Resuscitation of the Pediatric Patient with Pulmonary Hypertension

David L. Wessel, MD
Senior Vice President
IKARIA Distinguished Professor of Critical Care Medicine
Children's National Medical Center
Washington, DC

With special thanks to Alain de Cain

Worksheet Specific Conflict Of Interest Disclosure

- Commercial/industry
  - Dr. Adatia is a member of the advisory committee to create a Canadian pediatric pulmonary hypertension database funded by Actelion. He is also a member of an advisory committee for the pediatric sildenafil trial and for the pediatric investigator protocol for sitaxsentan for Pfizer.
- Dr. Wessel has in the past been a consultant for IKARIA and for Pfizer (> 5 years ago)

Worksheet (WS) Question Development (n=55)

Worksheet (WS) Assignment to 2 Authors (total n = 69)

Evidence Evaluation Expert

ILCOR Pediatric Task Force

2005

International Liaison Committee on Resuscitation
Pediatric Task Force

2010 ILCOR CoSTR Statement

2010 Council (e.g. AHA) Guidelines Statement

What's new?

Is there a pulse?

Tibballs, Resuscitation, 2009 and 2010

Physicians and nurses, blinded to the pulse status of infants/children on VADs/ECMO, asked to assess within 10 sec. whether there was or was not a pulse present
- pulse palpation accurate only 80% of the time
- mistakenly perceived a non-existent pulse up to 24% of the time
- average time to confirm absence of pulse: 30 sec
**2010 AHA Guidelines: Pulse Check**

*New (2010)*

- If the infant or child is unresponsive and not breathing (gasp do not count), healthcare providers may take up to 10 seconds to attempt to feel for a pulse (brachial in an infant and carotid or femoral in a child). If, within 10 seconds, you don't feel a pulse or are not sure if you feel a pulse, begin chest compressions.

No change in recommendation, just stronger science de-emphasizing the role for pulse check by all rescuers.

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**2010 AHA Guidelines: CPR Sequence**

- Lay rescuers to initiate CPR on victims of all ages with chest compressions rather than rescue breaths (C-A-B, not A-B-C).

- With most adult OHCA being cardiac in etiology, and most bystanders not doing any CPR for collapsed victims, a simple and consistent approach to all victims would increase the likelihood that lay rescuers would provide some CPR for victims of all ages: NOT HANDS ONLY CPR!

- Rescue breaths will only be delayed by ~18 seconds.

**BUT...**

CPR in the in-hospital setting is performed by HCPs as a number of simultaneous acts, not in series...

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**2010 AHA Guidelines: Ventilation & Pediatric CPR**

- Prior to advanced airway placement
  - Conventional (15:2) CPR to infants and children in cardiac arrest

- Newborns with a primary cardiac etiology of arrest, regardless of location (eg. NICU vs PICU):
  - Resuscitate according to infant guidelines (15:2, not 3:1); increased emphasis on chest compressions

- After advanced airway placement
  - >100 CC/min, and no more than 8-10 breaths/ min

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**2010 AHA Guidelines: Using EtCO2 during CPR**

- Adult and animal data suggests that a failure to increase EtCO2 to >15 mm Hg during CPR should prompt a change in CPR technique or drug therapy.

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**2010 AHA Guidelines: EtCO2 for prognostication during CPR**

- Animal and adult human data suggests a possible "cut-off" EtCO2 which if not exceeded suggests futility of on-going resuscitation, but there is insufficient pediatric data with which to be able to predict outcome based upon a specific initial EtCO2 or EtCO2 measured at 20 min of CPR.

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**Pediatric Defibrillation**

*Limited available pediatric clinical data:*

- Suggest that higher doses might be more likely to successfully defibrillate, and to do so faster, **BUT**

- Do not show a consistent relationship between defibrillation dose and survival to hospital discharge/neurologic outcome from VF/pulseless VT.

(Tibbals, 2010; Rossano, 2006; Rodriguez-Nunez 2006)
Pediatric Defibrillation

Limited available pediatric clinical data

- An initial dose of 2 J/kg may only be effective at terminating VF 18% of the time
- Higher electrical doses (even biphasic) are associated with greater myocardial injury
- The need to use multiple shocks is associated with a lack of ROSC
  (Tibballs, 2010; Rosano, 2006; Rodriguez-Nunez 2006)

2010 AHA Guidelines: Defibrillation

- It is acceptable to use an initial dose of 2 to 4 J/kg for defibrillation but for ease of teaching
  an initial dose of 2 J/kg may also be considered.
- For refractory VF, it is reasonable to increase the dose. Subsequent energy levels should be
  at least 4 J/kg and higher energy levels, not to exceed 10 J/kg or the adult maximum
dose, may be considered.

