PDA LIGATION Management. Physiology Meets Clinical Care??

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Mistaken Beliefs

- FLAT DISK COSMOGRAPHY and EARTH CENTRALITY - Ancient philosophers and writers (Aristotle, Homer)
“on the subject of resuscitation, knowledge and experience have now reached a very satisfactory level of completion”

Henderson 1928 JAMA
### Evidence from Human Studies

<table>
<thead>
<tr>
<th></th>
<th>Neonate</th>
<th>Child</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>Yes *</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ventilation</td>
<td>Limited</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Chest compressions</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>No</td>
<td>Yes *</td>
<td>Yes *</td>
</tr>
<tr>
<td>Sodium Bicarbonate</td>
<td>No</td>
<td>No</td>
<td>Yes *</td>
</tr>
</tbody>
</table>
Is intravenous Vasopressin superior to Epinephrine in a neonatal model of asphyxial cardiac arrest?
Methods: Study Design

- **Model**: Neonatal Porcine model of Ashyxial Cardiac arrest

- **Standardized Resuscitation**:
  - Single resuscitator performing chest compressions
  - Compression to ventilation rate of 5:1

- **Intervention**: Placebo controlled randomized control trial of single dose Vasopressin vs Epinephrine
  - Block randomization
  - Resuscitation medications prepared in standardized solution to ensure a consistent dose of 0.1 mls/kg administered
Interventions

• Placebo (0.9% saline)

• Low-dose epinephrine (LDE) - 0.01 mg/kg

• High-dose epinephrine (HDE) - 0.03 mg/kg

• Low-dose vasopressin (LDV) - 0.2 U/kg
Evaluation time-points

A-I (Baseline)
1. Vital signs
2. 2D echo
3. ABG / Lac
4. Plasma catecholamine, vasopressin & troponin levels

A-II (Serial Assessments)
1. Vital signs: T2, 10, 30, 60 & 90 mins
2. 2D echo: T2, 10, 30, 60 & 90 mins
3. ABG / Lac: T10, 30 & 120 mins

A-III (Final)
1. Vital signs
2. 2D echo
3. ABG / Lac
4. Plasma catecholamine, vasopressin & troponin levels
5. Histology
6. Wet dry ratio

Asphyxial insult started
4 mins Arrest
CPR

4 mins
T0
T2
T10
T30
T60
T90
T120

CPR

4 mins
Asphyxial insult started

4 mins
T0
T2
T10
T30
T60
T90
T120

CPR

4 mins
Asphyxial insult started

4 mins
T0
T2
T10
T30
T60
T90
T120

CPR

4 mins
Asphyxial insult started
Improved survival with vasopressin vs control, p=0.01 ANOVA
Plasma Troponin - Survivors

Elevated troponin levels in all groups but no intergroup difference
Patent Ductus Arteriosus (PDA)

- Incidence:
  - 60% in infants born < 28 wks GA
  - 80% in infants born < 26 wks GA

- 1st line treatment: NSAID but failure rate 35-40% needing surgical closure

- Need for surgery is most common in extreme preterm infants
HSDA

Pulmonary Overcirculation
- Pulmonary edema
- Prolonged ventilation
- Lung compliance

- Alveolar Protein Leakage
- Surfactant Inhibition

Systemic Hypoperfusion
- Hypotension or LCOS
- End-organ Hypoperfusion

Chronic Lung Disease

NEC, IVH, PVL

Teixeira 2006 Acta Paed
Closure of the patent ductus arteriosus with ligation and indomethacin: A consecutive experience

This report summarizes a consecutive experience with 59 preterm infants with clinical, radiographic, and echocardiographic findings of a large patent ductus arteriosus. Thirty-five infants who met defined criteria received indomethacin, and 24 infants underwent PDA ligation. Analysis of the clinical course of these infants revealed no selective indomethacin morbidity and suggests that infants undergoing ligation require more prolonged ventilator therapy with increased exposure to \( F_iO_2 \) \( \geq 0.3 \). Mortality rates between ligated and pharmacologically treated groups were similar. This study documents that inhibition of prostaglandin synthesis to constrict and close the PDA in the premature infant is an effective alternative to operative closure.


