Patent Ductus Ateriosus

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Ductus arteriosus is derived from the distal left sixth embryonic arch

- The 6 pairs of embryonic aortic arches are demonstrated (left-sided arches are numbered).
- The portions that normally involute are indicated by broken lines.
- The distal left sixth embryonic arch normally persists and becomes the PDA, connecting the left pulmonary artery to the proximal descending aorta.
- The right distal sixth arch normally involutes, as does the eighth segment of the right dorsal aorta (*), which results in a leftward aortic arch.
- RCA indicates right carotid artery; LCA, left carotid artery; RSCA, right subclavian artery; and LSCA, left subclavian artery.

Schneider D J, Moore J W Circulation 2006;114:1873-1882
• Normally, blood flows from right side of heart to the left.
• Blood travels to the lungs through the pulmonary artery to become oxygenated.
• Left atrium then receives the oxygenated blood.
• From the left atrium, blood travels to the left ventricle and then out via the aorta.
• **However, in fetal circulation, blood in the heart is shunted away from the lungs.**
• In the fetal circulation, there are two shunts (foramen ovale and ductus arteriosus) that direct blood flow away from the lungs.
• Oxygen and carbon dioxide exchange takes place at the placenta along with the elimination of waste products.
Ductus Arteriosus

• In the fetus, the **Ductus arteriosus** is an important conduit that allows **deoxygenated blood to bypass the collapsed lungs and enter the placenta** through the descending aorta and umbilical arteries.

• The placenta acts as an oxygenator and **returns oxygen rich blood** through the umbilical vein and ductus venosus to the fetal heart.
Ductus Arteriosus

• Placenta produces prostaglandins, which maintain prenatal patency of the ductus and, in early gestation, inhibit the ability of the ductus to contract in response to oxygen.

• The ductus arteriosus itself also produces prostaglandins and nitric oxide-like vasodilators.
Fetal Circulation

During Fetal Life:
1. What is the resistance in the Pulmonary Vasculature?
2. What is the systemic vascular resistance?
3. Which direction does blood shunt through the Ductus Arteriosus?

PDA: R→L Shunting

Pulmonary Vascular Resistance: HIGH

Systemic Vascular Resistance: LOW
What Major Changes in Infant Circulation occur following birth?

• Lungs:
  – Lungs expand
  – PaO2↑’s → Pulmonary vasodilatation
  – Drop in pulmonary vascular resistance.

• Systemic Circulation:
  – Resistance ↑’s with removal of placenta

• PDA:
  – flow reverses to L → R shunting
  – Begins to functionally close due to ↑ PaO2, and decreased PGE2 levels
Patent Ductus Arteriosus
Final closure of ductus arteriosus results from increased production of local vasoconstrictors (like endothelin) in response to:

- Higher arterial oxygen
- Removal of placental prostaglandin and
- Decrease in the number of prostaglandin E2 receptors in the ductal wall
PDA Closure

- In the first 60 hours of life, spontaneous closure of the ductus occurs in 55% of full-term newborn infants.

- By 2-6 months of age, closure occurs in more than 95% of healthy infants.
Reopening of a Constricted Ductus

• Before true anatomic closure occurs, the functionally closed ductus may be dilated by a reduced arterial pO2 or an increased PGE2 concentration.

• Reopening of the constricted ductus may also occur in asphyxia and various pulmonary diseases (as hypoxia and acidosis relax ductal tissues).
Persistent patency of ductus arteriosus after birth is inversely related to gestational age.
May be due to the smaller amount of muscular tissue in the media with lower intrinsic tone
Lower responsiveness to oxygen but higher sensitivity to vasodilating effects of prostaglandin E2 and nitric oxide.
PDA

- Occurs in 8 out of every 1,000 premature babies, as compared to 2 out of every 1,000 full-term babies.
- Twice as common in girls than in boys.
- Genetics may play a role. A defect in one or more genes might prevent the DA from closing after birth.
- PDA is more common in:
  - Infants who have genetic conditions, such as Down syndrome.
  - Infants whose mothers had German measles (rubella) during pregnancy.
Pathophysiology of PDA

