td></td>
<td></td>
<td>★★★★ Moderate</td>
</tr>
<tr>
<td>Midline shift &gt;0 mm</td>
<td></td>
<td></td>
<td>★★★★ Moderate</td>
</tr>
<tr>
<td>Midline shift &gt;5 mm</td>
<td></td>
<td></td>
<td>★★★☆ Moderate</td>
</tr>
<tr>
<td>Midline shift &gt;10 mm</td>
<td></td>
<td></td>
<td>★★★★ High</td>
</tr>
<tr>
<td>Marshall score ≥3</td>
<td></td>
<td></td>
<td>★★★☆ Low</td>
</tr>
<tr>
<td>Marshall score ≥4</td>
<td></td>
<td></td>
<td>★★★☆ Low</td>
</tr>
<tr>
<td>Marshall score ≥5</td>
<td></td>
<td></td>
<td>★★★☆ Low</td>
</tr>
</tbody>
</table>
Limitations of CT Scans in Trauma

- Single center retrospective review
- 280 children with severe TBI
- 68 w/ normal admission head CT
  - 9 received ICP monitors
  - 7 of 9 (77.8%) had increased ICP within 24 h of monitoring

“Excluding the possibility of elevated ICP on the basis of an initial (0-6 hr after injury) CT examination of the brain is not suggested in comatose pediatric patients”

Pupillometry: Enhanced Physical Exam

• Neurologic pupillary index (NPI)
  – Computed index (0-5; abnormal if <3)
    • Pupillary constriction, latency, velocity of constriction, dilation

youtube.com, courtesy of NeurOptics
Pupillometry: Enhanced Physical Exam

- NPi correlates with ICP after TBI
  - 54 adults with severe TBI, ICP monitors
  - Cumulative time burden with abnormal NPI correlates with poor outcome (GOS)

Jahns et al, Critical Care, 2019
Optic Nerve Sheath Diameter

- Sonographic optic nerve sheath diameter (ONSD) correlates with ICP ($r = 0.72$) \(^1\)

- ONSD is highly predictive of ICP $\geq 20$
  - Pooled AUROC 0.94 [0.91-0.96] \(^2\)

1. Wang et al, JAMA Ophthalmology, 2018
2. Fernando et al, BMJ, 2019
Optic Nerve Sheath Diameter

• ONSD may be useful in monitoring patients with acute liver failure (ALF)

• Prospective study of 74 pediatric patients with ALF
  – ONSD predictive of hepatic encephalopathy
  – ONSD > 5.1 mm predicts poor outcome (death without liver transplant)
    • AUROC 0.82

Das et al, Liver Int, 2019

Wang et al, JAMA Ophthalmology, 2018
Noninvasive Assessment of Cerebral Blood Flow, Autoregulation, and Brain Oxygenation
Transcranial Doppler (TCD)

- Elevated ICP
  - Pulsatility Index (PI)
  - (Vs-Ved)/Vm
- Vasospasm:
  - $V_{mca}$, Lindegaard’s ratio
    - (Vmca / Vica)
- Static rate of autoregulation = Autoregulatory Index (ARI)
  - Impaired in 25-80% of pediatric TBI patients
  - Abnormal in ~17% of children with diabetic ketoacidosis
- ↑cerebral blood flow velocity associated with worse outcome in children after global hypoxic-ischemic insult

High ICP after AVM rupture:
- Increased MCA flow velocity and PI

LaRovere et al, J Ultrasound Med, 2015

1. LaRovere et al, Neurotrauma, 2016
2. Ma et al, PCCM, 2014
3. Lovett et al, Resuscitation, 2017
Transcranial Doppler (TCD)

- 160 children with cerebral malaria in Democratic Republic of the Congo
  - Impaired autoregulation in 80%
  - 24% mortality
  - Neurologic deficits in 21% of survivors
  - Early (day 1-3) impairment of autoregulation associated with neurologic sequelae and death
  - Specific TCD findings associated with outcome

