Cardio Pulmonary Cerebral Resuscitation

Brain Under Pressure
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Canadian Critical Care Forum
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SickKids®
Disclosures - Pediatrician

Financial:
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Volunteer for Pediatric Resuscitation
Task Forces:
Heart and Stroke Foundation of Canada
AHA GWTG Pediatric Research Task Force
Ontario Neurotrauma Foundation

International Liaison Committee on Resuscitation
‘CardioPulmonary Cerebral Resuscitation’ CPCR by Peter Safar

“Resuscitation Research that is applied to terminal states: asphyxia, severe shock, severe trauma, and cardiac arrest”

CPCR is the Sequence of BLS-ALS-PLS

• Basic Life Support
• Advanced Life Support
• Prolonged Life Support

Cerebral Resuscitation from Temporary Complete Global Brain Ischemia by Peter Safar
Post Cardiac Arrest Syndrome & Post Arrest Care – Peds & Adults

- Clock Time: *short is better*
- Therapies
- Monitoring
- Tests to assist decision making
  - Diagnosis
  - Prognosis
  - *Study designs limited*
Post Arrest Care Or Resuscitation Care Targeted To The Brain
WHY IS IT IMPORTANT?
Acute Critical Neurological Disease in Children

Fink et al Pediatr Crit Care Med. 2017 Feb 15

107 PICUs
23 Countries
Acute Neurological Insults

Prevalence 16.2%
107 PICUs

Fink et al  Pediatr Crit Care Med. 2017 Feb 15
Acute Neurological Insults
Associated with higher mortality

1# Mode of death
‘Withdrawal of life support because of poor neurologic status’

Fink et al Pediatr Crit Care Med. 2017 Feb 15
WHAT IS POST CARDIAC ARREST SYNDROME?

Neumar et al 2008 Circulation
Cerebral Blood Flow & O$_2$
Basic Pathophysiology
Ischemia & Reperfusion Injury

\[
\text{Normal} \quad \text{Low} \quad \text{None} \quad \text{Low and/or High} \quad \text{Normal}
\]

\[
\text{Time} \quad t0 \quad t1 \quad t2 \quad t3
\]
Post Cardiac Arrest Syndrome

1. Post-cardiac arrest brain injury
2. Post-cardiac arrest myocardial dysfunction
3. Systemic ischemic/reperfusion response
4. Persistent precipitating disease
Phases
Clinical & Research

Immediate
• 0-20 min

Early
• 20 min to 6-12 hours

Intermediate
• 12-72 hours

Recovery
• 72 hours - disposition

Rehabilitation
• Rehabilitation hospital

Limit ongoing injury
Provide organ support

Prognostication

Prevent recurrence
Clock Time

- Short vs long ischemia
- Challenges related to measurement
- Cardiac arrest: Time-to-return of circulation
- Stroke: Time-to-needle
Clock Time: Duration

- Quality resuscitation measures
- Decisions related to advanced interventions
- Performance metric for best functional outcomes among survivors
- Surrogate for severity of ischemia
  - Decisions to change goals of care
Ischemia & Reperfusion Brain Injury

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Stupor</th>
<th>Agitation</th>
<th>Coma</th>
<th>Delirium</th>
<th>Seizures</th>
<th>Normal</th>
<th>Dysomnia</th>
<th>Dysfunction</th>
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</thead>
<tbody>
<tr>
<td>Time</td>
<td>t0</td>
<td>t1</td>
<td>t2</td>
<td>t3</td>
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**Neurovascular Unit**

- Monitoring, Imaging & Electrical

**Cell Signaling**

- Neurons: ATP Energy failure, Membrane failure
- Glial cells: Excitotoxicity, Apoptosis, Necrosis,
- Endothelial cells: Mitochondrial failure, Oxidative Stress & Redox pathways
Post Cardiac Arrest Brain Injury

Pathophysiology

Impaired neurovascular unit function & vasoreactivity

Cerebral edema

Post ischemic neurodegeneration
Post Cardiac Arrest Brain Injury

Clinically
Coma
Seizures & Myoclonus
Cognitive dysfunction
Persistent coma
Strokes: cortical or spinal
Cerebral circulatory arrest or brain death
Post Cardiac Arrest Myocardial Dysfunction