- Left to Right shunting
- Increased pulmonary blood flow (depending on pulmonary vascular resistance)
- Left atrial dilation
- Left ventricular over load
- Increased left ventricular stroke volume
- Congestive heart failure
Relationship to Systemic Organ Perfusion with PDA

• Redistribution of systemic blood flow occurs even with moderate shunts.
• Retrograde aortic flow, decreased systemic blood flow, and moderate hypotension are common in premature infants with PDA.
• It may lead to decreased perfusion in many organs, with potential clinical consequences to each.
Relationship to Systemic Organ Perfusion with PDA

• Reduced cerebral blood flow or changes in cerebral blood flow velocity patterns have been implicated in the occurrence of intraventricular hemorrhage.

• Renal function may be compromised, and myocardial perfusion, particularly subendocardial blood flow, may be reduced.
# PDA Consequences

<table>
<thead>
<tr>
<th>Pulmonary Overcirculation (↑ Qp)</th>
<th>Systemic Hypoperfusion (↓ Qs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygenation failure</td>
<td>Systemic Hypotension</td>
</tr>
<tr>
<td>Increased Vent Requirements</td>
<td>End-Organ Hypoperfusion</td>
</tr>
<tr>
<td>Pulmonary Edema</td>
<td>Renal Insufficiency</td>
</tr>
<tr>
<td>Pulmonary Hemorrhage</td>
<td>Necrotizing Enterocolitis</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>Intra-Ventricular Hemorrhage</td>
</tr>
<tr>
<td>Bronchopulmonary Dysplasia</td>
<td>Acidosis (metabolic, lactic)</td>
</tr>
</tbody>
</table>
Signs and Symptoms

- 2-3 days after birth up to 1 week of life
  - later in those treated with surfactant
- Prominent left ventricular impulse
- Bounding pulses
- Widened pulse pressure (>25 mmHg)
- Murmur
  - can be initially silent
  - initially systolic becoming continuous
  - machinery like
Murmur: Systolic at LUSB/ Left Infracavicular, may progress to continuous (machinery like)

http://depts.washington.edu/physdx/audio/pda.mp3
Signs and Symptoms

• Deterioration of respiratory status
• Circulatory instability
• Cardiac enlargement
• Tachypnea / apnea
• Increased CO2 retention
• Increased requirements for mechanical ventilation

• Diagnosis confirmed by echocardiography
What findings on this CXR are suggestive of a PDA?

- Increased Pulmonary vascular markings
- Cardiomegaly
Echocardiogram with Doppler

• Most reliable non-invasive diagnostic tool.
• Modified parasternal short axis view offers best window for PDA visualization and measurement.
• Enlargement of left atrium (that reflects magnitude of the shunt), is further supported by left atrial-to-aortic root ratio of >1.3
• Continuous wave Doppler can estimate pulmonary artery pressures by measuring Doppler velocities of PDA flow and tricuspid regurgitation.
Echocardiogram

- Gold standard for diagnosing PDA

Fig 1. Shows the ultrasound ductal cut with two dimensional imaging on the left and with color Doppler on the right. This wide open duct with a mainly left to right shunt was reported in a preterm baby just a few hours old.

Ductal diameter at 5 hours and later symptomatic PDA

Figure: Plots Ductal diameter against gestation at 5 hours of age in 124 babies born before 30 weeks. The closed blue triangle label babies who later needed treatment for a clinically apparent PDA.