Since the first report by Powell' in 1963 of closure of the patent ductus arteriosus in the preterm infant with the respiratory distress syndrome, controversy has existed regarding the optimal management of these infants. A substantial left-to-right shunt through the PDA
Role of the Ductus Arteriosus

- Transitional Physiology

- PPHN, RV dysfunction

- Duct dependant cardiac lesions

- Systemic-pulmonary shunting
Trends in Ductal Care

- End of the era
- Era of the Permissive Ductus (2008-2008)
# PDA Ligation & Outcome

**Table III. Risk of adverse outcomes after surgical closure of PDA**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PDA subgroup</th>
<th>Event rate</th>
<th>Unadjusted</th>
<th>Adjusted analyses*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Odds ratio</td>
<td>P value</td>
</tr>
<tr>
<td>BPD</td>
<td>PDA-no surgery</td>
<td>127/251 (51%)</td>
<td>1.98</td>
<td>.0057</td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>67/100 (67%)</td>
<td>1.98</td>
<td>.0057</td>
</tr>
<tr>
<td>Severe ROP</td>
<td>PDA-no surgery</td>
<td>32/251 (13%)</td>
<td>2.53</td>
<td>.0016</td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>27/100 (27%)</td>
<td>2.53</td>
<td>.0016</td>
</tr>
<tr>
<td>Death or neurosensory impairment at 18 months</td>
<td>PDA-no surgery</td>
<td>155/316 (49%)</td>
<td>1.50</td>
<td>.07</td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>65/110 (59%)</td>
<td>1.50</td>
<td>.07</td>
</tr>
<tr>
<td>Death before 18 months</td>
<td>PDA-no surgery</td>
<td>71/316 (22%)</td>
<td>0.55</td>
<td>.049</td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>15/110 (14%)</td>
<td>0.55</td>
<td>.049</td>
</tr>
<tr>
<td>Neurosensory impairment at 18 months</td>
<td>PDA-no surgery</td>
<td>84/245 (34%)</td>
<td>2.13</td>
<td>.0021</td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>50/95 (53%)</td>
<td>2.13</td>
<td>.0021</td>
</tr>
<tr>
<td>Cognitive delay</td>
<td>PDA-no surgery</td>
<td>66/239 (28%)</td>
<td>2.11</td>
<td>.0034</td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>41/92 (45%)</td>
<td>2.11</td>
<td>.0034</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>PDA-no surgery</td>
<td>35/245 (14%)</td>
<td>1.40</td>
<td>.29</td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>18/95 (19%)</td>
<td>1.40</td>
<td>.29</td>
</tr>
</tbody>
</table>

*Analysis adjusted for the use of antenatal steroids, gestational age at birth, sex, multiple births, mother’s education, and total dose of indomethacin received per kg bodyweight between

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**PDA-Related Variables**

<table>
<thead>
<tr>
<th></th>
<th>Model 1: Unadjusted OR (95% CI)</th>
<th>Model 2: Adjusted for Gestational Age, OR (95% CI)</th>
<th>Model 3: Adjusted for Perinatal and Neonatal Factors, OR (95% CI)*</th>
<th>Model 4: Adjusted for Gestational Age and Ligation, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indomethacin doses</td>
<td>2.09 (1.26-3.47)P</td>
<td>1.69 (1.00-2.86)</td>
<td>1.35 (0.75-2.44)</td>
<td>1.32 (0.71-2.45)</td>
</tr>
<tr>
<td>Prophylactic doses &gt;3</td>
<td>1.83 (1.13-2.95)P</td>
<td>1.44 (0.87-2.38)</td>
<td>1.23 (0.70-2.16)</td>
<td>1.02 (0.54-1.94)</td>
</tr>
<tr>
<td>Total doses &gt;3</td>
<td>2.33 (1.25-4.36)P</td>
<td>1.79 (0.93-3.45)</td>
<td>1.54 (0.75-3.18)</td>
<td>1.09 (0.44-2.70)</td>
</tr>
<tr>
<td>Ductus patent after prophylactic indomethacin</td>
<td>2.81 (1.65-4.78)P</td>
<td>1.54 (0.90-2.64)</td>
<td>1.55 (0.85-2.81)</td>
<td>0.45 (0.10-2.06)</td>
</tr>
<tr>
<td>Symptomatic PDA</td>
<td>2.14 (1.29-3.55)P</td>
<td>1.97 (1.11-3.47)</td>
<td>1.91 (1.02-3.57)</td>
<td>—</td>
</tr>
</tbody>
</table>
PRETERM INFANT

Hemodynamically significant Ductus Arteriosus (HSDA)

NEONATAL MORBIDITY e.g. NEC, PVL

ADVERSE OUTCOME

THERAPEUTIC INTERVENTION
Issues.....

• Variable role of the Ductus arteriosus

• Challenges of making the diagnosis
  – Clinical confounders
  – Echocardiography confounders

• Failure to streamline those patients where the ductus arteriosus is an innocent bystander from a hemodynamically significant ductus arteriosus (HSDA)

• Oversimplification of study designs and remoteness of long term outcomes
Scenario I

31 day old (27/40 weeks) referred for emergency PDA ligation

**Issues:** Oxygenation failure (HFOV) and hypotension (Dobutamine 20)

**fECHO:** 3.2 mm HSDA with L-R flow, dilated LA LV, LVO 420 mls/kg/min

- Refractory hypotension – dobutamine, dopamine, epinephrine, hydrocortisone
- Respiratory Failure
- Died day 2 postop
Therapeutic window of opportunity

