Brain Resuscitation

Neurocritical Care – Monitoring & Therapies
CCCF November 2, 2016
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Disclosures

Pediatrician

- Financial: none
- Volunteer:
  
  Heart and Stroke Foundation of Canada
  Resuscitation Paediatric Task Force
  International Liaison Committee on Resuscitation Pediatric Task Force 2015
Resuscitation and early post resuscitation care targeted to the brain
Terminology?
C-CPR or N-CPR or B-Resuscitation?

Cerebral - CardioPulmonary Resuscitation?

Neuro - CardioPulmonary Resuscitation?

Brain Resuscitation?
Flow in cardiopulmonary arrest (CPA), resuscitation and post resuscitation care period

Cerebral blood flow

<table>
<thead>
<tr>
<th>Time</th>
<th>Normal</th>
<th>Low</th>
<th>None</th>
<th>Some, high and/or low</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPA</td>
<td>t0</td>
<td>t1</td>
<td>t2</td>
<td>t3</td>
<td>CPR</td>
</tr>
</tbody>
</table>

ROSC or ROC
# Ischemia and reperfusion injury

<table>
<thead>
<tr>
<th>Time</th>
<th>Clinical correlates</th>
<th>Neurovascular Unit</th>
<th>Cell Signaling</th>
</tr>
</thead>
<tbody>
<tr>
<td>t0</td>
<td>Normal</td>
<td>Structural, Electrical, Hemodynamic correlates</td>
<td>Energy failure (ATP), Membrane failure, Excitotoxicity, Apoptosis, Necrosis, Mitochondrial failure, Oxidative stress &amp; Redox pathways</td>
</tr>
<tr>
<td>t1</td>
<td>Obtundated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t2</td>
<td>Coma</td>
<td>Monitoring, Imaging &amp; Electrical</td>
<td></td>
</tr>
<tr>
<td>t3</td>
<td>Recovery</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Cell Signaling**
- Energy failure (ATP), Membrane failure
- Excitotoxicity, Apoptosis, Necrosis, Mitochondrial failure, Oxidative stress & Redox pathways

**Clinical correlates**
- Normal
- Obtundated
- Coma
- Recovery
- Normal

**Neurovascular Unit**
- Structural, Electrical, Hemodynamic correlates

**Time**
- t0
- t1
- t2
- t3

**CPA**
- CPR
- ROSC or ROC
ILCOR, HSFC & AHA 2015

* Most if not all systematic reviews in PICO format incorporated a functional neurological outcome in their constructs

http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.9298365/k.7519/2015_Canadian_Resuscitation_and_First_Aid_Guidelines.htm

http://circ.ahajournals.org/content/132/16_suppl_1.toc
## Learning objectives: recent literature

<table>
<thead>
<tr>
<th></th>
<th>Monitoring</th>
<th>Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to reperfusion</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>TTM Temperature Targeted Management</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Brain Imaging - CT</td>
<td>✔</td>
<td>✔ (?)</td>
</tr>
<tr>
<td>Electrophysiology - EEG</td>
<td>✔</td>
<td>✔ (?)</td>
</tr>
</tbody>
</table>
Intervals of time: duration of ischemia and reperfusion

- Performance metric: measuring time
- CPA to ROC: \( t_2 - (t_1 - t_0) \) minutes
- As short as possible for best functional outcomes among survivors
Importance of clock time

- Quality resuscitation measures
  - *time-to-actions*
- Decisions related to advanced interventions
  - *Conventional CPR vs E-CPR*
- Surrogate for severity of ischemia
  - *Decisions to change goals of care*
GWTG Registry In Hospital Cardiac Arrest in Children

Duration of Cardiopulmonary Resuscitation and Illness Category Impact Survival and Neurologic Outcomes for In-hospital Pediatric Cardiac Arrests
Renee I. Matos, R. Scott Watson, Vinay M. Nadkarni, Hsin-Hui Huang, Robert A. Berg, Peter A. Meaney, Christopher L. Carroll, Richard J. Berens, Amy Praestgaard, Lisa Weissfeld and Philip C. Spinella