Royal Prince Alfred Hospital
Our findings


•The PDA size does not affect cerebral and renal tissue oxygenation, but the mesenteric tissue oxygenation is decreased in infants with a large PDA on NCPAP.
Overview of Management

- Conservative
- Prophylactic Indomethacin/Ibuprofen
- Medical Treatment
  - Indomethacin
  - Ibuprofen
- Surgical Treatment
Management
Conservative

- Neutral Thermal Environment
- Ventilator Strategies:
  - Adequate Oxygenation
  - Permissive Hypercapnea
  - Use of PEEP
- Hct at 35-40
- Avoid exacerbating factors
  - furosemide
  - excessive fluids (>170 cc/kg/day)
  - no evidence that fluid restriction reduces PDA
    (some still use mild fluid restriction: 110-130 ml/kg/day)
Diuretics

• Although furosemide is a prostaglandin agonist, it does not interfere with PDA closure.

• Short-term use of furosemide and fluid restriction requires a close vigilance to prevent dehydration.

Management
Medical

• **Indomethacin**
  • 3 doses at 12 or 24 hr intervals (0.2 mg/kg)
  • increased risk for NEC, Renal failure, Platelet dysfunction and BPD
  • Dopamine may prevent Renal tubular dysfunction
  • Regular measurement of creatinine and platelets

• **Ibuprofen**
  • 10 mg/kg 1st dose then 5 mg/kg 2 doses daily
  • less oliguria
  • increased risk for NEC and platelet dysfunction
  • increased risk for kernicterus
Indomethacin

• Mode of Action:
  – Cyclooxygenase inhibitor
  – COX enzyme necessary for generating PGE2 (potent vasodilator)

• Adverse-Effects:
  – reduces cerebral, gastrointestinal, and renal blood flow
  – Decreased urine output
  – Platelet dysfunction

• Would you continue/start feeds on this infant?
  – given concern for increased risk of NEC many neonatologists hold feeds during indomethacin therapy
Some Contraindications to Indomethacin

- Proven/ suspected infection
- Active bleeding
  - e.g. IVH, NEC
- Thrombocytopenia and/or coagulation defects
- Necrotizing enterocolitis
- Severe Renal Impairment
- Congenital heart disease with ductal dependent lesion
**Long-Term Effects of Indomethacin Prophylaxis in ELBW: Primary Outcomes (TIPP)**

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>EVENT RATE</th>
<th>ODDS RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INDOMETHACIN GROUP</td>
<td>PLACEBO GROUP</td>
</tr>
<tr>
<td>no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or impairment</td>
<td>271/574 (47)</td>
<td>261/569 (46)</td>
</tr>
<tr>
<td>Components</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death before 18 mo of corrected age†</td>
<td>125/595 (21)</td>
<td>111/594 (19)</td>
</tr>
<tr>
<td>Cerebral palsy‡</td>
<td>58/467 (12)</td>
<td>55/477 (12)</td>
</tr>
<tr>
<td>Cognitive delay (MDI &lt;70)‡</td>
<td>118/444 (27)</td>
<td>117/457 (26)</td>
</tr>
<tr>
<td>Hearing loss requiring amplification‡</td>
<td>10/456 (2)</td>
<td>10/466 (2)</td>
</tr>
<tr>
<td>Bilateral blindness‡</td>
<td>9/465 (2)</td>
<td>7/472 (1)</td>
</tr>
</tbody>
</table>

*Odds ratios have been adjusted for the birth-weight stratum and center, except for the odds ratios for hearing loss and bilateral blindness, which were adjusted only for the birth-weight stratum. P values are for the adjusted odds ratios. CI denotes confidence interval, and MDI Mental Development Index.

†These data do not include the 13 infants who were lost to follow-up at 18 months.

‡Data for this outcome exclude infants who died before scheduled tests and those who were alive but were not tested or were lost to follow-up.