D1 3 17 28 31
RDS Extubated Desaturations Referral (CIII) Ligation (CI)
Surf nCPAP 0.2-0.3 Cardiomegaly Pulmonary edema Reintubated Full enteral feeds
Lessons learned

• Hazards of an expectant approach and “All or none” approach to care

• Disconnect between clinical scenario and findings on 2D echo

• Intervention may have saved this life
Pre-Ligation

FiO2  30%

MAP   7

Post-Ligation

FiO2  50%

MAP   11
### Perioperative Management of Hypotension

<table>
<thead>
<tr>
<th></th>
<th>Early Group (n=32)</th>
<th>Late Group (n=33)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid bolus</td>
<td>7 (24.1)</td>
<td>8 (22.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Post op inotropes</td>
<td>8 (27.6)</td>
<td>2 (5.6)</td>
<td>0.019*</td>
</tr>
</tbody>
</table>

*Teixeira et al. J Perinat 2008*
Post-Ligation Cardiac Syndrome (PLCS)

Clinical deterioration with **predictable onset** at 8-12 hours characterized by:

- **Oxygenation Failure**
  - $\uparrow$ 20% < 1000g ($p<0.01$)

- **Systolic Hypotension**
  - $\times$ 8 fold increase < 1000g

- **Need for cardiotropes**

*Teixeira et al. J Perinat 2008*
Systemic blood flow

PRE-OP
[Normal]

8 HOURS
[Impaired LV function]
Study II

Is this an effect of LV exposed afterload on myocardial performance?

Hypothesis: Increased LVE-VR (Left ventricle exposed vascular resistance), after PDA ligation, was associated with impaired myocardial performance.
Left Ventricle Exposed Vascular Resistance (LVER)
Stress-Velocity Relationship (Afterload)

Rowland 1995 Am J Card
LV dysfunction after PDA ligation in preterm baboon

Taylor 1990 J Surg Res

**Diagram:**

- **Left Graph:**
  - Title: Shortening Fraction
  - X-axis: Hours (1, 6, 12, 24)
  - Y-axis: Shortening Fraction
  - Legend: FORM, LIG
  - Data points with error bars
  - *p < 0.05

- **Right Graph:**
  - Title: Systemic Resistance
  - X-axis: Hours (1, 6, 12, 24)
  - Y-axis: Systemic Resistance
  - Legend: FORM, LIG
  - Data points with error bars
  - *p < 0.05
  - **p < 0.01
Myocardial Performance

LV Exposed Vascular Resistance

- $p < 0.001$

mVCFc

- $p < 0.001$

- $# p < 0.05$ vs baseline

McNamara, 2010 J Thorac Cardiovasc Surg
<table>
<thead>
<tr>
<th></th>
<th>&lt; 1000 g</th>
<th>&gt; 1000 g</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LVO &lt; 170 mls/kg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (4.3)</td>
<td>0 (0)</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>3 (13)</td>
<td>4 (17.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>8</td>
<td>7 (30.4)</td>
<td>2 (8.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>24</td>
<td>1 (4.3)</td>
<td>3 (13)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>FS &lt; 25%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>2 (8.7)</td>
<td>3 (13)</td>
<td>1.0</td>
</tr>
<tr>
<td>8</td>
<td>7 (30.4)</td>
<td>1 (4.3)</td>
<td>0.02 *</td>
</tr>
<tr>
<td>24</td>
<td>1 (4.3)</td>
<td>3 (13)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Data presented as number (%)
Stress-Velocity < 1000g

Stress-Velocity > 1000g

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>y</th>
<th>x</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.83</td>
<td>-0.015</td>
<td>0.36</td>
</tr>
<tr>
<td>1</td>
<td>1.73</td>
<td>-0.014</td>
<td>0.31</td>
</tr>
<tr>
<td>8</td>
<td>1.94</td>
<td>-0.03</td>
<td>0.65</td>
</tr>
<tr>
<td>24</td>
<td>1.7</td>
<td>-0.013</td>
<td>0.37</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>y</th>
<th>X</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.1</td>
<td>-0.018</td>
<td>0.46</td>
</tr>
<tr>
<td>1</td>
<td>1.75</td>
<td>-0.02</td>
<td>0.56</td>
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<tr>
<td>8</td>
<td>1.61</td>
<td>-0.014</td>
<td>0.6</td>
</tr>
<tr>
<td>24</td>
<td>1.72</td>
<td>-0.018</td>
<td>0.53</td>
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</tbody>
</table>
Speckle Tracking and Strain Analysis
Strain Analysis and PDA Ligation

Four Chamber

Two Chamber

Three Chamber
Global Strain (n=15)
Tissue Doppler Imaging
Transmitral Flow

A wave

IVCT        IVRT

Transmitral flow        Aortic flow        Transmitral flow
Tissue Doppler measurements during the three time points

