Near Infrared Spectroscopy in Neonatal Intensive Care

Adré J. du Plessis, MBChB
Fetal-Neonatal Neurology, Children’s Hospital,
Boston, MA
Disclosure Statement

I have no relevant financial relationships to disclose or conflicts of interest to resolve.

I will not discuss any unapproved or off-label, experimental or investigational use of a product, drug or device.
Overview

- Cerebrovascular insults are the major cause of brain injury in the preterm and sick term infant and have lifelong personal, familial, and societal impact.

- Hypoxia-ischemia/reperfusion is the most common trigger for cellular cascades leading to irreversible brain cell injury.

- Hemorrhage and its complications are the most commonly recognized forms of brain injury identified during the neonatal period.
Current lack of reliable and safe brain monitoring impedes development of truly effective and rational brain-oriented intensive care for high risk newborns.
Noninvasive, Infrared Monitoring of Cerebral and Myocardial Oxygen Sufficiency and Circulatory Parameters

Frans F. Jöbsis

*Science, 1977;198:1264-1267*

**Abstract.** The relatively good transparency of biological materials in the near infrared region of the spectrum permits sufficient photon transmission through organs in situ for the monitoring of cellular events. Observations by infrared transillumination in the exposed heart and in the brain in cephalo without surgical intervention show that oxygen sufficiency for cytochrome a,a₃, function, changes in tissue blood volume, and the average hemoglobin-oxyhemoglobin equilibrium can be recorded effectively and in continuous fashion for research and clinical purposes. The copper atom associated with heme a₃ did not respond to anoxia and may be reduced under normoxic conditions, whereas the heme-a copper was at least partially reducible.
Principles of Near Infrared Spectroscopy

Spectrum of Light

400  Wavelength (nm)  750

Ultraviolet  Visible Light  Infrared

Near Infrared
## Principles of Near Infrared Spectroscopy

### Absorption of Near Infrared Light

<table>
<thead>
<tr>
<th>Chromophores</th>
<th>Max Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxyhemoglobin (HbO₂)</td>
<td>900 nm</td>
</tr>
<tr>
<td>Deoxyhemoglobin (Hb)</td>
<td>760 nm</td>
</tr>
<tr>
<td>Cytochrome aa 3 (Cyt aa3)</td>
<td>830 nm</td>
</tr>
</tbody>
</table>
The Beer-Lambert Law

\[
\Delta \text{ Concentration (\(\mu\text{M/L}\))} = \frac{\Delta \text{ Absorption (OD)}}{a \times \text{ IOD} \times \text{ PLF}}
\]
Near Infrared Spectroscopy

Scattering
Absorption

Skin/Scalp/Skull

Transmitting Optode

NIR Photons

Fiberoptic Cable

Receiving Optode
Challenges to Absolute Quantitation

NIR Light Scattering and the Pathlength Factor
Near Infrared Spectroscopy

Photon Counter and Photomultiplier Tube

Laser Diodes

Computer Algorithm

Screen Display

$HbO_2$

$Hb$

$THb$

$CytO_2$
Clinical Applications of NIRS

Discrete measurements
• point measurements in time
• response to induced and measured perturbations of the system
• assume steady state conditions

Continuous monitoring
• measures continuous changes in response to random endogenous changes in the system
Discrete Cerebral Hemodynamic Measurements

Measures of Distinct Hemodynamic Parameters

- Cerebral blood flow (CBF)
- Cerebral blood volume (CBV)
- Cerebral venous oxygen saturation (CvSO$_2$)
- Cerebral oxygen extraction (COE)
- Cerebral metabolic rate of oxygen (CMRO$_2$)
Fick principle states that the rate of accumulation of a substance in tissue is related to the rate of arrival and rate of departure of the substance.

Previous studies used exogenous often radioactive tracers.

Quantitative CBF can be derived by inducing a sudden change in FiO₂ and measuring the changes in systemic (SaO₂) and cerebral (HbO₂) concentration within cerebral transit time.
Cerebral Blood Flow Measurement by Near Infrared Spectroscopy

![Graph showing cerebral blood flow metrics with time.](image)

- $\int SaO_2 dt$
- $HbO_2$
- $\Delta HbO_2$
- CBF = 20.5 ml/100g/min
CBF Measurement During CPB

Systemic

Cerebral

NIRS

$HbO_2$

CPB

ICG

Oximeter
NIRS Measurements of Cerebral Blood Volume

- Indicator dilution technique
- Small change in FiO₂ is used to change the cerebral HbO₂ concentration and steady state allowed to develop over about 5 minutes
- Difficult to achieve in infants with critical lung disease or with normal pulmonary function
Cerebral Blood Volume

\[
CBV = \frac{\Delta (HbO_2 - Hb)}{2 \times [Hb_{sys}] \times R \Delta SaO_2}
\]
Cerebral Blood Volume by NIRS

