24. Brain Chemistry
Current bedside monitors of brain blood flow and oxygen delivery

Global monitors
- Cannot detect regional abnormalities

Local monitors
- Sample only a small region of the brain and highly dependent on accurate placement

Thanks to Mr. P. Hutchinson
Brain probes

Peter Hutchinson, 2000
Neurotrend Sensor Technology

Thanks to Mr. P. Hutchinson
Brain Oxygen Tension Monitoring: LICOX®

- Adjustment of cerebral perfusion pressure levels based on the needs of each patient
- Early warning of differences between brain tissue oxygen supply and demand
- Independent, sensitive outcome prediction

Monitoring Brain Oxygen

LICOX®
Brain Tissue Oxygen Monitoring System
Changes in PbO$_2$ with SjvO$_2$ in areas with no focal pathology

$\Delta$ PbO$_2$(kPa)

$\Delta$ SjvO$_2$ (%)

$(r^2 = 0.69)$

Long-term brain tissue oxygenation monitoring
Overall, there seems to be no correlation between PbtiO2 and ICP /CPP
If you are lucky and ‘click’ on more coherent area, correlation sometimes appears. Is it physiology or ‘click’ phenomenon?
Transient changes in brain tissue oxygenation seem to follow changes in CPP.

**Plateau wave of ICP**

**Arterial hypertension**

**Transient Changes in Brain Tissue Oxygen in Response to Modifications of Cerebral Perfusion Pressure: An Observational Study**

Elena, K. Rydzewicz, M.D.
Marek Czyczynka, M.D.
Ivan Timoteev, M.D.C.S.
Andrzej Lejewski, M.D.
Dejan Jovicic, M.D.
Matthias Jager, M.D.
Peter Hutchinson, Ph.D.
Ann Culpin, Ph.D.
John D. Pickard, M.Chr., F.Med.Sc.
Peter Smielewski, Ph.D.

**METHODS:** This was a retrospective analysis and observational study. 
PbO, arterial blood pressure (ABP), and ICP waveforms were digitized simultaneously in 23 head-injured patients, admitted to the Neuroscience Critical Care Unit, who were sedated, paralyzed, and ventilated. Computer recordings were retrospectively reviewed. The dynamic changes in PtO, in response to transient changes in ABP and ICP were investigated.

**RESULTS:** Several patterns of response to short-lasting, arterial hypertension and hypertension, intracranial hypertension, cerebral vasodilation, and cerebral hypoxia were observed and characterized. Using the majority of the transient events, PtO, generally followed the direction of changes in CPP. Only during episodes of hypertension, CPP and PtO, changed in the opposite direction. Changes in PtO, were delayed after changes observed in ABP, ICP, and CPP. The CPI-PtO, delay during changes provoked by variations in ABP was 25±12 s, changes maximum 22±4 s, minimum 4±0 s, the difference was significant (P < 0.0001).

**CONCLUSIONS:** PbO, is more than a number; it is rather a waveform following rapid changes in ICP and ABP. We show that PbO, generally tracks the direction of CPP irrespective of the state of cerebral autoregulation.
Arterial hypotension

Hyphaemia.... Exception?
Continuous assessment of cerebrovascular autoregulation after traumatic brain injury using brain tissue oxygen pressure reactivity.

Jaeger M, Schuhmann MU, Soehle M, Meixensberger J.
Department of Neurosurgery, University of Leipzig, Leipzig, Germany. jaem@medizin.uni-leipzig.de

Comment in:

We could not find any correlation between Orx and PRx
Near Infrared spectroscopy: Basic Principle

LIGHT IN (650-900nm)

Fixed Scattering and Absorbing Medium
(melanin, bilirubin, bone, water, lipid, etc...)