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>1 hour post op</th>
<th>18 hours post op</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MV Annulus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>5.3 (1.1)*§</td>
<td>3.4 (0.9)*</td>
<td>4.1 (0.9)*§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E</td>
<td>8.8 (4.3)*§</td>
<td>4.1 (1.7)*</td>
<td>4.5 (1.6)*§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A</td>
<td>9.5 (3.3)*§</td>
<td>6.3 (2.6)*</td>
<td>5.4 (1.6)*§</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>IVS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>5.0 (0.7)*</td>
<td>3.3 (0.9)*</td>
<td>4.0 (0.5)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E</td>
<td>6.4 (1.9)*</td>
<td>4.1 (2.1)*</td>
<td>4.9 (2.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>A</td>
<td>7.0 (1.3)*§</td>
<td>5.3 (1.4)*</td>
<td>5.7 (1.3) §</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>TV Annulus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>7.8 (2.0)*</td>
<td>6.7 (2.2)</td>
<td>6.3 (1.2)*</td>
<td>0.37</td>
</tr>
<tr>
<td>E</td>
<td>9.2 (3.4)*</td>
<td>7.4 (3.2)*</td>
<td>8.3 (3.4)</td>
<td>0.17</td>
</tr>
<tr>
<td>A</td>
<td>10.4 (2.6)</td>
<td>14.1 (21.1)</td>
<td>9.1 (2.6)</td>
<td>0.41</td>
</tr>
</tbody>
</table>
Isovolemic relaxation

Isovolemic contraction
## Isovolemic Phases: Mitral valve

<table>
<thead>
<tr>
<th></th>
<th>Pre Op</th>
<th>1 hour post op</th>
<th>24 hour post op</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVCT (ms)</td>
<td>36.2 [29.4-38.7]*</td>
<td>54.8 [49.2-58.3]*</td>
<td>47.9 [36.2-51.4]*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVC velocity (cm/s)</td>
<td>5.1 [3.9-7.4]*</td>
<td>7.2 [4.8-8.8]*</td>
<td>5.2 [4.1-7.8]</td>
<td>0.039</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>43.0 [33.9-48.5]*§</td>
<td>70.2 [58.2-73.24]*</td>
<td>60.8 [47.8-71.2]*§</td>
<td>0.001</td>
</tr>
<tr>
<td>IVR velocity (cm/s)</td>
<td>5.0 [4.2-5.6] *§</td>
<td>3.0 [2.8-3.9] *</td>
<td>3.0 [2.6-3.5] §</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MPI</td>
<td>0.47 [0.40-0.54]*</td>
<td>0.82 [0.74-0.98]*</td>
<td>0.73 [0.68-0.76]*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
**Isovolumic Contractile Time**

Pearson: $r=0.799$, $p<0.001$

Pearson: $r=-0.739$, $p<0.001$
↑ Afterload

↑ Duration of Ventricular Relaxation

↑ IVRT, IVCT, Tau index

↓ E wave

↓ Passive filling with increased residual atrial blood

Abnormal cardiac output

Ishida 1986 Circulation
Scenario II

7 day old (24/40 weeks) referred for PDA ligation

Issues

- Anuric, creatinine 260 mmol/l
- Refractory shock (Dobutamine 20 & Dopamine 10 μg/kg/min)
- Metabolic acidosis (7.0-7.15) with ↑ lactate 6-10 mmol/l

2d ECHO

- 3.8 mm HSDA with unrestrictive L-R flow
- Dilated LA and LV, cardiac output 380 mls/kgmin
- Reversed end-diastolic flow in SMA, MCA & renal artery
Optimize perfusion
Lung compliance

LV dysfunction

BENEFIT

HARM
Study III

- Can high risk patients be identified earlier?
Understand the Physiology!

Phase I

PDA Ligation

- Systemic bld flow (LV afterload)↑
- Pulmonary bld flow (LV preload)↓
- Impaired LV relaxation (diastolic dysfunction)→
- Impaired LV contraction (systolic dysfunction)→

Low Cardiac Output State
+ Clinical decompensation

Noori 2007 J Pediatrics,
McNamara et al. 2010 J Thorac Cardiovasc Surg
Post-Ligation Cardiac Syndrome

Increased PDA ligation

Clinical instability

Increased morbidity

- hypotension (30%)
- ↑ ventilation (45%)
- ↑ oxygen (60%)

High risk pts

PDA ligation

6 – 12 hrs

prophylaxis

Teixeira et al. J Perinat 2008
Natarajan et al. Am J Perinatol 2010
Schmidt et al. Pediatrics 2007
Left Ventricular Output

$r = 0.63, p<0.001$

Sahni 2008 PAS
Outcomes for infants with LVO < 200 mls/min/kg on first postoperative ECHO

