Understanding the Ductus Arteriosus. Are we hemodynamically naive?

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Hospital for Sick Children, Toronto
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 $F_{O_2} \geq 0.3$. 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
# 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>2.53</td>
<td>.0016</td>
</tr>
<tr>
<td>Severe ROP</td>
<td>PDA-no surgery</td>
<td>32/251 (13%)</td>
<td>1.50</td>
<td>.07</td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>27/100 (27%)</td>
<td>0.55</td>
<td>.049</td>
</tr>
<tr>
<td>Death or neurosensory impairment at 18 months</td>
<td>PDA-no surgery</td>
<td>155/316 (49%)</td>
<td>2.13</td>
<td>.0021</td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>65/110 (59%)</td>
<td>2.11</td>
<td>.0034</td>
</tr>
<tr>
<td>Death before 18 months</td>
<td>PDA-no surgery</td>
<td>71/316 (22%)</td>
<td>1.40</td>
<td>.29</td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>15/110 (14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurosensory impairment at 18 months</td>
<td>PDA-no surgery</td>
<td>84/245 (34%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>50/95 (53%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive delay</td>
<td>PDA-no surgery</td>
<td>66/239 (28%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>41/92 (45%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>PDA-no surgery</td>
<td>35/245 (14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PDA-surgical closure</td>
<td>18/95 (19%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Analysis adjusted for the use of antenatal steroids, gestational age at birth, sex, multiple births, mother's education, and total days of hospital stay during early hospital stay.

Kabra 2007 J Pediatrics

Chorne 2007 Pediatrics
PRETERM INFANT

Hemodynamically significant Ductus Arteriosus (HSDA)

NEONATAL MORBIDITY
e.g. NEC, PVL

ADVERSE OUTCOME

THERAPEUTIC INTERVENTION
Myths of the Modern Era

1. “PATENT” ductus arteriosus = “PROBLEMATIC” ductus arteriosus

2. “All ducti are equal”

3. Murmur = ductus

Oversimplification of Ductal Disease as an All or None Phenomenon
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
Role of the Ductus Arteriosus

- Transitional Physiology
- PPHN, RV dysfunction
- Duct dependant cardiac lesions
- Systemic-pulmonary shunting
## Ductal Continuum

<table>
<thead>
<tr>
<th>Innocent Bystander</th>
<th>Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0 mm DA, urL-R flow</td>
<td>3.0 mm DA, urL-R flow</td>
</tr>
<tr>
<td>Full feeds</td>
<td>HFOV [MAP 16, FiO2 0.8]</td>
</tr>
<tr>
<td>Room air</td>
<td>Pulmonary hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Systemic Hypotension</td>
</tr>
<tr>
<td></td>
<td>Anuria, Creatinine 360</td>
</tr>
<tr>
<td></td>
<td>Abdominal distension</td>
</tr>
</tbody>
</table>
Is their hemodynamic impact?

• Is the clinical and/or physiologic instability related to increased ductal severity?

• Does the clinical and/or physiologic alteration resolve after ductal treatment?

If YES, then the DA is likely to be contributing to ongoing patient instability
Early clinical findings ...........

- Classical signs absent
- Hypotension (day 2-3) - inotropes
- Increased ventilator requirements
- Persistent metabolic acidosis – volume, bicarbonate
Does echocardiography facilitate determination of hemodynamic significance attributable to the ductus arteriosus?

Arvind Sehgal · Patrick J. McNamara

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Quantification of the volume of blood flow across the Ductus Arteriosus would provide the best measure of hemodynamic significant
Is the ductus patent?

What is transductal diameter?