- Normal Newborn (25-40wk) 2.2 ml/100gm
- Asphyxiated Term 4.4 ml/100gm

Wyatt et al, 1989, 1990
Cerebral Blood Volume

Total Hb

Oxy Hb

Deoxy Hb

Cerebral Blood Volume (ml / 100gm)

SaO₂

3.79

3.81

3.72

0 10 20 30 40
Cerebral venous oxygen saturation (CvSO\textsubscript{2})

- CvSO\textsubscript{2} reflects balance between cerebral oxygen delivery (CaO\textsubscript{2} and CBF) and cerebral oxygen extraction (COE)
- Direct measurement of CvSO\textsubscript{2} from jugular bulb sampling is invasive, difficult and high-risk
- Any stimulus that induces a sudden brief decrease in cerebral venous drainage will cause a brief increase in cerebral venous volume
- Techniques used include downward head tilt and jugular compression
Cerebral Venous Oxygen Saturation

\[ \text{CSvO}_2 = \frac{\Delta \text{HbO}_2}{\Delta (\text{HbO}_2 + \text{Hb})} \]
Cerebral Metabolic Rate of Oxygen

\[ \text{CMRO}_2 = (\text{SaO}_2 - \text{CSvO}_2) \times \text{CBF} \times \text{CaO}_2 \]  
\[ (\text{ml O}_2 / 100 \text{ gm/min}) \]
Measuring intrinsic cerebrovascular reactivity by Near Infrared Spectroscopy
Measuring intrinsic cerebrovascular reactivity

- Perfusion pressure-blood flow coupling
- Carbon dioxide-blood flow coupling
- Oxygen-blood flow coupling
- Glucose-blood flow coupling
- Neuronal activation-blood flow coupling
Cerebral vasoreactivity to CO$_2$ (CVR-CO$_2$)

- Changes in circulating CO$_2$ trigger changes in caliber of cerebral resistance vessels and CBV
- Cerebral immaturity and preceding cerebral insults may decrease CVR-CO$_2$
- Changing the ventilator rate and measuring subsequent changes in CO$_2$ and THb by NIRS allows calculation of CVR-CO$_2$
CVR$_{CO_2}$ Measurement

Graph showing:
- THb ($\mu$mol/L) increasing over time.
- CVR$_{CO_2}$ (0.45 ml/100 g/kPa) increasing over time.
- CO$_2$ (mmHg) increasing over time.

Time (min) range from 1 to 14.
# Cerebral CO2 Vasoreactivity (CVR$_{CO2}$)

- **Normal Newborn:** 26 - 40 wk (n=17)
  - CVR$_{CO2}$: ml / 100gm / kPa
    - < 29 wk: 0.15
    - 29-38 wk: 0.24
    - 38+ wk: 0.56
  - CVR$_{CO2}$: % / kPa
    - 26 wk: 4%
    - 40 wk: 25%

*Wyatt, et al 1991*
Neuronal activation-blood flow coupling

- Neuronal activation triggers localized vasodilation and an increase in blood flow
- Strategically placed NIRS optodes detect these hemodynamic responses
- Has been ‘validated’ in studies combining NIRS and functional MRI
- Stimuli used in the newborn include flashed visual, auditory, and olfactory stimuli
Continuous NIRS Monitoring of Cerebral Hemodynamics
Continuous Cerebral Hemodynamic Monitoring

- Oxygenation indices
  - Cytochrome aa3 monitoring
  - Brain hemoglobin indices
  - Brain oxyhemoglobin saturation indices

- Transfer function indices
NIRS: Cytochrome aa₃

NADH → 2 e⁻ → Cyt C → Electron transport chain → NIRS → Cytochrome aa₃

2 ADP → 2 ATP

ADP → ATP

H₂O → O₂
Spatially-resolved spectroscopy
Brain Oxyhemoglobin Saturation Indices

- Spatially-resolved spectroscopy measures absolute brain tissue oxygen-hemoglobin saturation
- Expressed as indices of hemoglobin oxygen saturation (percentage of HbO₂/THb)
- Somanetics (INVOS 3100/5100) rSO₂
- Hamamatsu (NIRO-300; NIRO-200) TOI
- Agreement ‘reasonable’ between 50-70% when compared to SjO₂ (Shimizu et al; Child Nerv Syst, 2005)
- Other studies have differed significantly in reported agreement between these indices and SjO₂
Continuous transfer function-based monitoring of cerebral hemodynamics and oxygenation
Near Infrared Spectroscopy