75%  Critically low LVO

42%  Systolic hypotension

38%  Need for inotropes

Sensitivity 1.0
Specificity .86

Sensitivity .83
Specificity .72

Sensitivity 1.0
Specificity .71

Targeted neonatal ECHO directed therapy program

– introduced in January 2009

1. TnECHO at 1 hour post surgery
   LVO < 200 mls/min/kg → MILRINONE infusion at 0.33 mics/kg/min

   LVO > 200 ml/min/kg → continue observation

2. Comparative evaluation of postoperative course before and after introduction of new program

3. Matched for gestation and LVO

   Jain 2011 J Pediatr
Study V

To compare the rate and components of PLCS in infants who have undergone PDA ligation \textbf{before} and \textbf{after} the introduction of targeted neonatal echocardiography (TnECHO) directed therapy program
Comparison of clinical stability

**Systolic Arterial Pressure**

- Epoch I
- Epoch II

**Oxygenation index**

- Epoch I
- Epoch II

SAP [mmHg] vs. Time [hours]

- Time points: Pre, 1, 8

- Graph shows a decrease in SAP over time, with Epoch II showing a more significant decrease compared to Epoch I.

- Statistical significance: p = 0.007

- Note: * denotes a significant difference between Epochs.

O2 index vs. Time hours

- Time points: Pre, 1, 8

- Graph shows a decrease in O2 index over time, with Epoch II showing a more significant decrease compared to Epoch I.

- Statistical significance: p = 0.002

- Note: * and # denote significant differences between Epochs.
**Primary outcome**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Epoch I (N=25)</th>
<th>Epoch II (N=27)</th>
<th>$p$</th>
<th>ARR</th>
<th>NTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLCS n</td>
<td>11 (44%)</td>
<td>3 (11%)</td>
<td>.01</td>
<td>0.33</td>
<td>3</td>
</tr>
</tbody>
</table>

*PLCS: composite outcome of need of inotropes and either oxygenation or ventilation failure in the absence of any other etiology

## Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Epoch I (N=25)</th>
<th>Epoch II (N=27)</th>
<th>p</th>
<th>ARR</th>
<th>NTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for inotropes n (%)</td>
<td>14 (56%)</td>
<td>5 (19%)</td>
<td>.01</td>
<td>.37</td>
<td>2.7</td>
</tr>
<tr>
<td>Oxygenation failure n (%)</td>
<td>13 (52%)</td>
<td>7 (26%)</td>
<td>.08</td>
<td>.26</td>
<td>3.8</td>
</tr>
<tr>
<td>Ventilation failure n (%)</td>
<td>12 (48%)</td>
<td>4 (15%)</td>
<td>.02</td>
<td>.33</td>
<td>3</td>
</tr>
<tr>
<td>Corticosteroids use n (%)</td>
<td>4 (16%)</td>
<td>0</td>
<td>.03</td>
<td>na</td>
<td>na</td>
</tr>
</tbody>
</table>
Conclusion

Targeted prophylactic milrinone therapy after PDA ligation for babies with LVO <200 ml/min/kg at 1 hour appears safe and associated with improved hemodynamic and respiratory stability and reduced the need for inotropes and steroids.
Evolution of post-operative care

TnECHO, dobutamine

Use of vasodilators, PLCS

ECHO Research/analysis

TnECHO Directed Therapy

ACTH
Focused ICU care
• Prophylactic milrinone (afterload reduction)
• Serial functional echocardiography

Intermediary outcome
• Off cardiotropes within 72 hours

• Creatinine 125 within 12 hours of surgical intervention, normal by day 5

• Extubated 10 days after surgical intervention

• Uneventful neonatal course
Preterm infant

Hemodynamically significant DA

Neonatal morbidities

PDA ligation

ADVERSE OUTCOME
Preterm infant

Developmental / maturational factors
Co-treatments

ADVERSE OUTCOME

Neonatal morbidities

↓ cerebral blood flow
↓ cerebral oxygen saturation
Altered EEG

IVH
White matter injury

ADVERSE OUTCOME

HSDA

PDA ligation

↓ cardiac output
↓ cerebral oxygen saturation

ADVERSE OUTCOME

↓ cerebral oxygen saturation
Altered EEG

ADVERSE OUTCOME
PDA ligation and aEEG

<table>
<thead>
<tr>
<th>aEEG</th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECHO</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clinical</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Pre op</td>
<td>4h</td>
<td>8h</td>
<td>24h</td>
<td>p</td>
</tr>
<tr>
<td>------------------</td>
<td>--------</td>
<td>-------</td>
<td>-------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>2D ECHO</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVO (ml/min/kg)</td>
<td>390 (316-504)</td>
<td>203 (155-310) *</td>
<td>233 (178-243) *</td>
<td>280 (227-288) *</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVFS</td>
<td>41±10.5</td>
<td>36±8.9</td>
<td>34±6.9</td>
<td>38±8.3</td>
<td>NS</td>
</tr>
<tr>
<td><strong>aEEG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower border (μV)</td>
<td>4.2 (3.2-5)</td>
<td>3 (2.3-3.6) *</td>
<td>3 (2.7-3.5) *</td>
<td>3.5 (2.8-3.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Upper border (μV)</td>
<td>24.1 (17-26.8)</td>
<td>9.4 (5.1-11.7)</td>
<td>7.2 (5.5-12)</td>
<td>9.4 (7.1-14)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