**Issues**: Measurement error, Variability in architecture and longitudinal diameter of the ductus arteriosus, Size is **NOT STATIC**
Diagnosis of HSDA

Transductal Diameter $> 1.5$ mm

AND

Unrestrictive L-R flow

AND

Clinical signs of pulmonary overcirculation $\pm$ systemic hypoperfusion

AND

Echocardiography signs of pulmonary overcirculation $\pm$ systemic hypoperfusion
Ductal Evaluation
PDA – size, flow direction & quality

Pulmonary Overcirculation
- LA:Ao, E:A ratio, IVRT
- ASD size & flow
- LPA diastolic flow

Systemic Hypoperfusion
- LVO or LVO:SVC flow
- Desc Ao Doppler
- End-organ Dopplers
  (MCA, celiac, renal)
Transmitral Flow

Transmitral flow  Aortic flow  Transmitral flow

E wave

A wave

IVCT  IVRT

1  2  3  4  5
TRANSMITRAL FLOW

Transductal diameter [mm] 1.5 2.0 2.5 3.0 3.5 4.0 4.5

IVRT [msec] 10 20 30 40 50 60 70

E wave

p < 0.001, r = 0.4

p < 0.001, r = 0.5

IVRT

E wave

Sehgal 2007 E-PAS
End-organ flow and Ductal size

Middle Cerebral Artery

<table>
<thead>
<tr>
<th>Size (mm)</th>
<th>Anterograde</th>
<th>Retrograde</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.5</td>
<td>58/61(95%)</td>
<td>0</td>
</tr>
<tr>
<td>&gt;1.7</td>
<td>1/58(1.7%)</td>
<td>50/58(86.3%)</td>
</tr>
</tbody>
</table>

Increased transductal diameter leads to **absence or reversal** of diastolic flow to vital organs

*Evans 1995 Arch Dis Child*
HSDA

Reversed EDF in post-ductal aorta

Closed DA

Normal EDF in post-ductal aorta

Reverse EDF in SMA

Normal EDF in SMA
Troponin & HSDA

Al Khuffash 2008 Arch Dis Child
CORONARY ARTERY FLOW and HSDA

Sehgal 2007 E-PAS

p < 0.001, r = 0.53

CA: LVO flow

p = 0.001
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></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>
# Ductal Staging

*McNamara 2007 Arch Dis Child*

## Table 1

Proposed staging system (adapted from McNamara and Hellman, unpublished clinical triaging system for ligation of a patent ductus arteriosus (PDA)) for determining the magnitude of the haemodynamically significant ductus arteriosus (HSDA), which is based on clinical and echocardiographic criteria.

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Echocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C1</strong> Asymptomatic</td>
<td><strong>E1</strong> No evidence of ductal flow on two-dimensional or Doppler interrogation</td>
</tr>
<tr>
<td><strong>C2</strong> Mild</td>
<td><strong>E2</strong> 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 (&lt;6) episodes of oxygen desaturation, bradycardia or apnoea</td>
<td>Restrictive continuous transductal flow (DA V&lt;sub&gt;max&lt;/sub&gt; &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><strong>C3</strong> Moderate</td>
<td><strong>E3</strong> 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&lt;sub&gt;max&lt;/sub&gt; &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 cardiotoxic agent</td>
<td></td>
</tr>
<tr>
<td>Radiological 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><strong>C4</strong> Severe</td>
<td><strong>E4</strong> 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>Prolonged 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>&quot;NEC-like&quot; 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 cardiotoxic agent</td>
<td></td>
</tr>
<tr>
<td>Moderate-severe metabolic acidosis (pH&lt;7.1) or base deficit ≥−12.0</td>
<td></td>
</tr>
</tbody>
</table>
Benefits of this approach

- Streamline Innocent bystanders from Pathological cases
  - ↓ ligation rates [82/year (2005) to 38 /year (2009)]
  - 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
A hemodynamically significant ductus arteriosus is associated with **acute reversible physiologic disturbance**……

• BUT what about neonatal morbidities?
HSDA and increased Respiratory morbidity.....