? improvement in incidence of severe IVH (13%→9%, OR 0.6 (0.4–0.9), p =0.02)

No long-term neurodevelopmental benefit

Prophylactic Treatment: No Reduction in CLD/BPD

- **Review:** Indomethacin for asymptomatic patent ductus arteriosus in preterm infants
- **Comparison:** 01 Indomethacin vs Placebo
- **Outcome:** 02 Chronic lung disease in survivors

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Indomethacin n/N</th>
<th>Control n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammerman 1987</td>
<td>9/10</td>
<td>12/14</td>
<td>1.05 [0.78, 1.41]</td>
<td>72.41</td>
<td></td>
</tr>
<tr>
<td>Weesner 1987</td>
<td>2/10</td>
<td>4/11</td>
<td>0.55 [0.13, 2.38]</td>
<td>27.59</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>20</td>
<td>25</td>
<td>0.91 [0.62, 1.35]</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 11 (Indomethacin), 16 (Control)
Test for heterogeneity: Chi² = 1.32, df = 1 (P = 0.25), I² = 24.2%
Test for overall effect: Z = 0.46 (P = 0.64)
Ibuprofen

• More recently, ibuprofen has been evaluated as a possible alternative to indomethacin in preterm infants.

• A meta-analysis of the available studies has shown a comparable rate of ductal closure after ibuprofen treatment.
Ibuprofen

• Some evidence exists that there may be less effect of ibuprofen on renal function and urine output.

• In addition, ibuprofen has less effect on cerebral vasculature and cerebral blood flow but has not shown a decreased risk for intraventricular hemorrhage.
Our findings


• Treatment of PDA with either INDO or IBU is associated with a 30-40 % risk for a reduction in regional tissue oxygenation, which is more pronounced in mesenteric tissue than in cerebral or renal tissue.

• Reduction of regional tissue oxygenation in preterm infants with PDA is more likely to be associated with the administration of INDO than with IBU.
Surgical Ligation

• Indications?
  – Persistent Symptomatic PDA after 1-2 trials of Indomethacin or Motrin
  – Contraindication to Indomethacin or Motrin

• Complications?
  – recurrent laryngeal nerve paralysis
  – blood pressure fluctuations
  – respiratory compromise
  – chylothorax
  – BPD
  – infection
  – intraventricular hemorrhage
  – Neurosensory impairment
  – death
Surgical Ligation

• Long Term Outcomes
  – Current studies do not demonstrate that ligation decreases incidence of BPD
  – Some data to suggest infants that have surgical ligation are at greater risk for neurocognitive delays

• Surgery should only be used for infants that have failed medical management and are symptomatic
Controversies

• **Conservative Management**
  • high rate of spontaneous closure
  • established adverse effects of intervention
  • lack of evidence that treatment results in a decrease in neonatal morbidity and mortality

• **Prophylactic Indomethacin**
  • 0.1 mg/kg/day q24 hrs after birth x 3 days
  • no effect on mortality, pulmonary outcome or reducing the risk of NEC
  • early treatment more likely to be successful

• **Medical vs Surgical Treatment**
  • no difference in mortality
  • higher adverse events with surgery
Trans-catheter closure

- A large short PDA, which is the typical anatomy in symptomatic newborns and premature infants, is difficult to close.
- In addition, there is a significant risk of obstructing the descending aorta or left pulmonary artery, which are small caliber vessels in neonates.
- Out of the neonatal period, cardiac catheterization with coil occlusion of the PDA has become the primary mode of closure.
Closure of a PDA by coil catheterization

(A) Injection into the aorta reveals a large PDA at baseline.

(B) Following placement of a coil the angiographic dye no longer crosses into the pulmonary artery confirming ductal closure.

MPA = main pulmonary artery
PDA = patent ductus arteriosus
DA = descending aorta
Pathological PDA

• A PDA is considered pathological when it persists beyond 3 months of age or is associated with symptoms.
• Spontaneous closure after 5 months is rare in the full-term infant.
• Untreated, patients with a large PDA may develop the Eisenmenger Syndrome, in which pulmonary vascular resistance exceeds systemic vascular resistance, and the usual left-to-right shunting reverses to a right-to-left.
• At this stage, pulmonary vascular disease is irreversible, closure of PDA is contraindicated, and lung transplantation may be only hope for long-term survival.
Conditions where a PDA is beneficial

• Lesions which will depend on flow via the ductus arteriosus to maintain systemic circulation
  – Coarctation of the aorta
  – Critical aortic stenosis
  – Hypoplastic left heart syndrome