- Median % change in lower band voltage was 26%
- Altered lower bandwidth was associated with gestation and PDA diameter on univariate analysis
Conclusions

• PDA ligation was associated with altered cerebral electrical activity independent of any change in LVO.
Implications for clinical practice

- PDA ligation may be followed by postoperative cardiorespiratory instability
  - Risk related to postnatal age, weight < 1000 grams, preoperative need for inotropes

- Need for **early identification** of infants at increased risk of PLCS
  - Early fECHO (1 hour)
  - Targeted prophylaxis (LVO<200 mls/min/kg) appears promising

- Rationalization of candidates for PDA ligation needed
## Ductal Staging

McNamara 2007 Arch Dis Child

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Echocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 Asymptomatic</td>
<td>E1 No evidence of ductal flow on two-dimensional or Doppler interrogation</td>
</tr>
<tr>
<td>C2 Mild</td>
<td>E2 Small non-significant ductus arteriosus</td>
</tr>
<tr>
<td>- Oxygenation difficulty (OI &lt; 6)</td>
<td>- Transductal diameter &lt; 1.5 mm</td>
</tr>
<tr>
<td>- Occasional (6) episodes of oxygen desaturation, bradycardia or apnoea</td>
<td>- Restrictive continuous transductal flow (DA V\text{max} &gt; 2.0 cm/s)</td>
</tr>
<tr>
<td>- Need for respiratory support (nCPAP) or mechanical ventilation (MAP &lt; 8)</td>
<td>- No signs of left heart volume loading (eg, mitral regurgitant jet &gt; 2.0 cm/s or LA:Ao ratio &gt; 1.5:1)</td>
</tr>
<tr>
<td>- Feeding intolerance (&gt; 20% gastric aspirates)</td>
<td>- No signs of left heart pressure loading (eg, E/A ratio &gt; 1.0 or IVRT &gt; 50)</td>
</tr>
<tr>
<td>- Radiologic evidence of increased pulmonary vascularity</td>
<td>- Normal end-organ (eg, superior mesenteric, middle cerebral) arterial diastolic flow</td>
</tr>
<tr>
<td>C3 Moderate</td>
<td>E3 Moderate HSDA</td>
</tr>
<tr>
<td>- Oxygenation difficulty (OI 7–14)</td>
<td>- Transductal diameter 1.5–3.0 mm</td>
</tr>
<tr>
<td>- Frequent (hourly) episodes of oxygen desaturation, bradycardia or apnoea</td>
<td>- Unrestrictive pulsatile transductal flow (DA V\text{min} &lt; 2.0 cm/s)</td>
</tr>
<tr>
<td>- Increasing ventilation requirements (MAP 9–12)</td>
<td>- Mild-moderate left heart volume loading (eg, LA:Ao ratio 1.5 to 2:1)</td>
</tr>
<tr>
<td>- Inability to feed due to marked abdominal distension or emesis</td>
<td>- Mild-moderate left heart pressure loading (eg, E/A ratio &gt; 1.0 or IVRT 50–60)</td>
</tr>
<tr>
<td>- Oliguria with mild elevation in plasma creatinine</td>
<td>- Decreased or absent diastolic flow in superior mesenteric artery, middle cerebral artery or renal artery</td>
</tr>
<tr>
<td>- Systemic hypotension (low mean or diastolic BP) requiring a single cardiotropic agent</td>
<td></td>
</tr>
<tr>
<td>- Radiologic evidence of cardiomegaly or pulmonary oedema</td>
<td></td>
</tr>
<tr>
<td>- Mild metabolic acidosis (pH 7.1–7.25 and/or base deficit 7 to −12.0)</td>
<td></td>
</tr>
<tr>
<td>C4 Severe</td>
<td>E4 Large HSDA</td>
</tr>
<tr>
<td>- Oxygenation difficulty (OI &gt; 15)</td>
<td>- Transductal diameter &gt; 3.0 mm</td>
</tr>
<tr>
<td>- High ventilation requirements (MAP &gt; 12) or need for high-frequency modes of ventilation</td>
<td>- Unrestrictive pulsatile transductal flow</td>
</tr>
<tr>
<td>- Profound or recurrent pulmonary haemorrhage</td>
<td>- Severe left heart volume loading (eg, LA:Ao ratio &gt; 2:1, mitral regurgitant jet &gt; 2.0 cm/s)</td>
</tr>
<tr>
<td>- “NEC-like” abdominal distension with tenderness or erythema</td>
<td>- Severe left heart pressure loading (eg, E/A ratio &gt; 1.5 or IVRT &gt; 60)</td>
</tr>
<tr>
<td>- Acute renal failure</td>
<td>- Reversal of end-diastolic flow in superior mesenteric artery, middle cerebral artery or renal artery</td>
</tr>
<tr>
<td>- Haemodynamic instability requiring &gt; 1 cardiotropic agent</td>
<td></td>
</tr>
<tr>
<td>- Moderate-severe metabolic acidosis (pH &lt; 7.1) or base deficit &gt; −12.0</td>
<td></td>
</tr>
</tbody>
</table>
Benefits of this approach