AHA Guidelines 2010: Defibrillation

- Single (non-stacked) shocks
- Successful defibrillation is predicated on effective CPR preceding and following the
  shock
- Despite a lack of evidence of survival benefit in humans, biphasic waveforms/defibrillators
  have become the clinical standard due to industry’s shift away from monophasic
  defibrillators

Epinephrine for pediatric cardiac arrest

No change in AHA recommendation

- Epinephrine, 0.01 mg/kg (10 µg/kg), maximum 1 mg.
  The same epinephrine dose is repeated 3-5 minutes.
  There is no survival benefit from high-dose epinephrine, and it may be harmful, particularly in
  asphyxia
- High-dose epinephrine may be considered in exceptional circumstances, such as β-blocker
  overdose
- Outstanding questions
  - How many doses of epinephrine are too many?
  - Are other drugs more efficacious than epinephrine
    (e.g. Vasopressin), and in what scenarios?

Post-ROSC oxygenation

Multiple animal studies have shown that ventilation with 100% oxygen during and following
resuscitation contributes to free radical-mediated reperfusion injury to the brain, and may be associated with
more neurologic deficit than ventilation with room air.

What about human studies?

- Two LOE 5 meta-analyses of several randomized controlled trials comparing
  neonatal resuscitation initiated with room air versus 100% oxygen showed increased
  survival when resuscitation was initiated with room air.
  Davis, Lancet, 2004; Rabi, Resuscitation, 2007
Association between arterial hyperoxia following cardiac resuscitation from cardiac arrest and in-hospital mortality
Kilgannon JAMA 2010

- Multicentre cohort study (multiple American ICUs) between 2001-2005
- First ABG performed after admission to ICU after non-traumatic cardiac arrest (n=6326 patients)
  - Hyperoxia (PaO2>300) 18% of pts
  - Hypoxia (PaO2<60) 63% of pts
  - Normoxia (PaO2 61-299) 19% of pts

AHA Guidelines 2010: Oxygenation post ROSC

- Once ROSC is achieved, adjust the FiO2 to achieve arterial oxyhemoglobin saturation between 94% and 98%.
- Should other biochemical/physiologic markers also be targeted (lactate, Svo2 sat)?
- What is the oxygenation target for the patient with cyanotic heart disease?

AHA Guidelines 2010: Calcium and Pediatric Cardiac Arrest

- Calcium administration is not recommended for pediatric cardiopulmonary arrest in the absence of documented hypocalcemia, calcium channel blocker overdose, hypermagnesemia, or hyperkalemia
- Routine calcium administration in cardiac arrest provides no benefit and may be harmful.

AHA Guidelines 2010: ECPR

- ECPR may be beneficial for infants and children with cardiac arrest if they have heart disease amenable to recovery or transplantation and the arrest occurs in a highly supervised environment such as an ICU with existing clinical protocols and available expertise and equipment to rapidly initiate ECPR.
- There is insufficient evidence for any specific threshold for CPR duration beyond which survival with ECPR is unlikely

Is PALS 2010 relevant to the Ped CICU?

- Worksheet author involvement from the Pediatric Cardiac Critical Care community
- CVICU specific worksheets
- Make the guidelines relevant to the CVICU
- The future: Use the guidelines to create an evidence-based multidisciplinary Pediatric Cardiac Critical Care curriculum

The Question

For infants and children in cardiac arrest with pulmonary hypertension (prehospital or in-hospital), do any specific modifications to resuscitation techniques compared with standard resuscitation techniques, improve outcome (ROSC, survival to discharge, favorable neurologic survival)?

Authors: Ian Adatia, John Berger, David Wessel
Affiliation: Stollery Children’s Hospital, University of Alberta, Edmonton, Canada
Children’s National Medical Center, Washington, DC
Key studies

There are no studies that deal specifically with resuscitation from cardiac arrest in children with pulmonary hypertension.

<table>
<thead>
<tr>
<th>Study</th>
<th>Level of Evidence</th>
<th>Description</th>
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<tbody>
<tr>
<td>A = Return of spontaneous circulation</td>
<td>1</td>
<td>Survival of event</td>
</tr>
<tr>
<td>B = Survival to hospital discharge</td>
<td>2</td>
<td>Intact neurological survival</td>
</tr>
<tr>
<td>C,D = Other endpoint</td>
<td>3</td>
<td>Good</td>
</tr>
<tr>
<td>E = Animal studies</td>
<td>4</td>
<td>Fair</td>
</tr>
<tr>
<td>F = Other studies</td>
<td>5</td>
<td>Poor</td>
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Journois, et al JTCVS 1994;107 Inhaled NO after cardiac surgery