Measures absolute changes in the cerebral concentration of:

- Oxygenated Hemoglobin (HbO₂)
- Deoxygenated Hemoglobin (Hb)

- $\text{HbO}_2 + \text{Hb} = \text{THb} \ (\sim \text{CBV})$
- $\text{HbO}_2 - \text{Hb} = \text{HbD} \ (\sim \text{CBF})$
Validation studies of HbD as indicator of CBF

Piglet model using radioactive microspheres
Changes in cerebral perfusion pressure induced by

- Aortic ligature technique
- Intracranial hypertension technique
Validation of the HbD Signal vs CBF (microspheres) in model of decreasing CPP using increasing ICP

\[
\Delta \text{HbD (\(\mu\text{mol/L*dpf}\))}
\]

\[
\Delta \text{rCBF (mL/100g/min)}
\]

\[r = 0.9\]

\[p < 0.0001\]
Stages and Thresholds of Cerebral Hemodynamic Failure

Blood Pressure

CBF
CBV
COE
CMRO$_2$
Stages and Thresholds of Cerebral Hemodynamic Failure

Blood Pressure

CBF

CBV

COE

THb

↓HbO2  ↑Hb

HbD

Autoregulating  Pressure Passive
Depth of Interrogation
Muscularis is confined to pial and proximal penetrating arteries
Pressure-Passive Cerebral Circulation

Tsuji M, Pediatrics 2000
## Preliminary Studies

### Results of Cranial US

<table>
<thead>
<tr>
<th>HbD vs MAP Correlation</th>
<th>Normal</th>
<th>Severe US Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoregulating (15)</td>
<td>13</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Pressure Passive (17)</td>
<td>7</td>
<td>8 (47%)</td>
</tr>
</tbody>
</table>

Severe US Abnormality: 80% coherent

_Tsuji M, Pediatrics 2000_
Analysis of Cerebral Autoregulation

Input signal

- \( \Delta \text{CPP} \)
- \( \Delta \text{MAP} \)
- \( \Delta \text{CVP} \)
- Ventilator pressure

Cerebral Pressure Autoregulation

Output signal

- \( \Delta \text{CPP} \)
- \( \Delta \text{HbD} \)

- Maturation
- Hypotension
- Hypoxia, Hypercapnea
- Hypoxia-ischemia
- Infection
Coherence and Transfer Function

- **Coherence function** describes what fraction of the variability in one time series at each frequency arises from variability in the other time series at the same frequency.

- **Transfer gain** is the degree to which input energy is translated into output energy at a specific frequency.

- **Transfer phase** describes the temporal response between input and output signals at different frequencies.
Data epochs of analysis

Date/time

SaO2 → Desaturation
HbD → Autoregulation
MAP (≤10th percentile) → CoVar
HR → Baroreceptor Function

0 minutes 5
Cerebral Pressure Passive Index

Pressure-passive index (PPI) = coherent epochs/total epochs

Coherent (pressure-passive) epochs

Non-coherent epochs
Higher frequency coherence

Case 2B028-8A
Pressure Passive State over Five Days (25 GA infant)
Autoregulation in the Sick Preterm

- 90 infants BW <1500gm and <12 hrs age
- 87 had at least one pressure-passive epoch
- PPI overall 20% (0-48%)
- PPI and HOI inversely related to GA and BW
- Pressure-passivity and hypotension (epochs) not correlated
# Pressure Passivity in Premature Infants

*(n=90 infants <30 wk GA)*

<table>
<thead>
<tr>
<th>GA</th>
<th>PPI %</th>
<th>HOI %</th>
</tr>
</thead>
<tbody>
<tr>
<td>23-25 (n= 25)</td>
<td>22.5 ± 12.0</td>
<td>8.1 ± 11.1</td>
</tr>
<tr>
<td>26-28 (n= 54)</td>
<td>20.0 ± 8.7</td>
<td>5.7 ± 10.0</td>
</tr>
<tr>
<td>29-30 (n= 11)</td>
<td>16.5 ± 7.5</td>
<td>1.1 ± 2.0</td>
</tr>
</tbody>
</table>

*p = 0.02  p = 0.01*
Near infrared spectroscopy: Conclusions

Strengths
• Non-invasive, safe, and portable to bedside
• Continuous and inobtrusive
• Hemodynamics and oxygenation
• Excellent temporal resolution in real time

Weaknesses
• Absolute quantitation
• Prone to artifact
• Limited spatial resolution
• Requires some expertise in interpretation