• **Streamline** Innocent bystanders from Pathological cases
  - ↓ ligation rates [82/year (2005) to 30/year (2019)]
  - Prevent transfers or cancellations

• **Categorization & Prioritization**
  - determine urgency and level of intervention

• Facilitates a more **physiologic** approach

• Evaluate **response** to therapy and better define responders

---

*PDA Ligation [Toronto]*

El-Khuffash 2011 J Pediatr
Early Surgical Ligation Versus a Conservative Approach for Management of Patent Ductus Arteriosus That Fails to Close after Indomethacin Treatment

Nami Jhaveri, MD, Anita Moon-Grady, MD, and Ronald I. Clyman, MD

“We found that a conservative approach that tolerates the presence of a PDA as long as signs of cardiopulmonary compromise do not develop is associated with a 28% decrease in the rate of ductus ligation and lower rates of NEC. These findings support the need for new RCTs to reexamine the benefits and risks of different approaches to treating PDA in the modern era.”
**Table IV.** Comparison of an early surgical approach and a more conservative approach for infants who failed indomethacin treatment: Effects on neonatal morbidity (adjusted for gestation, year of admission, and perinatal/neonatal variables)

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Conservative approach versus early surgery, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC</td>
<td>0.26 (0.07-0.95)*</td>
</tr>
<tr>
<td>NEC occurring after failing indomethacin treatment</td>
<td>0.25 (0.06-1.01)†</td>
</tr>
<tr>
<td>Sepsis occurring after failing indomethacin treatment</td>
<td>0.86 (0.32-2.31)</td>
</tr>
<tr>
<td>ICH ≥ grade 3</td>
<td>0.33 (0.07-1.48)</td>
</tr>
<tr>
<td>Neurologic insult</td>
<td>0.40 (0.11-1.48)</td>
</tr>
<tr>
<td>BPD</td>
<td>0.53 (0.18-1.50)</td>
</tr>
<tr>
<td>ROP</td>
<td>1.04 (0.30-3.72)</td>
</tr>
<tr>
<td>Death</td>
<td>0.55 (0.12-2.50)</td>
</tr>
<tr>
<td>Death or BPD</td>
<td>0.49 (0.18-1.30)</td>
</tr>
</tbody>
</table>
Future Directions

• Predictive value of troponin in the setting of PDA ligation

• Evaluation of neonates undergoing PDA ligation using MRI
Special Thanks

Neonatal Research Fellows
Arvind Sehgal    Lilian Teixeira
Sandesh Shivananda Emer Finan

Research Assistants
Wendy Mak

Derek Stephens (Statistical support)
Glen Van Arsdell & CVS team
aEEG and PDA ligation

Lemmers 2010 ADC
Biomarkers and Ductal significance

B-Natriuretic Peptide

- Reflective of left heart volume loading and systemic hypoperfusion respectively
- Beneficial if lack of access to serial echocardiography
- Useful as an adjunct to clinical care

Troponin T

- Movement of Tropomyosin
- Conformational change
- Myosin binding sites
- Low Calcium
- High Calcium
### NTpBNP and PDA

**Table 2** Median N-terminal pro-B-type natriuretic peptide (NTpBNP) levels (pmol/l) in the two study groups on days 1, 3 and after treatment for the patent ductus arteriosus (PDA)

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 3</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>PDA</td>
<td>Control</td>
</tr>
<tr>
<td>NTpBNP</td>
<td>1435</td>
<td>1267</td>
<td>1127</td>
</tr>
<tr>
<td>p Value</td>
<td>0.735</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Levels were significantly higher in the PDA group on day 3 and post treatment. Mann–Whitney U test was used to compare the medians.

Troponin & HSDA

Al Khuffash 2008 Arch Dis Child
CORONARY ARTERY FLOW and HSDA

Sehgal 2007 E-PAS

\[ p < 0.001, r = 0.53 \]

Transductal diameter [mm]

\[ VTI [cm] \]

CA:LVO flow

\[ p = 0.001 \]

Time [hrs]
Plasma cTnT and NTpBNP in first 48 hours of life

El-Khuffash Arch Dis Child (In press)
Figure 2: ROC for cTnT, NTpBNP and PDA score in predicting outcome

