Precision Medicine in Neurocritical Care: Should we individualize care?

Victoria McCredie

Toronto Western Hospital
Critical Care Canada Forum
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Conflicts of interest

None
Outline

1. Precision medicine
2. Translation into Neurocritical Care
3. Novel methods to individualize care at the bedside
4. Is it ready for primetime?
"an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."

https://ghr.nlm.nih.gov/primer/precisionmedicine/definition
“One-size-fits-all-approach”
1. Should we individualize care?

2. How do we individualize care?

3. Does it improve outcome?
1. Should we individualize care?

2. How do we individualize care?

3. Does it improve outcome?
Association Between Use of Lung-Protective Ventilation With Lower Tidal Volumes and Clinical Outcomes Among Patients Without Acute Respiratory Distress Syndrome

A Meta-analysis

Ary Serpa Neto, MD, MSc
Cerebral autoregulation

Cerebral blood flow and oxygen consumption in man. Lassen NA. Physiol Rev. 1959 Apr;39(2):183-238
Artery Collapse | Autoregulation | Passive Dilation

CBF (ml/min/100g) vs MAP (mmHg) graph.
Autoregulation
Cerebral pressure reactivity

Adapted from Drs Sekhon/Griesdale
How do we do this at the bedside?
Calculating pressure reactivity (PRx)

INPUT SIGNALS: ICP, ABP

OUTPUT TREND: PRx

10 sec window

Mean(ABP) → Mean(ICP)

5 min window

MAP → MICP

Correlation(MAP, MICP)

Adapted from Dr. P. Smielewski
Optimal CPP
Feasibility

- 61% had a CPPopt U-shaped curve
- 28% had either ascending or descending curves
- 11% had no fitted curve
Continuous Monitoring of Cerebrovascular Pressure Reactivity After Traumatic Brain Injury in Children

Authors: Ken M. Brady, MD, a Donald H. Shaffner, MD, a Jennifer K. Lee, MD, a R. Blaine Easley, MD, a Peter Smielewski, PhD, b Marek Czosnyka, PhD, b George I. Jallo, MD, c and Anne-Marie Guerguerian, MD, e

Departments of aAnesthesiology and Critical Care Medicine and aNeurosurgery, School of Medicine, Johns Hopkins University, Baltimore, Maryland; bDepartment of Academic Neurosurgery, Addenbrooke's Hospital, Cambridge, United Kingdom; and Departments of aCritical Care and aPediatrics, Hospital for Sick Children, Toronto, Canada

Keywords: traumatic brain injury, cerebrovascular pressure reactivity, autoregulation

What's known on this subject: Optimal CPP for children with brain injury is critical and unknown. Pressure reactivity monitoring has been used to show the range of CPPs that allow autoregulation for individual adult patients.

What this study adds: This study shows that pressure reactivity can be monitored in children, loss of pressure reactivity is associated with death, and pressure reactivity monitoring indicates a putative optimal range of CPPs for individual patients.

• strong association between lack of pressure reactivity and death in children with TBI
Prognostic and predictive value

- Dynamic CA is a strong prognostic factor in severe TBI:
  - Impaired autoregulation had worse outcome

- Impaired autoregulation after SAH are more likely to develop delayed cerebral ischemia (independent of incidence of vasospasm)

Stroke. 2012 Dec;43(12):3230-7. Budohoski KP et al...
Is this ready for primetime?

High Accuracy
Low Precision

Low Accuracy
Low Precision

High Accuracy
High Precision

Low Accuracy
High Precision
Validity

Assessment of Cerebrovascular Autoregulation in Head-Injured Patients
A Validation Study

Luzius A. Steiner, MD; Jonathan P. Coles, FRCA; Andrew J. Johnston, FRCA; Doris A. Chatfield, BSc; Peter Smielewski, PhD; Tim D. Fryer, PhD; Franklin I. Aigbirhio, PhD; John C. Clark, PhD, DSc; John D. Pickard, MChir, FRCS, FMedSci; David K. Menon, MD, PhD, FRCA, FRCP, FMedSci; Marek Czosnyka, PhD, DSc

- Pressure reactivity (PRx) correlated with PET-static rate of autoregulation.
- CMRO$_2$ was not constant
- Measurements may reflect autoregulation AND also variable flow-metabolism coupling.
External validation in Canada

Resuscitation 106 (2016) 120–125

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Using the relationship between brain tissue regional saturation of oxygen and mean arterial pressure to determine the optimal mean arterial pressure in patients following cardiac arrest: A pilot proof-of-concept study

Mypinder S. Sekhon, Peter Smielewski, Tahara D. Bhat, Penelope M. Brasher, Denise Foster, David K. Menon, Arun K. Gupta, Marek Czosnyka, William R. Henderson, Kenneth Gin, Graham Wong, Donald E. Griesdale

UNIVERSITY OF TORONTO
Interdepartmental Division of Critical Care Medicine
1. Should we individualize care?

2. How do we individualize care?

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It remains to be demonstrated whether “optimal CPP management” is able to improve outcome.
• Recommended target CPP value for survival and favorable outcomes between 60-70 mmHg

• Whether 60 or 70 mm Hg is the minimum optimal CPP threshold is unclear
  • May depend upon the patient’s autoregulatory status

Systolic blood pressure to decrease mortality/improve outcomes:

- Patients 15 to 49 yrs: SBP $\geq$110 mmHg
- Patients 50 to 69 yrs: at $\geq$100 mmHg
- Patients >70 yrs: SBP $\geq$110 mmHg

What can we do in the meantime?

- Understand limitations of evidence
- How we are currently measuring CPP?
Difference in CPP estimation

MAP at heart = CPP 60
MAP at head = CPP 44-49

45° head of bed elevation
16 mmHg

30° head of bed elevation
11 mmHg

15° head of bed elevation
6 mmHg
# MAP reference point

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>MAP reference for CPP measurement</th>
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<tbody>
<tr>
<td>Robertson et al.</td>
<td>1999</td>
<td>Foramen of Monro</td>
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<tr>
<td>Cruz et al.</td>
<td>1998</td>
<td>ICP and MAP levelled in relation to the head tilt</td>
</tr>
<tr>
<td>Rosner &amp; Daughton</td>
<td>1990</td>
<td>Supine position. Systemic ABP transducer at same level as ICP</td>
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<tr>
<td>Howells et al.</td>
<td>2005</td>
<td>Phlebostatic axis</td>
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<tr>
<td>Gerber et al.</td>
<td>2013</td>
<td>Unknown</td>
</tr>
<tr>
<td>Johnson et al.</td>
<td>2011</td>
<td>Unknown</td>
</tr>
<tr>
<td>Huang et al.</td>
<td>2006</td>
<td>Unknown</td>
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Joint position statement:

- Councils of the Neuroanaesthesia and Critical Care Society of Great Britain and Ireland (NACCS)
- Society of British Neurological Surgeons (SBNS)

For TBI, the arterial transducer should be positioned at the **level of the tragus.**
Conclusion

• Dynamic CA can be measured at the bedside

• CA assessment appears to have prognostic value

• Further studies needed to assess whether an ‘optimal CPP’ management paradigm improves outcomes

• Decide as a group how we will measure CPP
Thank You.

Victoria.mccredie@uhn.ca
Personalized vs precision

• There was concern that the word "personalized" could be misinterpreted to imply that treatments and preventions are being developed uniquely for each individual.

• Precision medicine, the focus is on identifying which approaches will be effective for which patients based on genetic, environmental, and lifestyle factors.