**NO v. AEROSOLIZED ILOPROST**

Rimensberger et al Circ 2001;103

Hemodynamic Changes with Inhaled Nitric Oxide in TAPVC

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Mean Percentage Change Compared to Baseline</th>
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<tbody>
<tr>
<td>HR (b/min)</td>
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<tr>
<td>CI (l/min)</td>
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<tr>
<td>DP (mm Hg)</td>
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<tr>
<td>SVR (mm Hg)</td>
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<tr>
<td>mPAP (mm Hg)</td>
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<tr>
<td>PVR (U m²)</td>
<td>11.5</td>
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INHALED NITRIC OXIDE

Congenital Heart Disease (blinded, randomized)

In two placebo controlled trials NO reduced Pap immediately after CPB

Miller et al. Lancet 2000 N = 124

Prophylactic use of NO:
- Reduced time to extubation (30h)
- Reduced PH crises (4 vs 7)

But...

Key points

- Pulmonary hypertensive crises maybe precursor of cardiac arrest
- Pulmonary hypertensive crises maybe precipitated by withdrawal of NO and prostacyclin
- Pulmonary hypertensive crises maybe reversed by reinstition of pulmonary hypertensive specific therapy

Key studies

- There is one retrospective multicenter description of the outcome of cardiac arrest in adult patients with pulmonary artery hypertension.
- 513 out of 3,130 patients with pulmonary hypertension suffered cardiac arrest and CPR was attempted in 132.
- There was no return of circulation in 104 and only 8 patients survived longer than 90 days, all without neurological deficit. The majority (96%) was in hospital cardiac arrests with rapid institution of resuscitation efforts. (Hoeper, 2002)

- Seven patients had a correctable cause for the cardiac arrest including tamponade during cardiac catheterization (1), digitalis toxicity (1), epilepsy (1) but of note 3 of the survivors either received inhaled nitric oxide or an intravenous bolus of 50μg of iloprost.
- CPR was ineffective, as observed by the authors, because in patients with a severely elevated pulmonary vascular resistance, chest compressions are unlikely to result in pulmonary blood flow or left ventricular preload (Hoeper, 2002).

- There are 4 case reports documenting successful resuscitation from cardiac arrest in patients with known pulmonary artery hypertension (Myles, 1994; Haas, 1995; King, 2000; Passarani, 2004).
- Two adults were resuscitated with inhaled nitric oxide and infused prostacyclin (King, 2000; Passarani, 2004). One adult suffered a cardiac arrest during anesthetic induction for a lung transplant and failed to recover with CPR, epinephrine and intravenous prostacyclin at 5 ng/kg/min. He was cannulated for cardiac bypass and recovered well following lung transplant (Myles, 1994).
- One 15 yr old child failed to respond to inhaled NO, IV and aerosolized low dose prostacyclin but responded immediately to intra tracheal delivery of 1μg/kg prostacyclin (Haas, 1995).
Key studies

There are 2 retrospective reports of complications from cardiac catheterization in children with pulmonary hypertension {Carmosino, 2007 ;Taylor, 2007}.

In the report by Carmosino et al 6 patients suffered cardiac arrest or pulmonary hypertensive crisis. Four were resuscitated and therapy included inhaled NO in 3 and inhaled NO with epoprostenol in 1. Two died despite inhaled NO and epoprostenol administration {Carmosino, 2007}.

In the second study 4 patients required CPR. One patient died and 2/4 had arrhythmias. Further details are not provided {Taylor, 2007}.

Consensus on Science statements

There are no studies that demonstrate efficacy of a specific therapy for resuscitation of pulmonary hypertensive children from cardiac arrest.

-One retrospective study in adults suggests that the few patients who do well have a reversible cause and receive a bolus of intravenous iloprost or inhaled NO. (LOE 4) Hoeper,2004: 341

-Inhaled NO and aerosolized prostacyclin or analogues appear to be equally efficacious in reducing pulmonary vascular resistance LOE 1 Khan 2009,1417, LOE 2 Rimensberger,2001:544, LOE 4 Samankatiwat, 2008 333.

2010 Treatment Recommendations

Search for a reversible component

-If interruption of pulmonary hypertensive specific medications has occurred they should be reinstituted

-Inhaled NO or aerosolized prostacyclin are equally efficacious and safe and maybe considered in the resuscitation. If either are unavailable an intravenous bolus of prostacyclin seems a reasonable alternative

-If pulmonary hypertensive specific medications are unavailable alkalosis may reduce pulmonary vascular resistance.

-Conventional CPR and resuscitative drugs are unsuccessful in most cases and if available, mechanical unloading of the right ventricular should be considered early.

Knowledge Gaps

-It is assumed, but unknown, that therapy for pulmonary hypertensive crises is appropriate during cardiac arrest in a patient with known pulmonary hypertension

-It is unknown if epinephrine, a pulmonary vasoconstrictor, is harmful