- Increased risk of CLD with combination of sepsis and HSDA
  [OR 29.6 (4.5, >100)]

- PDA is a risk factor for wheezing in children at 1 year of age
  [OR 1.7 (1.0, 3.1)]

Gonzalez 1996 J Pediatr

Palta 2001 Am J Perinat
# Ductal stage and Respiratory outcomes

<table>
<thead>
<tr>
<th></th>
<th>Low grade (n=10)</th>
<th>Intermediate grade (n=16)</th>
<th>High grade (n=18)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of oxygen (d)</td>
<td>60.2 ± 40.6 #</td>
<td>79.9 ± 38.2 #</td>
<td>124.9 ± 61.9</td>
<td>0.009</td>
</tr>
<tr>
<td>Home oxygen (n)</td>
<td>0 *</td>
<td>0 *</td>
<td>8</td>
<td>0.009</td>
</tr>
<tr>
<td>CLD (n, %)</td>
<td>5 (50%)</td>
<td>7 (44%)</td>
<td>14 (78%)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

# p <0.05 vs group I, *p< 0.05 vs III

Sehgal 2010 Am J Perinat
HSDA & increased risk of NEC...

<table>
<thead>
<tr>
<th>PDA and indomethacin therapy</th>
<th>Adjusted OR (95% CI) All gestational ages (N = 6135)</th>
<th>Adjusted OR (95% CI) 24–27 weeks gestation (N = 1476)</th>
<th>Adjusted OR (95% CI) 28–34 weeks gestation (N = 4659)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neither</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Indomethacin only</td>
<td>0.72 (0.25–1.66)</td>
<td>0.83 (0.24–2.15)</td>
<td>0.45 (0.02–2.14)</td>
</tr>
<tr>
<td>PDA only</td>
<td>1.85 (1.24–2.69)</td>
<td>1.77 (1.00–3.02)</td>
<td>2.05 (1.16–3.44)</td>
</tr>
<tr>
<td>PDA + indomethacin</td>
<td>1.53 (1.15–2.02)</td>
<td>1.47 (1.01–2.16)</td>
<td>1.66 (1.08–2.51)</td>
</tr>
</tbody>
</table>

Odds ratios adjusted for maternal hypertensive disorder, gestational age; small for gestational age, multiple pregnancy and respiratory disorders. NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus; OR = odds ratios; CI = confidence interval.

Prospective data collected from Israel Neonatal Network

NEC rate 5.5% (all) & 9.4% of neonates with a PDA

*Dollberg 2005 J Pediatr Gastro & Nutrition*

NEC rate 23% in neonates requiring PDA Ligation

*Teixeira 2008 J Perinat*
Mesenteric Tissue Oxygenation

Lemmers 2008 Pediatrics
Is there evidence that intervention is beneficial?

The viewpoint of the “permissivist”

“there is NO evidence that treatment of the DA improves long term outcomes”

No placebo controlled trials of therapeutic intervention
Effect of Medical Treatment

<table>
<thead>
<tr>
<th></th>
<th>Proph vs. Early (17)</th>
<th>Early vs. Late (8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>264</td>
<td>1580</td>
</tr>
<tr>
<td>Ligation</td>
<td>0.37 (0.2-0.68) *</td>
<td>0.18 (0.08-0.41) *</td>
</tr>
<tr>
<td>Pulmonary Morbidity</td>
<td>1.04 (0.81-1.31)</td>
<td>0.39 (0.21-0.76) *</td>
</tr>
<tr>
<td>NEC</td>
<td>1.39 (0.76-2.51)</td>
<td>0.24 (0.06-0.96) *</td>
</tr>
<tr>
<td>Pulmonary Hemorrhage</td>
<td>0.54 (0.3-0.96)</td>
<td></td>
</tr>
</tbody>
</table>

*Clyman 1996 J Pediatr*
Trends in Ductal Care

- **Era of prophylactic NSAIDs**
- **Alternative agents**
- **End of the era**
- **Era of the Permissive Ductus**
NSAIDs vs Placebo: acute physiology