Pathophysiology & Clinically

Myocardial stunning
Acute coronary syndrome
Decreased cardiac output
Hypotension
Cardiovascular collapse
Dysrhythmias
Systemic Ischemia/Reperfusion Response

Pathophysiology & Clinically
Systemic inflammatory response
Altered vasoregulation
Altered coagulation
Adrenal suppression
Impaired tissue oxygenation & utilization
Impaired resistance to infection
Monitoring & Therapies - Brain

- Temperature targeted management: Normothermia or Hypothermia
- Measured re-oxygenation and CO$_2$ normalization
- Hemodynamic stability with set targets
- Seizure detection and control
- Overall supportive care
Monitoring & Therapies - Myocardium

- Revascularization
- Hemodynamic optimization
- Intravenous fluids & Inotropes
- Mechanical support with ECMO, VAD or other devices
- Overall supportive care
Monitoring & Therapies - Systemic

- Temperature targeted therapy
- Mechanical ventilation
- Seizure control to minimize $O_2$ demand
- Controlled re-oxygenation
- Overall supportive care
TEMPERATURE
Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children
2015 Out of Hospital THAPCA

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.
Kaplan–Meier Estimates of Survival from 0 to 365 Days after Cardiac Arrest.

‘Among comatose children who survived in-hospital cardiac arrest, therapeutic hypothermia, as compared with therapeutic normothermia, did not confer a significant benefit in survival with a favorable functional outcome at 1 year.’

ILCOR Guidelines 2015

TTM Post cardiac arrest

TTM be used in the post–cardiac arrest period hypothermia (32°C–34°C) or normothermia (36°C–37.5°C)
THERAPIES – RETURN OF CIRCULATION

As soon as possible
Benchmark < 30 min to ROC

A + B + C < 30 min
A: 0 min
B: < 0-10 min for C-CPR
C: < 20 min for E-CPR
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. Caldarone, 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.
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;

![Event Analysis Chart]

**Figure 1.** Utstein diagram. CPR indicates cardiopulmonary resuscitation; Neuro, neurological outcome; and ROSC, return of spontaneous circulation.
Registry data from GWTG
2000-2009 Data
Conventional CPR vs E-CPR
Survival & Survival 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 >= 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

THAPCA ECMO Sub-Group

More than 50% of patients enrolled in the in-hospital Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) trial cohort contributing to the evaluation of the trial’s primary outcome were supported with ECMO in the post-arrest care period.
THAPCA ECMO Sub-Group

Proportion of patients exposed to ECMO with favorable outcome at one year was significantly lower than patients not exposed to ECMO (approximately 30% vs 50%), irrespective of the temperature control strategy…
CPA, CPR & RETURN OF CIRCULATION (ROC)

EVENT CPA C-CPR ROSC

EVENT CPA CPR ECMO ROC

E-CPR
MORE RESEARCH REQUIRED…
MONITORING MODALITIES

- Pulse oximetry
- Cerebral oximetry
- Capnography
- Arterial blood pressure
- Temperature
- Continuous EEG
Post Resuscitation Care
Oxygenation

• To measure PaO$_2$ after ROSC
• To target a value appropriate to the specific patient condition
• Normoxemia
• Upcoming Indices Cerebral Autoregulation
Post Resuscitation Care
Ventilation i.e., Capnia

• To measure PaCO$_2$ after ROSC
• To target a value appropriate to the specific patient condition
• Integrated in comprehensive bedside monitoring beyond… ventilators
Post Resuscitation Care

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.

CCM 2014
Early Postresuscitation Hypotension Is Associated With Increased Mortality Following Pediatric Cardiac Arrest

Alexis A. Topjian, MD, MSCE; Benjamin French, PhD; Robert M. Sutton, MD, MSCE; Thomas Conlon, MD; Vinay M. Nadkarni, MD, MS; Frank W. Moler, MD, MS; J. Michael Dean, MD, MBA; Robert A. Berg, MD
CONTINUOUS EEG
- BACKGROUND
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
Neuroimaging