Oxygenated Haemoglobin (Hb\textsubscript{O\textsubscript{2}})

De-oxygenated Haemoglobin (Hb)

Oxidised Cytochrome Oxidase (CtOx)

LIGHT OUT

Thanks to Dr.K.Brady
NIRS Can Trend CBF and CBV

- Cerebral Oximetry:
  - CBF
  - CMRO$_2$
  - HCT
  - SaO$_2$

- BVI:
  - CBV
  - HCT

Thanks to Dr. K. Brady
Principle of NIRO 300

- Bone
- CSF
- Brain Tissue
- Skin

Detectors

Emitter

775nm
810nm
850nm
910nm

4.5-5.0 cm

Thanks to Mrs. P. All-Rawi
Measurement of TOI

\[ \mu_a \times \mu_s \approx \left( \frac{\delta A}{\delta d} - \frac{2}{d} \right)^2 \]

where
- \( \mu_a \) = absorption coefficient
- \( \mu_s \) = scattering coefficient
- \( A \) = attenuation
- \( d \) = distance

Diffusion theory model + \textit{in vivo} experiments = \( \mu_s \)

Total Hb & HbO\textsubscript{2} concentration

Regression model equation

\( \mu_a \) Total tissue absorption coefficient

TOI

Thanks to Mrs. P. All-Rawi
NIRS measurements

NIRS is can be easily used *longtime* and is *non-invasive*


Thanks to M.Ch.Zweifel
Plateau waves

Thanks to M.Ch.Zweifel
Coughing

Thanks to M.Ch.Zweifel
Change in ventilation and position

Thanks to M.Ch.Zweifel
NIRS and change in ventilation

Thanks to M.Ch.Zweifel
NIRS and slow waves

Thanks to M.Ch.Zweifel
Comparison of changes in brain tissue oxygenation, tissue oxygen index and tissue hemoglobin index in response to transient changes in cerebral hemodynamics.

KP Budhoski¹, C Zweifel¹, J Diedler¹, M Kasprowicz¹, E Sorrentino¹, C Haubrich¹, KM Brady², P Smielewski¹, JD Pickard¹, PJ Kirkpatrick¹, M Czosnyka¹

¹ Division of Neurosurgery, University of Cambridge, Addenbrooke’s Hospital, Cambridge, UK
² Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

**Aims:**

1. To determine the pattern of changes in PbtO₂ and NIRS in response to transient fluctuations of arterial blood pressure (ABP) and ICP,
2. To determine the time delays between the initiation of the observed changes in PbtO₂ and NIRS.

**Methods:**

**Design:** Retrospective analysis of data from 41 head - injured patients.

**Signals analyzed:**

1. ABP,
2. ICP/CPP,
3. Cerebral blood flow velocity (CBFV),
4. PbtO₂,
5. NIRS – derived signals:  
   - Tissue oxygenation index (TOI),
   - Tissue hemoglobin index (THI).

**Results:**

\[
\text{ABP} \quad \rightarrow \quad \text{TCD} \quad \rightarrow \quad \text{NIRS} \quad \rightarrow \quad \text{PbtO₂}
\]
### Grouping of events:

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td>ABP – led events during intact cerebrovascular reactivity (PRx &lt; 0.3)</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td>ABP – led events during impaired cerebrovascular reactivity (PRx ≥ 0.3)</td>
</tr>
<tr>
<td><strong>Group 3</strong></td>
<td>ICP – led events</td>
</tr>
<tr>
<td><strong>Group 4</strong></td>
<td>Oxygenation - led events</td>
</tr>
</tbody>
</table>

![Group 1](image1.png)

![Group 2A](image2.png)
Data from Porto, TBI, thanks to Dr. Celesta Dias
Microdialysis

• A technique for sampling the extracellular space
• The microdialysis catheter consists of two concentric tubes separated from the external environment by a semi-permeable membrane
• Molecules diffuse into the catheter and the fluid can be recovered and assayed for molecules of interest
• Metabolic intermediaries such as glucose, lactate and pyruvate diffuse out of cells into the extracellular space