McCurnin 2008 Pediatrics
SUPPORTIVE ICU CARE

Surfactant
Hypocapnia
Oxygen or Nitric oxide
Hypocapnia / Alkalosis

Pressors
Oxygen
Hypothermia

PVR
+++++

SVR
+++ +

PDA
Ao

Truncus Arteriosus

Continued Aorta and Pulmonary Artery
Opening Between Ventriles

Left Ventricle

Patent Ductus Arteriosus (PDA)

Vessel connecting Aorta and Pulmonary Artery

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

Oxygen-rich Blood
Oxygen-poor Blood
Mixed Blood
HSDA

**Therapeutic**
- Indomethacin (fECHO guided)
- PDA Ligation

**Supportive**
- Permissive acidosis (pH 7.25-7.3)
- Permissive Hypercapnemia (50-60 mmHg)
- Minimize oxygen exposure (SpO2 85-92%)
Fluid Restriction, Diuretics, Feeding & HSDA

• Fluid restriction not effective in reducing the rates of HSDA or improving outcomes
  
  – May compromise end-organ perfusion further by reducing LV stroke volume
  
  Reller 1985 Ped Card

• Furosemide stimulates renal production of PgE₂
  

• Limited data regarding feeding and HSDA
• Is surgical intervention preferable?
Scenario II

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

**Focused ICU care**
- Prophylactic milrinone, hydrocortisone, serial fECHO
- Profound low cardiac output, MOF
- Radiological evidence of NEC
- Died day 2 postop
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

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
Fig. 1. Illustration of mechanical ventilator dependence of the study groups. The patients who died were considered never to have been successfully extubated.

Cotton 1978 J Pediatr
Early Ligation reduces NEC rates....

Neonates < 1000 g (n=84) with ↓ rate of NEC (30 vs 8%)
The hemodynamically significant ductus ..... 

- May lead to **acute physiological change**, hemodynamic disturbance and clinical instability

- is associated with important **neonatal morbidities** and mortality

- May require **early therapeutic intervention** to minimize morbidity and improve patient outcomes
Treatment is BAD?
Treatment doesn’t work!
<table>
<thead>
<tr>
<th>Demographics</th>
<th>Day 3: 25/40 gestation, 650 grams</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical problem</strong></td>
<td>Oxygenation failure</td>
</tr>
<tr>
<td></td>
<td>SpO₂ 85%, FiO₂ 1.0</td>
</tr>
<tr>
<td></td>
<td>Systemic hypotension</td>
</tr>
<tr>
<td></td>
<td>Respiratory failure</td>
</tr>
<tr>
<td></td>
<td>SpO₂ 95%, FiO₂ 0.5</td>
</tr>
<tr>
<td><strong>Laboratory findings</strong></td>
<td>pH 7.28, pCO₂ 42, pO₂ 38, Bxs -7.0, Lac 3.1</td>
</tr>
<tr>
<td></td>
<td>pH 7.12, pCO₂ 65, pO₂ 68, Bxs -8.0, Lac 4.1</td>
</tr>
<tr>
<td><strong>2D Echo</strong></td>
<td>3.0 mm DA with R-L flow</td>
</tr>
<tr>
<td></td>
<td>RVSP 65 mmHg</td>
</tr>
<tr>
<td></td>
<td>Hypokinetnic RV</td>
</tr>
<tr>
<td></td>
<td>3.0 mm DA with L-R flow</td>
</tr>
<tr>
<td></td>
<td>LVO: SVC flow ratio 6:1</td>
</tr>
<tr>
<td></td>
<td>E:A 1.3, LA:Ao 2.5:1, rEDF SMA</td>
</tr>
</tbody>
</table>
Scenario II

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

**Issues**
- Anuric, creatinine 260 mmol/l
- Refractory shock (Dobutamine 20 & Dopamine10 $\mu$g/kg/min)
- Metabolic acidosis (7.0-7.15) with ↑ lactate 6-10 mmol/l