*Circulation.* published online January 22, 2013;

Figure 1. Utstein diagram. CPR indicates cardiopulmonary resuscitation; Neuro, neurological outcome; and ROSC, return of spontaneous circulation.
Registry data from GWTG
2000-2009 Data
Survival outcomes after rescue extracorporeal cardiopulmonary resuscitation in pediatric patients with refractory cardiac arrest

Bahaaldin Alsoufi, MD, Osman O. Al-Radi, MD, Rakan I. Nazer, MD, Colleen Gruenwald, CCP, CPC, Celeste Foreman, CCP, CPC, William G. Williams, MD, John G. Coles, MD, Christopher A. Caldareone, MD, Desmond G. Bohn, MD, and Glen S. Van Arsdell, MD

2000-2005
80 children
54% survived ECMO
34% survived hospital discharge
Cause of death ischemic brain injury

Figure 1. Graph showing the relationship between the probability of unfavorable outcome (death or stroke) as related to pre-ECMO CPR duration.

JTCVS 2007
Benchmark < 30 min
How to reduce *time to ROC*?

A + B + C < 30 min
A: 0 min
B: < 10 min for C-CPR
C: < 20 min for E-CPR
Conventional CPR vs E-CPR
Survival & survival with favorable outcomes
27% & 18% vs E-CPR 40% and 27%

GWTG Registry 2000-2011
Survival to hospital discharge & survival with favorable neurological outcome in CPA $\geq$ 10 min

E-CPR vs C-CPR:

Adjusted: OR, 2.80; 95% CI 2.13-3.69; $P<0.001$

OR, 2.64; 95% CI 1.91-3.64; $P<0.001$

Propensity Matched

OR, 1.70; 95% CI 1.33-2.18; $P<0.001$

OR, 1.78; 95% CI 1.31-2.41; $P<0.001$

Note median E-CPR 45 min vs 27 min

Benchmark < 20 min? How to reduce *time to ROC*?

A + B + C < 20 min

A: 0 min

B: < 0 min for C-CPR

C: < 20 min for E-CPR
Post resuscitation care period
POST RESUSCITATION CARE

Monitoring and Therapies

• TTM: Normothermia or Hypothermia
• Controlled re-oxygenation and CO₂ normalization
• Hemodynamic stability
• Seizure detection and control
• Overall supportive care
Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children
In comatose children who survived out-of-hospital cardiac arrest, therapeutic hypothermia vs therapeutic normothermia, did not confer a significant benefit in survival with a good functional outcome at 1 year.
ILCOR Guidelines 2015 Peds

TTM Post cardiac arrest in OHCA

TTM be used in the post–cardiac arrest period hypothermia (32°C–34°C) or normothermia (36°C–37.5°C)
Post resuscitation care period - Oxygenation

- To measure $\text{PaO}_2$ after ROSC
- To target a value appropriate to the specific patient condition
- Normoxemia
Post resuscitation care period - Ventilation

• To measure \( \text{PaCO}_2 \) after ROSC
• To target a value appropriate to the specific patient condition
Early Postresuscitation Hypotension Is Associated With Increased Mortality Following Pediatric Cardiac Arrest

Alexis A. Topjian, MD, MSCE\(^1\); Benjamin French, PhD\(^2\); Robert M. Sutton, MD, MSCE\(^1\); Thomas Conlon, MD\(^1\); Vinay M. Nadkarni, MD, MS\(^1\); Frank W. Moler, MD, MS\(^3\); J. Michael Dean, MD, MBA\(^4\); Robert A. Berg, MD\(^1\)
PECARN Registry

491 patients in database

No age, gender, SBP
N=13

Died within 6 hours
N=41

ECMO within 2 hours
N=54

383 patients analyzed

Hypotension
214 (56%)

Survived
100 (47%)

Died
114 (53%)

No Hypotension
169 (44%)

Survived
99 (59%)

