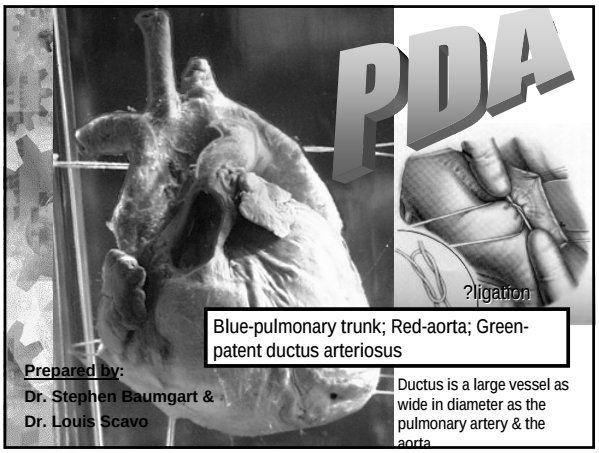


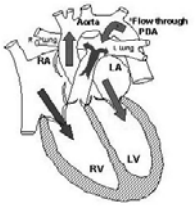
Blue-pulmonary trunk; Red-aorta; Green-patent ductus arteriosus

Prepared by:
Dr. Stephen Baumgart &
Dr. Louis Scavo

Ductus is a large vessel as wide in diameter as the pulmonary artery & the aorta

Ductus Arteriosis in the Fetus

- Due to the high PVR and low SVR of the fetus, the ductus arteriosus permits the pulmonary to systemic shunt (LPA to descending Ao) required for survival
- Only 8 to 12% of C.O. goes through the lungs in the fetus in utero
- Pathological closure of the fetal ductus leads to ↓PBF *in utero*, resulting in vascular s.m. proliferative Pulmonary Hypertension



Ductus Arteriosis in the Newborn

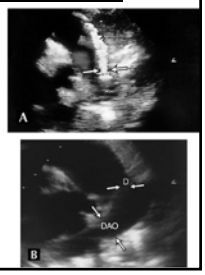
- At birth an acute ↑PVR (1st breath) and ↓SVR (cord cut) leads to functional closure of the PFO with consequent increased PBF and establishment of the in series circulation.
- While the Ductus remains open, the direction and magnitude of any shunt depends on the ratio of PVR to SVR and on the size of the Ductus (restrictive or not).

Ductus Arteriosis in the Newborn

- A slow phase of continued PVR decline follows the acute PVR ↱ seen at birth
- The time it takes for the PVR to fully decrease is lengthened by any L to R shunt and proportional to shunt magnitude, which grows as the PVR drops
- Excessive PBF (Qp/Qs>1.5) is almost always associated with the development of Pulmonary Hypertension, regardless of the location of the shunt.

Diagnosis of Symptomatic PDA

- Echocardiography gives the picture of anatomic patency to an otherwise asymptomatic PDA without significant L ☞ R shunting.
- Clinical signs occur only with significant left-to-right shunts:
  - Pan-systolic murmur
  - Bounding peripheral pulses
  - Visibly active precordium [PMI]
  - Widened pulse pressure:
    - [systolic - diastolic] >50% systolic
  - Continued need or escalation of ventilator support
  - S3[rarely appreciated]



Expected Times of Ductal Closure by Gestational Age

- **At full term ductus functionally closes by 3 days**
- **Preterm >30 wks most PDA's close by 5 days, in babies having little or no lung disease**
- **≤30 wks 2/3 do not close & have sig lung disease**

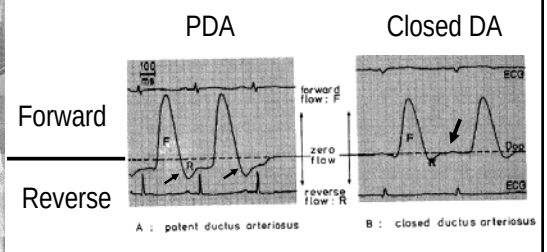
Postnatal Patency of the Ductus Arteriosus : is it Pathologic?

- PDA results in Left to Right Shunt when PVR < SVR, similar to VSD. Shunt depends on size of PDA and ratio of PVR to SVR
- With PDA Pulmonary Circulation exposed to Systemic Pressures and ↑ Flow, with all of the possible effects of that physiology
- Over time excessive PBF leads to Pulmonary Hypertension; rate depends on size of shunt
- Unlike VSD, no valves are involved in PDA, shunt can occur through diastole: Visceral "Steal " Syndrome results (See Slides That Follow)

Evidence of Potential Compromise of Vascular Beds

- Lower Doppler diastolic flow velocities in human prematures' renal and splanchnic beds [Shimada, Pediatr Int 2003, 45:255]
- ↓ blood flow terminal to ileum in premature lambs [Meyers, Pediatr Res, 1991, 29:569]; however O_2 consumption in ileum is unchanged with PDA closure –Therefore, was ileal circulation really distressed with PDA runoff? Perhaps not when they looked but is there ongoing risk?