Diagnostic

To detect an etiology

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

No unbiased studies

No diagnostic study designs
Neuroimaging

• Cerebral edema – necrotic without severe intracranial hypertension
• Cortex more vulnerable than brain stem
  • Basal ganglia more vulnerable than cortex
• Cerebral haemorrhage in patients with ECMO
Hypothermia for 24 Hours After Asphyxic Cardiac Arrest in Piglets Provides Striatal Neuroprotection That Is Sustained 10 Days After Rewarming
Dawn M. Agnew, Raymond C. Koehler, Anne-Marie Guerguerian, Donald H. Shaffner, Richard J. Traystman, Lee J. Martin, Rebecca N. Ichord
Pediatric Research 2003
CT Imaging For Diagnostics

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
CT Imaging for Cerebral Edema

Clinical paper

Head computed tomography for prognostication of poor outcome in comatose patients after out-of-hospital cardiac arrest of cardiac etiology

Clinical paper

Prognostic values of gray matter to white matter ratios on early brain computed tomography in adult comatose patients after out-of-hospital cardiac arrest of cardiac etiology

Byung Kook 1, Wook Jin Cho 1, Dong Hun Lee 1

Department of Emergency Medicine, Asan Medical Center, Korea University College of Medicine, Seoul, Korea

Short communication

Automated assessment of early hypoxic brain edema in non-enhanced CT predicts outcome in patients after cardiac arrest

Uta Hanning a,b,1, Peter Bernhard Sporns a,1, Pia Lebedz c, Thomas Niederstätter c, Tarek Zoubi a, Rene Schmidt d, Stefan Knecht e, Walter Heindel a, André Kemmler a

a Department of Clinical Radiology, University Hospital of Muenster, Germany
b Institute of Epidemiology and Social Medicine, University of Muenster, Germany
c Department of Emergency Medicine, Medical University of Vienna, Austria
d Department of Cardiovascular Medicine, University of Muenster, Germany
Combination of Tests

Clinical paper

Combination of initial neurologic examination, quantitative brain imaging and electroencephalography to predict outcome after cardiac arrest

Chun Song Youn\textsuperscript{a}, Clifton W. Callaway\textsuperscript{b}, Jon C. Rittenberger\textsuperscript{b,\,*}, the Post Cardiac Arrest Service

\textsuperscript{a} Department of Emergency Medicine, The Catholic University of Korea, Republic of Korea
\textsuperscript{b} Department of Emergency Medicine, University of Pittsburgh School of Medicine, United States

Comparison of brain computed tomography and diffusion-weighted magnetic resonance imaging to predict early neurologic outcome before target temperature management comatose cardiac arrest survivors

Chi Heon Jeon\textsuperscript{a}, Jung Soo Park\textsuperscript{a,f,\,*}, Ji Han Lee\textsuperscript{a}, Hoon Kim\textsuperscript{a,f}, Sang Chul Kim\textsuperscript{a}, Kyung Hye Park\textsuperscript{b}, Kyung Sik Yi\textsuperscript{c}, Sun Moon Kim\textsuperscript{g}, Chun Song Youn\textsuperscript{d}, Young-Min Kim\textsuperscript{d}, Byung Kook Lee\textsuperscript{e}

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\textsuperscript{d} Department of Emergency Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
\textsuperscript{e} Department of Emergency Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
## Relevant Factors

<table>
<thead>
<tr>
<th>‘Brain Wellness’</th>
<th>Good</th>
<th>Bad</th>
</tr>
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<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>Low</td>
</tr>
<tr>
<td>TTM</td>
<td>Either normo or hypo but</td>
<td>Fever or ignoring temperature</td>
</tr>
<tr>
<td></td>
<td>stable</td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td>If normal</td>
<td>Globally abnormal</td>
</tr>
<tr>
<td>EEG</td>
<td>If normal</td>
<td>If abnormal for a long time</td>
</tr>
</tbody>
</table>
No Role For
Hyperoxia or hypoxemia
Hypocapnia
Hypotension
Invasive intracranial pressure monitoring
Hyperthermia nor Fever
Gaps - Resuscitation Research

Targeted to recovery phase of brain function

- Duration of pharmacological coma or decreased cerebral activity?
- Duration of TTM Targeted Temperature Monitoring therapy?
- Transfusion therapy?
- Antimicrobial therapy?
- Nutrition: ketosis therapy?
Gaps – Resuscitation Research

• Comparative studies in IHCA or OHCA
• More trials – more studies – comparative but not only RCTs
• Quality of CPR and bedside care interventions
Merci
anne-marie.guerguerian@sickkids.ca
Thank you