Normal, Microvascular Obstruction, Hyperemia

Vasospasm, Low Flow, Posterior Hyperemia (IPH)

Table V. Predicted probabilities (with 95% CIs) of neurologic sequelae or death in children with cerebral malaria in each TCD diagnostic group

O’Brien et al, Journal of Pediatrics, 2018
Transcranial Doppler (TCD)

TCD predicts ↑ICP (≥ 20)

• Pulsatility index may detect ICP ≥ 20
  – AUROC 0.55-0.72

• TCD-ABP methods predict ICP≥ 20
  – Pooled AUROC: 0.85 [0.78-0.91]

Fernando et al, Diagnosis of elevated intracranial pressure in critically ill adults: systematic review and meta-analysis. BMJ, 2019
How We Use TCD

- Pediatric Neurocritical Care Research Group survey
  - 27/29 (93%) of centers used TCD
  - Variety of conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Hospitals</th>
<th>Clinical Use % Total (95% CI)</th>
<th>Research Use % Total (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hemorrhage</td>
<td>20</td>
<td>74.1 (55.3–86.8)</td>
<td>22.2 (10.6–40.8)</td>
</tr>
<tr>
<td>Arterial ischemic stroke</td>
<td>14</td>
<td>51.2 (34.0–69.3)</td>
<td>14.8 (5.9–32.5)</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>10</td>
<td>37.0 (21.5–55.8)</td>
<td>29.6 (15.9–48.5)</td>
</tr>
<tr>
<td>Cerebral vascular malformation</td>
<td>9</td>
<td>33.3 (18.6–52.2)</td>
<td>11.1 (3.9–28.1)</td>
</tr>
<tr>
<td>Mechanical circulatory support</td>
<td>8</td>
<td>29.6 (15.9–48.5)</td>
<td>18.5 (8.2–36.7)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>7</td>
<td>25.9 (13.2–44.7)</td>
<td>18.5 (8.2–36.7)</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>6</td>
<td>22.2 (10.6–40.8)</td>
<td>14.8 (5.9–32.5)</td>
</tr>
<tr>
<td>Cerebral venous infarction</td>
<td>5</td>
<td>18.5 (8.2–36.7)</td>
<td>18.5 (8.2–36.7)</td>
</tr>
<tr>
<td>Intraoperative monitoring</td>
<td>4</td>
<td>14.8 (5.9–32.5)</td>
<td>7.4 (2.1–23.4)</td>
</tr>
<tr>
<td>Other (meningitis, hydrocephalus)</td>
<td>4</td>
<td>14.8 (5.9–32.5)</td>
<td>11.1 (3.9–28.1)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3</td>
<td>11.1 (3.9–28.1)</td>
<td>11.1 (3.9–28.1)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>2</td>
<td>7.4 (2.1–23.4)</td>
<td>7.4 (2.1–23.4)</td>
</tr>
<tr>
<td>None/uncertain</td>
<td>4</td>
<td>14.8 (5.9–32.5)</td>
<td>22.2 (10.6–40.8)</td>
</tr>
</tbody>
</table>

LaRovere et al, *PCCM*, 2019
How We Use TCD

- Pediatric Neurocritical Care Research Group survey
  - Some centers use TCD to change management
  - Problematic? – *unclear impact on outcomes*

LaRovere et al, *PCCM*, 2019

**TABLE 4. Changes in Critical Care Management Based Upon Transcranial Doppler Examinations Performed for Clinical Reasons Across 27 Pediatric Neurocritical Care Centers**