**2d ECHO**
- 3.8 mm HSDA with unrestricted L-R flow
- Dilated LA and LV, cardiac output 380 mls/kg/min
- Reversed end-diastolic flow in SMA, MCA & renal artery
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*
<table>
<thead>
<tr>
<th></th>
<th>Pre-Ligation</th>
<th>Post-Ligation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FiO2</td>
<td>30%</td>
<td>50%</td>
</tr>
<tr>
<td>MAP</td>
<td>7</td>
<td>11</td>
</tr>
</tbody>
</table>
Systemic blood flow

PRE-OP
[Normal]

8 HOURS
[Impaired LV function]
Hypothesis I

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

Hypothosis: Increased LVE-VR (Left ventricle exposed vascular resistance), after PDA ligation, was associated with impaired myocardial performance
Left Ventricle Exposed Vascular Resistance (LVER)
LV dysfunction after PDA ligation in preterm baboon

Taylor 1990 J Surg Res
Myocardial Performance

LV Exposed Vascular Resistance

\[ p < 0.001 \]

mVCFc

\[ p < 0.001 \]

McNamara, 2010 J Thorac Cardiovasc Surg

# p < 0.05 vs baseline
<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 Relationship (Afterload)

Rowland 1995 Am J Card
### Stress-Velocity < 1000g

![Graph showing mVFC (circ/sec) vs. ESWS (g/cm²) for Stress-Velocity < 1000g.](image1.png)

- **Time (h)**: 0, 1, 8, 24
- **mVFC (circ/sec)**: 1.83, 1.73, 1.94, 1.7
- **ESWS (g/cm²)**: 0, 10, 20, 30, 40, 50
- **Correlation (r)**: 0.36, 0.31, 0.65, 0.37

### Stress-Velocity > 1000g

![Graph showing mVFC (circ/sec) vs. ESWS (g/cm²) for Stress-Velocity > 1000g.](image2.png)

- **Time (h)**: 0, 1, 8, 24
- **mVFC (circ/sec)**: 2.1, 1.75, 1.61, 1.72
- **ESWS (g/cm²)**: 0, 10, 20, 30, 40, 50
- **Correlation (r)**: 0.46, 0.56, 0.6, 0.53
Large HSDA
Risk Factors
Age at intervention
Weight at intervention
Preop cardiotropes

Window (8 hours) of Therapeutic Opportunity

PDA Ligation

Early fECHO

PLCS

Sahni 2008 PAS
Left Ventricular Output

\[ r = 0.63, \ p<0.001 \]

Sahni 2008 PAS
Systolic Pressure < 3rd Centile [8 hrs]

Threshold of LVO < 200 mls/min/kg at 1-hour will identify

- 83% neonates who develop SAP < 3rd centile (Sensitivity = 83.3%, Specificity = 96.1%)
- 100% neonates who required cardiotropes (Sensitivity = 100%, Specificity = 100%)
Summary

- Early fECHO may help anticipate postoperative cardiorespiratory instability

- LVO < 200 mls/min/kg is the best marker of clinical and echo indices of PLCS
Targeted neonatal ECHO directed therapy program

– introduced in January 2009
**Modifications since January 2009:**

- ACTH stimulation test pre-operatively
- 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

**Guideline for cardiovascular intervention:**

- SAP < 3rd centile & DAP > 3rd centile → iv. DOBUTAMINE
- SAP < 3rd centile & DAP < 3rd centile → VOLUME or DOPAMINE
- If failed ACTH stimulation test and refractory hypotension → consider HYDROCORTISONE
To compare the rate and components of PLCS in infants who have undergone PDA ligation **before** and **after** the introduction of targeted neonatal echocardiography (TnECHO) directed therapy program
Systolic Arterial Pressure

