Disclosures

• **Financial**

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Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure

José R. Maldonado
KEY MESSAGE
Critical illness causes brain damage which can manifest as acute and chronic neurological impairment
The Encephalopathy of Sepsis

Alan C. Jackson, Joseph J. Gilbert, G. Bryan Young and Charles F. Bolton

CJNS 1985 12 (4), 303-7
The Neuropathology of Septic Shock

Tarek Sharshar¹,²; Djillali Annane¹; Geoffroy Lorin de la Grandmaison²; Jean Philippe Brouland²; Nicholas S Hopkinson³; Françoise Gray²

Dead neurons in cortical and hippocampal areas are universal in critically ill patients.
Spectrum of acute CNS dysfunction related to critical illness

- Coma: defined as “unresponsive and unaware”
  - Complicated by many of our sedative/anaesthetic drugs

- Delirium: acute, fluctuating change in mental status with inattention and altered levels of consciousness or disorganized thinking
  - Affects up to 80% of critically ill patients
Hypoactive delirium
Why is ICU acquired delirium important?

Consequences of delirium

The presence of delirium increases the likelihood of nearly every patient-oriented ICU outcome:

- Mortality
- ICU Length of Stay
- Hospital Length of Stay
- Long Term Cognitive impairment

*Delirium of the endless, by night--wind*
Duration of delirium is independent risk factor for poor cognitive function (Pandharipande et al., 2013)

Lower limit of normal (Normal defined as 100, +/- 15)
...delirium, particularly when prolonged, may be associated with an increased likelihood of persistent cognitive impairment after ICU hospitalization.” (6 of 9 studies)

“High quality research on a large cohort of critically ill patients is necessary to better characterize potentially modifiable risk factors for persistent cognitive impairment after ICU hospitalization”.

In Canada, delirium causes more dementia than Alzheimer’s disease

- 230,800 ICU admission per year
  - 69,240-184,640 delirious patients
- Assuming 161,560 ICU survivors (70%)
  - 59,930 living with cognitive functioning at par with moderate traumatic brain injury
  - 40,390 living with cognitive function consistent with mild Alzheimer’s disease
- New cases of Alzheimer’s dementia reported in Canada each year = 25,000

*CIHI Aug 2016
Pandharipande et al., 2013
www.alzheimer.ca*
HYPOTHESIS:
- Decreased brain perfusion in patients with critical illness contributes to acute neurological dysfunction (e.g. delirium) and subsequent long term neurological dysfunction.
Near infrared spectroscopy to measure brain tissue oxygenation

• NIRS uses laser emitters and 2 detectors to provide real time assessments of oxy- and deoxyhemoglobin concentrations

• “subtracts scalp contamination” with proprietary algorithm

• Index of cerebral oxygenation (2.5 cm penetration)
NIRS and cerebral tissue oxygenation

• Almost 2 decades of experience in the cardiac OR

• Low cerebral oxygenation seem to correlate with increased risk of post-operative stroke and worse cognitive scores after cardiac surgery

• Poor cerebral oxygenation during cardiac surgery is associated with post-operative delirium
72 hours to 12 months

**Covariates Collected**

- Pre-existing cognitive dysfunction
- History of hypertension
- History of alcohol abuse
- Severity of illness
- Sedative dose
- Narcotic dose
- Blood urea nitrogen
- Length of ICU stay

- CAM-ICU (ICU)
- bCAM (Ward)

- NIRS

- Neurological/neurosurgical admitting diagnosis
- <24hr life expectancy
- Inability to participate in follow-up

- RBANS

- KINARM

>18 years old

>24hr mechanical ventilation due to respiratory failure

Shock
rSO$_2$ across neurological status

Wood et al., 2017
rSO2, fentanyl, and history of alcohol use are independent risk factors for the development of delirium

<table>
<thead>
<tr>
<th>Predictors from patient history or first 24 hours in ICU</th>
<th>Full Multivariable model</th>
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<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
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<tr>
<td>Per 10 % increase in mean rSO2</td>
<td>0.16 (0.05-0.56)</td>
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<tr>
<td>Per 1000 mcg increase in Fentanyl equivalents</td>
<td>2.02 (1.15-3.55)</td>
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<tr>
<td>Per 100 mg increase in Midazolam equivalents</td>
<td>0.96 (0.25-3.63)</td>
</tr>
<tr>
<td>Alcohol abuse (yes vs no)</td>
<td>6.83 (1.36-34.2)</td>
</tr>
<tr>
<td>Chronic hypertension (yes vs. no)</td>
<td>0.64 (0.17-2.34)</td>
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**Full multivariable model based on covariates selected a-priori:**
Hosmer-Lemeshow goodness of fit test of selected multivariable model = 0.11
C-index of selected model = 0.81