<table>
<thead>
<tr>
<th>Change in Clinical Management</th>
<th>No. of Hospitals</th>
<th>Percent of Total (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perform head imaging</td>
<td>18</td>
<td>66.7 (47.8–81.4)</td>
</tr>
<tr>
<td>Manipulation of cerebral perfusion pressure with fluids or vasopressors</td>
<td>13</td>
<td>48.2 (30.7–66.0)</td>
</tr>
<tr>
<td>None/uncertain</td>
<td>7</td>
<td>25.9 (13.2–44.7)</td>
</tr>
<tr>
<td>Neurosurgical or endovascular procedure</td>
<td>6</td>
<td>22.2 (10.6–40.8)</td>
</tr>
<tr>
<td>Manipulation of mechanical ventilation</td>
<td>5</td>
<td>18.5 (8.2–36.7)</td>
</tr>
<tr>
<td>Counseling of families</td>
<td>4</td>
<td>14.8 (5.9–32.5)</td>
</tr>
<tr>
<td>Placement of intracranial pressure monitor</td>
<td>3</td>
<td>11.1 (3.9–28.1)</td>
</tr>
<tr>
<td>Elevation of head of bed</td>
<td>1</td>
<td>3.7 (0.7–18.3)</td>
</tr>
<tr>
<td>Change in anticoagulation</td>
<td>1</td>
<td>3.7 (0.7–18.3)</td>
</tr>
</tbody>
</table>
How We Use TCD

- Pediatric Neurocritical Care Research Group survey

**TABLE 5. Emerging Clinical Applications for Transcranial Doppler in the PICU**

<table>
<thead>
<tr>
<th>Trigger</th>
<th>Purpose</th>
<th>When to perform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoasmp on imaging of condition associated with high risk of vasospasm (e.g., TBI, SAH, subarachnoid infection/inflammation)</td>
<td>May affect therapeutic strategies (initiation or advancement) in symptomatic patients</td>
<td>Within 72 hr of admission for TBI and aneurysmal SAH, and daily thereafter (23, 24)</td>
</tr>
<tr>
<td>Acute stroke symptoms with intracranial arterial stenosis on imaging with or without acute infarction</td>
<td>To evaluate progression or regression of intracranial steno-occlusive disease</td>
<td>Within 24 hr stroke symptom onset</td>
</tr>
<tr>
<td>To monitor effects of treatment (medical, endovascular)</td>
<td>Serial measurements for known intracranial arterial stenosis</td>
<td></td>
</tr>
<tr>
<td>To provide longitudinal follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI with known BCVI or any unmonitored child with TBI and Glasgow Coma Scale ≤ 8</td>
<td>To evaluate for indirect evidence of increased intracranial pressure</td>
<td>Within 72 hr of admission</td>
</tr>
<tr>
<td>To detect emboli which may be associated with increased risk of BCVI-related stroke (36, 37)</td>
<td>Frequency and duration may be guided by patient clinical presentation and early clinical course</td>
<td></td>
</tr>
<tr>
<td>To detect disordered perfusion (oligemia, hyperemia) which may guide BP/cerebral perfusion pressure management</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Limitations and caveats**

- Criteria for vasospasm (age-dependent cerebral blood flow velocities, Lindegaard ratio) are not established for children
- Aneurysmal SAH is rare in children and duration of risk period for vasospasm is not well characterized
- Clinically meaningful changes in cerebral blood flow velocity in pediatric stroke are not defined
- Results in TBI need interpretation in the context of pharmacologic management of BP, head of bed position
- Clinically meaningful emboli burden is not defined

Use depends on local resources, expertise in performing and interpreting studies

LaRovere et al, *PCCM*, 2019
Near-Infrared Spectroscopy (NIRS)

- **Regional oxyhemoglobin saturation (rSO$_2$)**
  - Gross estimate of cerebral blood flow, oxygenation

- **After TBI in adults:**
  - rSO$_2$ correlates positively with CPP, negatively with ICP
  - Mirrors changes in invasive brain tissue oxygen tension (PbO$_2$)

- **NIRS-derived Autoregulation Indices**
  - Total hemoglobin reactivity index (THx)
  - Cerebral oximetry index (COx)
  - Tissue oxygen reactivity index (TOx)

- **Strong correlation ($R^2 = 0.81$) between NIRS rSO$_2$ and CT perfusion-derived cerebral blood volume (but not flow)**

- Mathieu et al, J Neurosurg Anesthesiol, 2019
- Jakkula et al, Critical Care, 2019
Near-Infrared Spectroscopy (NIRS)