Died
70 (41%)

CCM 2014
Post resuscitation care period - Hemodynamics

Hypotension when measured is common 56% of patients during the first 6 hours. Early hypotension was associated with a higher rate of in-hospital mortality and worse neurologic outcome at hospital discharge.
Neuroimaging

Diagnostic

To detect an etiology

To detect visible structural changes
  (detectable evidence of pathological abnormalities)

No unbiased studies

No diagnostic study designs
CT imaging for diagnostics

Day 2

Day 2
CT imaging for diagnostics

Global ischemia
Day 2

Global & focal Ischemia
Day 2
CT imaging for cerebral edema

Early Head CT Findings Are Associated With Outcomes After Pediatric Out-of-Hospital Cardiac Arrest*

Rebecca M. Starling, MD¹; Karuna Shekdar, MD²; Dan Licht, MD³,⁴,⁵; Vinay M. Nadkarni, MD, MS¹,⁶; Robert A. Berg, MD¹,⁶; Alexis A. Topjian, MD, MSCE¹,⁶

Median time 3.3 hours post ROSC
Loss of GWM and sulcal effacement associated with poor outcome
Normal CT associated with favorable outcome
Electrophysiology - EEG

To detect electrical evidence of cortical function or dysfunction

To diagnose seizures

Not sufficient evidence for 2015 guidelines
Contemporary era
Single center retrospective 2010 – 2013
cEEG IH and OH cardiac arrest
Encephalopathy post event
Categorized early EEG < 12 h

- Normal
- Slow disorganized
- Discontinuous- burst suppression
- Attenuated-flat

Discharge PCPC 1, 2 vs 3,4,5,6
Probability of mortality

- Location
- initial rhythm
- # epinephrine doses
- witnessed status
- No EEG information
- with EEG background

Early Electroencephalographic Background Features Predict Outcomes in Children Resuscitated From Cardiac Arrest
A. Topjian PCCM 2016
Probability of unfavorable neurological outcome

- Arrest location
- initial rhythm
- # epinephrine doses
- witnessed status
- No EEG information
- with EEG background

Early Electroencephalographic Background Features Predict Outcomes in Children Resuscitated From Cardiac Arrest

A. Topjian PCCM 2016
CPA & BRAIN INJURY

- Clinical manifestations
  - Cerebral ischemia
  - Coma
  - Seizures
  - Myoclonus: abnormal movements
  - Cognitive dysfunction
  - Stroke- cortical and spinal
  - Cerebral edema and rarely brain death
    - Cortex more vulnerable than brain stem
    - Basal ganglia more vulnerable than cortex
    - Cerebral haemorrhage
<table>
<thead>
<tr>
<th></th>
<th>Good</th>
<th>Bad</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration CPA to ROC</td>
<td>Short</td>
<td>Long</td>
</tr>
<tr>
<td>Witnessed</td>
<td>Witnessed</td>
<td>Unknown</td>
</tr>
<tr>
<td>Conventional CPR</td>
<td>Short</td>
<td>Long</td>
</tr>
<tr>
<td>Quality</td>
<td>Good</td>
<td>Bad</td>
</tr>
<tr>
<td>E-CPR</td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>Normo</td>
<td>Not low nor high</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>Normo</td>
<td>Extremes</td>
</tr>
<tr>
<td>BP</td>
<td>Normo or high</td>
<td></td>
</tr>
<tr>
<td>TTM</td>
<td>Either normo or hypo but</td>
<td>stable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td>If normal</td>
<td>?</td>
</tr>
<tr>
<td>EEG</td>
<td>?</td>
<td>If abnormal</td>
</tr>
</tbody>
</table>
CHALLENGES

One of the largest obstacles identified in conducting traditional patient-level RCTs in some healthcare settings perceived absence of equipoise.
GAPS - QUESTIONS REMAIN?

• Comparative studies in IHCA or OHCA
• Quality of CPR and interventions difficult to measure
• More trials – more studies – but not only RCTs