<table>
<thead>
<tr>
<th>Source of the Curve</th>
<th>Area</th>
<th>p value</th>
<th>95% CI</th>
<th>Cut off</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTpBNP</td>
<td>0.84</td>
<td>&lt; 0.001</td>
<td>0.72 – 0.93</td>
<td>5200</td>
<td>80%</td>
<td>75%</td>
</tr>
<tr>
<td>cTnT</td>
<td>0.92</td>
<td>&lt; 0.001</td>
<td>0.85 – 0.99</td>
<td>0.49</td>
<td>87%</td>
<td>79%</td>
</tr>
<tr>
<td>PDA Score</td>
<td>0.77</td>
<td>0.003</td>
<td>0.63 – 0.91</td>
<td>4</td>
<td>67%</td>
<td>79%</td>
</tr>
</tbody>
</table>
# Baseline Hemodynamic and Respiratory Characteristics at the three time points

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>1 hour post op</th>
<th>18 hours post op</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>157 (13)</td>
<td>149 (13)</td>
<td>156 (20)</td>
<td>0.23</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>56 (9)</td>
<td>57 (12)</td>
<td>57 (17)</td>
<td>0.67</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>25 (4)*</td>
<td>37 (8)*</td>
<td>33 (10)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>38 (6)</td>
<td>43 (9)</td>
<td>42 (12)</td>
<td>0.21</td>
</tr>
<tr>
<td>MAP (cmH2O)</td>
<td>9.5 (1.6)</td>
<td>9.5 (2.2)</td>
<td>9.6 (2.4)</td>
<td>0.96</td>
</tr>
<tr>
<td>Oxygen requirement (%)</td>
<td>36 (11)</td>
<td>36 (15)</td>
<td>40 (18)</td>
<td>0.67</td>
</tr>
</tbody>
</table>
# Global and segmental strain

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>1 hour</th>
<th>18 hours</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Strain</td>
<td>-19.7 (-4.4)*</td>
<td>-11.9 (-3.6)*</td>
<td>-16.9 (-3.5)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Septal Wall</td>
<td>-21.3 (-3.6)*</td>
<td>-12.4 (-4.4)*</td>
<td>-15.8 (4.4)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lateral Wall</td>
<td>-18.5 (-2.5)*</td>
<td>-9.9 (-5.1) *§</td>
<td>-15.6 (4.8)§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferior Wall</td>
<td>-22.6 (-3.8)*</td>
<td>-12.7 (-5.3)*</td>
<td>-16.9 (-3.5)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Posterior Wall</td>
<td>-21.6 (-5.9)*</td>
<td>-14.2 (-4.3)*§</td>
<td>-19.4 (-6.4)§</td>
<td>0.002</td>
</tr>
<tr>
<td>Anterior Wall</td>
<td>-16.6 (-3.6)*§</td>
<td>-9.5 (-4.5)*</td>
<td>-10.9 (-2.8)§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anteroseptal wall</td>
<td>-19.0 (-5.5) *§</td>
<td>-10.6 (-2.9)*</td>
<td>-12.2 (-3.2)§</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Pearson: $r=-0.577$, $p=0.002$
CA Flow & Post-ligation instability

Cardiotropic Support

Increased risk of myocardial dysfunction may relate to chronic myocardial ischemia

Sehgal In press J Card Thor Surg

* p<0.05 vs no inotropes
Pearson: $r=-0.515$, $p=0.005$
Surfactant
Hypocapnia
Oxygen or Nitric oxide
Hypocapnia / Alkalosis

Pressors
Oxygen
Hypothermia

PVR
+++  PDA
Ao
SVR
++++++

Patent Ductus Arteriosus (PDA)

Truncus Arteriosus

Left Ventricle

AO = Aorta
PA = Pulmonary Artery
LA = Left Atrium
RA = Right Atrium
LV = Left Ventricle
RV = Right Ventricle

Continued Aorta and Pulmonary Artery
Opening Between Ventricles

Oxygen-rich Blood
Oxygen-poor Blood
Mixed Blood
INNOCENT BYSTANDER

Full feeds
Room air

PATHOPHYSIOLOGY

HFOV [MAP 16, FiO2 0.8]
Pulmonary hemorrhage
Systemic Hypotension
Anuria, Creatinine 360
Abdominal distension
Relationship between global longitudinal strain and LV fractional shortening, LVEDD and LVO

A. GLS and LV Fractional Shortening

B. GLS and LVEDD

C. GLS and LVO

D. GLS/LVO and LVEDD

R= 0.78, p<0.0001

R= 0.38, p>0.05

R= 0.68, p<0.0001

R= -0.40, p=0.03
## Risk factors for Cardiotropic support

<table>
<thead>
<tr>
<th>Parameter (n=166)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight @ surgery</td>
<td>0.001</td>
</tr>
<tr>
<td>Surgery &lt; 28 days of life</td>
<td>0.04</td>
</tr>
<tr>
<td>Pre-operative shock requiring cardiotropic support</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*PDA size, preoperative LV systolic performance not predictive of postoperative deterioration*

Finan et al