- In children with DKA, abnormal \( rSO_2 \) (>80%) seen in 17 of 19 patients
  - 2-27 hours into treatment course
  - Irrespective of fast vs. slow fluid administration

Computed Indices of Autoregulation

• Computational techniques meant to maximize clinical utility from monitor data
  – Not non-invasive per se...
Computation of Indices of Autoregulation

- **Pressure reactivity index (PRx)**
  - *Adult TBI*: Impaired autoregulation (PRx > 0.3) associated with unfavorable outcome
    - Zeiler et al, Neurotrauma, 2017
  - *Pediatric TBI*: longer duration of PRx > 0.2 associated with unfavorable outcome
    - Hockel et al, Acta Neurochir, 2017
New Approaches and Multimodal Monitoring
Continuous EEG: Beyond Seizures

- Periodic discharges ("interictal continuum")
  - Possibly indicative of neuronal hypoxia/ichemia
- **Quantitative EEG:**
  - Delta percentage correlates with CBF after focal ischemia
  - Alpha-delta ratio (ADR) correlates with CPP
  - 10% ↓ ADR after subarachnoid hemorrhage: 100% sensitive, 76% specific for delayed cerebral ischemia
- **Intracranial EEG:**
  - Seizures can precede scalp EEG findings
  - Abnormalities can precede focal infarct and global cerebral edema

  - Appavu et al, Neurocrit Care, 2019
  - Appavu et al, PCCM, 2019
Cerebral Oximetry Index (COx)

- Slow-wave correlation between rSO2 and MAP (lower = intact autoregulation)
- Optimal MAP = MAP at minimum COx
- In comatose adults with acute brain injury (varying diagnosis):
  - >80% time outside optimal MAP associated with higher 90-day mortality (HR 2.13 [0.04-4.41])

Rivera-Lara et al, Critical Care Medicine, 2019
Multimodal Approach: Calibrating TCD with ICP and ABP

Simultaneous ICP, arterial blood pressure (ABP), and MCA velocity (CBFV) → Noninvasive ICP estimate (nICP)
- Automated, model-based analysis
- Can be done in real time

nICP is predictive of actual ICP in children and young adults
- Still requires an arterial line
- Semi-noninvasive?

Fanelli et al, J Neurosurg Pediatr, 2019
Novel NIRS Device

- Diffuse correlation spectroscopy (DCS) measures cerebral blood flow
  - Non-invasive
  - Bedside compatible
  - Uses near-infrared light
  - High sampling rate for cardiac pulse measurements
- NIRS measures cerebral hemoglobin concentration

Courtesy of Alexander Ruesch
Induced ICP changes in non-human primate model

- Reference intraparenchymal ICP measurement
- Continuous DCS and NIRS measurements at 50 Hz

- Induced ICP changes by fluid pressure through a catheter into the lateral ventricle
  - Baseline changes between 5 and 40 mmHg
  - Oscillation by fluid reservoir rotation for frequency analysis

Courtesy of Alexander Ruesch
Novel NIRS Device

- Oxygenated hemoglobin changes (ΔHbO) follow ICP changes during slow oscillation
  - Transfer function analysis translates ΔHbO into ΔICP
  - High temporal resolution
  - 7 non-human primates

Cardiac pulsation in cerebral blood flow (ΔCBF) changes shape under elevated ICP
- Machine learning waveform analysis
- Estimates ICP offset
- 5 non-human primates

Courtesy of Alexander Ruesch
Novel NIRS Device

Ongoing Validation in PICU Patients:
External ventricular drain closure captured in HbO

Courtesy of Alexander Ruesch
Conclusions

• Many promising non-invasive modalities exist to assess ICP and cerebral blood flow, oxygenation
• Further development and validation is needed to standardize their use in neurocritical care
  – Invasive ICP monitoring remains standard of care in severe TBI
  – Neurologic outcome prediction remains a challenge after acute brain injury/illness
  – Novel techniques may further inform a proactive rather than reactive strategy
    • i.e. Event prediction, autoregulation-targeted therapy
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