• Lesions which will depend on flow via the ductus arteriosus to maintain pulmonary circulation
  – Pulmonary atresia
  – Critical pulmonary stenosis
  – Tricuspid atresia
  – Tetralogy of fallot

• Lesions where the systemic and pulmonary circulations are separated
  – Transposition of the great arteries (TGA)
Step-down of Pulmonary Artery Oxygen Saturation

- The term “step down” is used when the given chamber has oxygen saturation less than the proximal chamber.
- In TGA with PDA, the aorta (Ao) is connected to the pulmonary artery (PA) and has lower oxygen saturation.
- The PA is connected to the left ventricle (LV) receiving oxygenated blood from the left atrium.
- Hence when there is a PDA, de-saturated blood enters the PA from the Ao, causing a step down in oxygen saturation compared to the LV, which is the proximal chamber in this case.
Questions?
• **Question:** Which of the following statements about patent ductus arteriosus is INCORRECT?
  a- It occurs frequently as an isolated phenomenon
  b- Cyanosis is usually present
  c- It causes a pan-systolic 'machinery' murmur at the upper left sternal edge
  d- There is a wide pulse pressure
  e- Treatment is by surgical closure

• **Answer:** c- Cyanosis is usually not present

Pulse oximetry/arterial blood gas analysis usually demonstrates normal saturation because of pulmonary over-circulation. A large ductus arteriosus could cause hypercarbia and hypoxemia from congestive heart failure (CHF) and air space disease (atelectasis or intra-alveolar fluid/pulmonary edema). A PDA is considered pathological when it persists beyond 3 months of age or is associated with symptoms. Spontaneous closure after 5 months is rare in the full-term infant. Left untreated, patients with a large PDA are at risk to develop Eisenmenger Syndrome, in which the pulmonary vascular resistance can exceed systemic vascular resistance, and the usual left-to-right shunting reverses to a right-to-left direction. At this stage, the pulmonary vascular disease is irreversible, closure of the PDA is contraindicated, and lung transplantation may be the only hope for long-term survival.
In the fetus the ductus arteriosus is what stops blood going to the lungs from the RV. The ductus arteriosus goes from the pulmonary artery and attaches to the descending aorta. This shunt usually closes a few days after birth and becomes the ligamentum arteriosum. In a patent ductus arteriosus (PDA) there is effectively free circulation between the systemic and pulmonary circulations. This leads to pulmonary edema due to the pulmonary hypertension and dyspnea. On examination a palpable thrill may be felt in the 2nd intercostal space and there will be a loud continuous "machinery" type of murmur in the same place.

However, if the pulmonary resistance is high, there can be a Right-to-Left shunt so de-oxygenated blood will enter the descending aorta, this is a reversing of the shunt.

**Question:** Regarding the statement above, if de-oxygenated blood is entering the descending aorta which of the following could occur?

- a- Cyanosis of the Hands
- b- Cyanosis of the Feet
- c- Clubbing of the Feet
- d- Clubbing of the Hands

**Answer:** b and c- Cyanosis and clubbing of the feet.
• **Question:** Step down of pulmonary artery saturation in PDA (patent ductus arteriosus) is seen in:
  a- Eisenmenger PDA
  b- TOF (tetralogy of Fallot) with PDA
  c- TGA (transposition of great arteries) with PDA
  d- TAPVC (total anomalous pulmonary venous connection) with PDA
  e- AP (aorto-pulmonary) window

• **Answer:** c- TGA with PDA

The term step down is used when the given chamber has oxygen saturation less than that of the proximal chamber. In TGA, aorta is connected to the pulmonary artery and has lower oxygen saturation. Pulmonary artery is connected to the left ventricle receiving oxygenated blood from the left atrium. Hence when there is a PDA, de-saturated blood enters the pulmonary artery from the aorta causing a step down in oxygen saturation compared to left ventricle which is the proximal chamber in this case.