![Graph showing systolic arterial pressure over time with Epoch II and Epoch I data. The graph indicates a significant difference with p<0.05 ANOVA.]
## Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Epoch I (N=25)</th>
<th>Epoch II (N=27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCLS (n)</td>
<td>64%</td>
<td>37%</td>
<td>0.05</td>
</tr>
<tr>
<td>Oxygenation failure (n)</td>
<td>56%</td>
<td>29%</td>
<td>0.09</td>
</tr>
<tr>
<td>Need for cardiotropes (n)</td>
<td>36%</td>
<td>14%</td>
<td>0.14</td>
</tr>
<tr>
<td>Oxygenation failure &amp; need for cardiotropes (n)</td>
<td>28%</td>
<td>7.4%</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Only 1 case of need for inotropes in 2010

Jain 2010
Evolution of post-operative care

Use of vasodilators, PLCS

TnECHO, dobutamine

ECHO Research/analysis

TnECHO Directed Therapy

ACTH
HARM

LV dysfunction

BENEFIT

Optimize perfusion
Lung compliance
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
Take Home Messages

• PDA is a common neonatal problem with significant physiologic and hemodynamic consequences

• HSDA is a continuum from physiological normality to a pathological disease state with clinical instability and differential effects on bodily organs

• Ductal staging may help elicit those patients at greatest risk of duct-related morbidity where treatment is most beneficial and monitor therapeutic effects
Take Home Messages

• Merits of intervention (benefit-harm) remains controversial

• Early screening & targeted intervention guided by serial functional imaging is probably most desirable

• Current trial designs do not consider the heterogeneity of disease
  – Placebo controlled trial for early low grade DA (ANZAC, INDUCE)
  – Timing of intervention trial for high grade DA
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
**Request for PDA Ligation**

**PDA Team**

**Case Triage**
- Categorization (I-III)
- PLCS Risk Assignment
- Admission plan

**Peri-operative Care Plan**
- Consultation
- Monitoring (SBP, DBP)
- Intervention (choice of cardiotropes)
- Echo supported care

---

**PDA Ligations 2000-2007**

- Frequency vs. Year
- Graph showing frequency from 1998 to 2008

**Need for Cardiotropes**

- Probability vs. Category
- Graph showing probability for categories I, II, and III

Mittal 2008 PAS
<table>
<thead>
<tr>
<th><strong>Category</strong></th>
<th><strong>Clinical Indication</strong></th>
</tr>
</thead>
</table>
| I            | a. Profound pulmonary hemorrhage with significant oxygenation difficulties (OI > 15 or MAP >12 & FiO2 > 50%)  
               b. Low cardiac output syndrome or rapidly progressive cardiorespiratory failure requiring ≥ 2 inotropes |
| II           | a. Deteriorating respiratory status (OI > 15 or MAP >12 & FiO2 > 50%)  
               b. Preterm < 26 weeks with large HSDA & medical treatment is contra-indicated  
               c. Low cardiac output syndrome or cardiorespiratory failure requiring ≥ 1 inotropes  
               d. Neonate with NEC and large PDA which is felt to be contributing significantly to clinical instability |
| III          | a. Inability to extubate or wean respiratory support  
               b. Cardiac failure associated with failure to thrive |

Table 1. Clinical indicators for categorization of neonates for PDA ligation
Early ligation improves feeding tolerance