Thanks to Mr. A. Helmy
Diffusion of molecules across the dialysis membrane

Perfusion fluid 0.3 µl/min

Microdialysate

To collection vial

Dialysis membrane (PAES)
100 kDa MWCO

Thanks to Mr. A. Helmy
Thanks to Mr. A. Helmy

Microdialysis
Principles of Microdialysis

Blood capillary

Microdialysis catheter

Glucose
Lactate
Pyruvate
Glycerol
Glutamate

Thanks to Mr. A. Helmy
Microdialysis Parameters

• Glucose, Lactate, Pyruvate
  – Neuronal metabolic fuels
• Glutamate
  – Excitatory neurotransmitter
  – Commonest neurotransmitter in the brain
  – Implicated in excitotoxic damage
• Glycerol
  – Constituent of cellular membrane (phospholipid)
  – Released following cellular death

Thanks to Mr.A.Helmy
Lactate / Pyruvate Ratio

• The balance between lactate and pyruvate provides a measure of the balance between aerobic and anaerobic metabolism at the cellular level

The Redox State of the Cell

• Using the ratio between lactate and pyruvate is required to avoid the confounding effects of glucose availability

Thanks to Mr.A.Helmy
Summary of Metabolic Changes

Lactate | Pyruvate | L/P
-------|---------|------
Hypoxia | ↑       | ← →  | ↑
Ischemia | ↑       | ↓    | ↑↑
Hypoglycemia | ↓      | ↑    | ↓
Hyperglycemia | ↑    | ↑    | ↓

Thanks to Mr. A. Helmy
Interpreting Microdialysis Data

Thanks to Mr. A. Helmy
Interpreting Microdialysis Data

Thanks to Mr. A. Helmy
What does it mean?

• Microdialysis provides a very sensitive measure of local biochemistry
• Often precedes changes in ICP
• An ‘early warning indicator’
• Problems
  – Only reflects biochemistry in a small volume of brain
    • look for concordance with other monitoring
  – What parameters can you manipulate to improve tissue biochemistry?
    CPP    ICP    Hyperosmolar agent    Hyperoxia

Thanks to Mr.A.Helmy
Microdialysis (Peter Hutchinson). PET-microdialysis correlation

\[ r = 0.69 \quad p = 0.002 \]
Cerebral extracellular chemistry and outcome following traumatic brain injury: a microdialysis study of 223 patients

Ivan Timofeev,1 Keri L. H. Carpenter,1,2 Jürgens Nortje,2,3 Pippa G. Al-Rawi,1 Mark T. O’Connell,1,2 Marek Czosnyka,1 Peter Smielewski,1 John D. Pickard,1,2 David K. Menon,2,3 Peter J. Kirkpatrick,1 Arun K. Gupta3 and Peter J. Hutchinson1,2
Figure 1 Pooled values of monitoring parameters averaged by day of monitoring and split by outcome categories. Graphs display concentrations (in microdialysates) of glucose (mmol/l) (A), glutamate (µmol/l) (B), glycerol (µmol/l) (C), lactate (mmol/l) (D), pyruvate (µmol/l) (E), values of microdialysate lactate/pyruvate ratio (F), microdialysate lactate/glucose ratio (G), intracranial pressure (mmHg) (H) and cerebral perfusion pressure (mmHg) (I). CPP = cerebral perfusion pressure; ICP = intracranial pressure.
Table 1  Median (interquartile range) values of monitoring parameters and percentages beyond pathological thresholds split by outcome groups, with respective statistical significance for intergroup comparisons