Wood et al., 2017
Traditional indices of tissue oxygenation contribute to rSO2 signal

Regression Model (pooled data)

AIC Selection ($R^2=0.47$):
- Heart Rate
- $pCO_2$
- Hemoglobin

- $R^2 = 0.070$
  - $p < 0.05$

- $R^2 = 0.328$
  - $p < .001$

- $R^2 = 0.071$
  - $p < .01$
Purpose: to describe the use of NIRS in non-neuro, non-cardiac arrest patients. Where neurological outcomes are documented, those will be reported as well.

Search strategy: from 1946 to present, Medline, Embase, and Web of Science searched, as well as personal libraries and bibliographies from selected articles.
NIRS in critical illness: systematic review and meta-analysis:

RESULTS

1410 articles identified after duplicates excluded

17 articles retained for full text review

10 excluded as no primary data presented (4), primary CNS disease present (4), or not critically ill (2)

7 articles retained for systematic review

1393 excluded due to relevance (non-adult, cardiac arrest, cardiac surgery, or other structural brain injury)
NIRS in critical illness: systematic review and meta-analysis: RESULTS

Of the 7 studies:
• Generally small sample size, ranging 10 (Wood et al., 2015) to 103 (Wood et al., 2017)
• Different devices used:
  • FORESIGHT (3)
  • INVOS (3)
  • NIRO-200 (1)
• Also variable duration of recording
  • short sessions, repeated at various time points
  • continuously, for up to 72h
NIRS in critical illness: systematic review and meta-analysis: 
RESULTS-4 studies reported delirium
There is increasing interest in using NIRS in critically ill, non primary brain injured patients.

• The majority of papers were from 2014-present.

The variability in devices and recording duration precluded any meaningful meta-analysis.
Mean rSO$_2$ is only part of the story

Wood et al., 2017

Many delirious patient with high rSO2

Lots of intact patient with low rSO2
Dr. Kevin Lee:

Does impaired cerebral autoregulation relate to delirium in critically ill patients?
Integrity of cerebral autoregulation can be approximated by assessing correlation between rSO2 and MAP.

- **+ve correlation** = impaired autoregulation
- **no correlation** = intact autoregulation

Graph showing the relationship between regional cerebral oxygenation (rSO2; %) and mean arterial pressure (mmHg).
Non-invasively estimating cerebral autoregulation in critically ill patients

1. MAP and rSO2 data recorded during the first 24 hrs in ICU

Invasive MAP recording from radial artery

Regional cerebral oxygen saturation (rSO2) collected with the FORESIGHT NIRS monitor
Non-invasively estimating cerebral autoregulation in critically ill patients

2. Moving correlation analysis with variable window length

1. MAP and rSO2 data recorded during the first 24 hrs in ICU

Invasive MAP recording from radial artery
Non-invasively estimating cerebral autoregulation in critically ill patients

1. MAP and rSO2 data recorded during the first 24 hrs in ICU

2. Moving correlation analysis with variable window length

3. Construct correlation time-series

Invasive MAP recording from radial artery

Regional cerebral oxygen saturation (rSO2) collected with the FORESIGHT NIRS monitor

rSO2-MAP Correlation (Spearman rho)

Spearman rho = -0.2589
p = 0.0468
Disturbed cerebral autoregulation may be related to delirium
Other information regarding optimal MAP target may be extracted from this relationship:

\[ r = \sim 0 \]

i.e. optimal MAP

Usual ICU order - target MAP > 65 mmHg
MAP_{opt} may be 75-85 mmHg for this patient.
Summary

• Both low rSO2 and disturbed autoregulation may contribute to the development of delirium in critically ill patients

• Traditional indicies of tissue oxygenation (Hb, HR, venous O2) contribute significantly to the rSO2 signal
  • Suggesting that we already have the tools to optimize

• Findings need to be validated in a larger study before interventional study is performed.
Conclusions

• Delirium has transitioned from an epiphenomenon of critical illness to a warning signal of poor outcomes

• Pathophysiology is complex, but no more complex than acute kidney injury or acute renal failure
  • however, long-term consequences are likely more severe

• Over the next 5-10 years, delirium may become a resuscitation target, such as low urine output or rising creatinine