Table 2. Postoperative Parameters in the Two Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>&lt; 21 Days (range 5–20 days)</th>
<th>&gt; 21 Days (range 21–74 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 30)</td>
<td>(n = 28)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg), H6</td>
<td>38 (37–70)</td>
<td>42 (29–67)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg), H24</td>
<td>42 (30–81)</td>
<td>46 (29–65)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>145 (117–175)</td>
<td>149 (90–189)</td>
</tr>
<tr>
<td>Inotrope requirement</td>
<td>19 (63%)</td>
<td>16 (57%)</td>
</tr>
<tr>
<td>(F_1O_2) at H24</td>
<td>21 (21–60)</td>
<td>28 (21–65)</td>
</tr>
<tr>
<td>Extubation (day from surgery)</td>
<td>3 (1–26)</td>
<td>4.5 (1–64)</td>
</tr>
<tr>
<td>Extubation (day from birth)</td>
<td>10 (10–41)</td>
<td>35 (24–86)</td>
</tr>
<tr>
<td>Oxygen weaning (day from birth)</td>
<td>97 (12–187)</td>
<td>96 (57–195)</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia ((O_2) requirement at 36 weeks of CA)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Date of full oral feeding (days of life)</td>
<td>37.5 (4–84)</td>
<td>57 (25–136)</td>
</tr>
<tr>
<td>Weight at 36 weeks of CA (g)</td>
<td>1800 (1,250–2,750)</td>
<td>1607 (1,274–2,200)</td>
</tr>
</tbody>
</table>

CA = conceptional age.
CA Flow & Post-ligation instability

Cardiotropic Support

Increased risk of myocardial dysfunction may relate to chronic myocardial ischemia

* p<0.05 vs no inotropes
Transmitral Doppler

E wave

![Graph showing E wave over time with p=0.002](image)

IVRT

![Graph showing IVRT over time with p<0.001](image)

* p < 0.05 vs baseline
Pulmonary Artery Flow

Duct open, diastolic flow

Duct closed
Ductal Closure & Immaturity

Suboptimal Functional Closure
- Less responsive to oxygen (Murphy 1972 Ped Res) & more responsive to PG E2 (Clyman 1980 J Pediatr) & iNO
- Lacks intimal folds

Failure of Anatomic Remodeling
- DA wall hypoxia only if complete obliteration of intraluminal flow
- Thin walled lacking musc. so limited ability to ↑ avascular zone
- No intramural vasa vasorum

TERM PRETERM

PRETERM

TERM

Lumen

Muscle zone
↑ Afterload

↑ Duration of Ventricular Relaxation

↑ IVRT, Tau index

↓ Passive filling with increased residual atrial blood

↓ E wave

Abnormal cardiac output

Ishida 1986 Circulation
Diastolic Performance

PDA ligation followed by:

- ↓ E wave, E:A ratio (p<0.05, ANOVA)
- ↑ IVRT (p<0.05, ANOVA)
- ↑ CA: LVO flow (p<0.05, ANOVA)
The LA:Aortic ratio is increased at 2.3:1 (normal <1.4:1)
Implications for clinical practice

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

• **Focused** intensive care
  – *Systolic BP* is a better marker of early myocardial compromise & the need for cardiotropic agents
  – Avoid cardiotropic agents which increase vascular resistance (dopamine, epinephrine)
Prophylactic intervention

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Indomethacin n/N</th>
<th>Control n/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>105/771</td>
<td>132/796</td>
<td>0.82 [0.65, 1.03]</td>
</tr>
<tr>
<td>Chronic lung disease in surviving infants (36 weeks)</td>
<td>225/496</td>
<td>215/503</td>
<td>1.06 [0.92, 1.22]</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>84/1187</td>
<td>77/1214</td>
<td>1.09 [0.82, 1.46]</td>
</tr>
<tr>
<td>Symptomatic PDA</td>
<td>204/1093</td>
<td>471/1100</td>
<td>0.44 [0.38, 0.50]</td>
</tr>
<tr>
<td>PDA ligation</td>
<td>49/891</td>
<td>97/900</td>
<td>0.51 [0.37, 0.71]</td>
</tr>
<tr>
<td>IVH Grade 3 and 4</td>
<td>115/1285</td>
<td>177/1303</td>
<td>0.66 [0.53, 0.82]</td>
</tr>
</tbody>
</table>

Fowlie 2002 Cochrane database

35% reduction in severe pulmonary hemorrhage

Alfaleh 2008 Pediatrics