<table>
<thead>
<tr>
<th>Parameter (n of data-points)</th>
<th>Outcome groups (Glasgow Outcome Scale)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dead</td>
<td>Unfavourable</td>
</tr>
<tr>
<td>Glucose (n = 213) (mmol/l)</td>
<td>1.2 (0.6–1.7)</td>
<td>1.1 (0.5–1.9)</td>
</tr>
<tr>
<td>Glucose &lt; 1.0 mmol/l (%)</td>
<td>35.4 (6.3–85.7)</td>
<td>42.7 (7.2–89.4)</td>
</tr>
<tr>
<td>Glutamate (n = 155) (µmol/l)</td>
<td>3.2 (1.6–6.2)</td>
<td>2.3 (1.2–5.3)</td>
</tr>
<tr>
<td>Glutamate &gt; 10 µmol/l (%)</td>
<td>1.0 (0–12.9)</td>
<td>0 (0–7.8)</td>
</tr>
<tr>
<td>Glycerol (n = 118) (µmol/l)</td>
<td>72.5 (48.3–131.7)</td>
<td>56.5 (29.3–105.5)</td>
</tr>
<tr>
<td>Glycerol &gt; 150 µmol/l (%)</td>
<td>15.6 (0–36.1)</td>
<td>7.0 (0–37.5)</td>
</tr>
<tr>
<td>Lactate (n = 213) (mmol/l)</td>
<td>3.0 (2.3–4.2)</td>
<td>3.0 (2.5–4.8)</td>
</tr>
<tr>
<td>Lactate &gt; 4.0 mmol/l (%)</td>
<td>13.3 (1.8–57.1)</td>
<td>14.3 (2.1–78.3)</td>
</tr>
<tr>
<td>Pyruvate (n = 209) (µmol/l)</td>
<td>107 (82.8–141.9)</td>
<td>121.4 (97.2–170.8)</td>
</tr>
<tr>
<td>Pyruvate &lt; 50 µmol/l (%)</td>
<td>1.7 (0–5.5)</td>
<td>1.0 (0–2.9)</td>
</tr>
<tr>
<td>Lactate/pyruvate ratio (n = 208)</td>
<td>27.5 (21.6–33.1)</td>
<td>26.0 (20.8–29.5)</td>
</tr>
<tr>
<td>Lactate/pyruvate ratio &gt; 25 (%)</td>
<td>71.3 (14.2–91.7)</td>
<td>57.8 (21.5–85.7)</td>
</tr>
<tr>
<td>Lactate/pyruvate ratio &gt; 40 (%)</td>
<td>4.2 (0–25)</td>
<td>2.9 (0–13.5)</td>
</tr>
<tr>
<td>Lactate/glucose ratio (n = 212)</td>
<td>3.0 (1.4–5.6)</td>
<td>3.3 (2.0–8.0)</td>
</tr>
<tr>
<td>Lactate/glucose ratio &gt; 10 (%)</td>
<td>3.6 (0–23.1)</td>
<td>1.5 (0–40)</td>
</tr>
<tr>
<td>ICP mmHg (n = 137)</td>
<td>19.3 (15.1–22.2)</td>
<td>16.0 (13.8–19.1)</td>
</tr>
<tr>
<td>ICP &gt; 25 mmHg (%)</td>
<td>16.9 (2.9–38.6)</td>
<td>2.3 (0–10.9)</td>
</tr>
<tr>
<td>CPP (n = 137) (mmHg)</td>
<td>76.0 (71.3–81.6)</td>
<td>77.4 (73–80.3)</td>
</tr>
<tr>
<td>CPP &lt; 60 mmHg (%)</td>
<td>2.3 (0–5.9)</td>
<td>0.4 (0–2.2)</td>
</tr>
<tr>
<td>PRx (n = 133)</td>
<td>0.1 (0.01–0.22)</td>
<td>0.02 (–0.06–0.15)</td>
</tr>
<tr>
<td>PRx &gt; 0.2 (%)</td>
<td>32 (16.2–52.5)</td>
<td>22.3 (12.9–38.7)</td>
</tr>
</tbody>
</table>

Values represent the whole period of monitoring.
*Significant differences (P < 0.05) in bold type.
CPP = cerebral perfusion pressure; ICP = intracranial pressure.
Messages to take home

Brain tissue oxygenation: good for continuous monitoring, correlates with outcome, local, invasive

NIROS: continuous monitoring, more global, two sides, non-invasive, not validated clinically yet, extracranial contamination?

Microdialysis: invasive, local, intermittent. Is it clinical or research tool?