Flow in the Descending Aorta



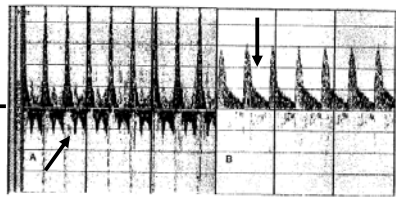
Ulmer, Knapp, Wolf, Wille and Seybrth: Aortic flow velocity curves …, Pediatric Pharmacology 3:167-174, 1983

Flow in the Renal Artery

PDA Closed DA

Forward

Reverse



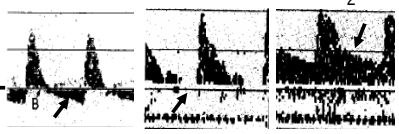
T. Bömelburg and G. Jorch European Journal of Pediatrics Volume 148, Number 7 / June, 1989 pg 660-66

Flow in the Middle Cerebral Artery

PDA_1 PDA_2 Closed DA_2

Forward

Reverse



Reversed Diastolic flow

Absent Diastolic flow

Normal, forward Diastolic flow

Late PDA Closure, Impact on LV

Low Qp/Qs. Little impact

High Qp/Qs, Large impact

Table Echocardiographic data in control subjects and patients

	Normal (n = 8)	PDA with Qp/Qs < 1.5: Before PDA coil closure (n = 4)	PDA with Qp/Qs < 1.5: After PDA coil closure (n = 4)	PDA with Qp/Qs > 1.5: Before PDA coil closure (n = 5)	PDA with Qp/Qs > 1.5: After PDA coil closure (n = 5)
Age (y)	1.8 ± 0.9	1.3 ± 0.5		1.8 ± 1.3	
Heart rate (bpm)	103 ± 12	113 ± 9	110 ± 8	110 ± 14	108 ± 14
Qp/Qs	1	1.20 ± 0.06	1	1.80 ± 0.29	1
Systolic blood pressure (mm Hg)	87 ± 9	78 ± 12	83 ± 15	88 ± 11	98 ± 12†
Diastolic blood pressure (mm Hg)	51 ± 7	49 ± 13	50 ± 16	47 ± 8	59 ± 7†
LV end-diastolic diameter (cm)	2.8 ± 0.2	2.6 ± 0.5	2.5 ± 0.5	3.6 ± 0.7*	3.4 ± 0.7†
* LV mass (g)	28 ± 6	27 ± 3	27 ± 3	57 ± 14*	57 ± 14*
LAD diameter (cm)	0.19 ± 0.03	0.18 ± 0.03		0.20 ± 0.03	
LAD MPV (cm/s)	31 ± 8	34 ± 5	35 ± 7	47 ± 6*	62 ± 16*†
LAD FVI (cm)	6.4 ± 1.6	6.4 ± 2.5	6.8 ± 2.9	9.1 ± 2.0*	12.5 ± 3.0*†
LAD flow (mL/min)	19 ± 8	23 ± 3	23 ± 4	27 ± 5*	36 ± 7*†
* LV flow/LV mass (mL/100 g)	66 ± 15	72 ± 12	75 ± 13	48 ± 10*	65 ± 15†

FVI, Flow velocity time integral; *LAD*, left anterior descending coronary artery; *LV*, left ventricular; *MPV*, maximum peak flow velocity; *PDA*, patent ductus arteriosus; *Qp/Qs*, pulmonary to systemic flow ratio.
*$P < .05$ vs normal; †$P < .05$ vs before PDA coil closure (Qp/Qs > 1.5).

Harada, Toyono and Tamura: Effects of Coil Closure of Patent Ductus…, Journal of the Am. Soc. of Echocardiography, June 2004

Points from the Previous Slide

- Small shunts through a PDA (Qp/Qs < 1.5) don't have much of an impact on the LV or coronary flow (a marker for diastolic steal as coronaries perfuse primarily in diastole).
- Large shunts have a serious and potentially long term impact: increased mass and diameter of the LV (increases metabolic demand) and decreased blood flow per unit mass (decreases metabolic supply). Not Good!

Clinical Evidence Treating PDA is Beneficial

- Early evidence from small trials that persistent PDA with left-to-right shunting results in impaired oxygenation and longer course of treatment or hospitalization etc. (Cotton et. al. J. Peds. 1978 93(4):647 and Kaapa et. al. Acta Paediatr Scand 1983 72(2):179). These findings resulted in reluctance to study effects of untreated PDA and most large trials investigate method or timing of closure, not closed versus patent ductus.
- Two small recent studies were done, one found that mortality was decreased by treating PDA (Brooks et. al. Arch. Dis. Child 2005, 90:F235-F239) and the other that PDA delayed feeding tolerance, but not as much as did sepsis. (Patole et. al. Arch Dis Child 2007 92(1):F53-F55)

Is treating PDA Always Necessary?

- A PDA is necessary, and often maintained open with PGE_2, for ductal dependent cardiac lesions or if Pulmonary Hypertension is so severe that ductal closure would lead to right heart failure.
- In a premature primate model a PDA was shown to be beneficial in augmenting PBF in animals with severe lung disease and high PVR (RDS): PDA provided more adequate PBF than ligated DA in those prematures and the same PBF as normal mature/term primates without RDS or PDA [Morrow, Crit Care Med, 1995, 23:179] until PVR begins to drop.

Is treating PDA Always Necessary?

- Cochrane Review 2005 looked at studies comparing treatment vs non treatment of asymptomatic PDAs and found that the incidence of symptomatic PDA and duration of supplemental oxygen were reduced in the treated group. Treat 3 patients with asymptomatic PDA to prevent 1 symptomatic PDA.
- Symtomatic PDA's were treated in the reviewed studies

Treatment of Symptomatic PDA

Gersony, *et al*: J Pediatr 1983, 102:895

- 421 of 3,559 subjects ≤1,750 gms developed a hemodynamically significant PDA:
  - ECHO at entry LA/Ao ratio ≥1.15 + ≥3 clinical signs of congestive heart failure
  - Failed fluid restriction 36-48 hrs
  - If signs persisted then randomized – given indocin 0.2 mg/kg q 12 hr X 3 doses, *versus* placebo control medication
  - 79 were surgically ligated if indocin failed
- 79% of PDA's closed with indocin alone while 35% closed with fluid management alone, all the rest were closed either with indocin or were ligated, *ie* there were no untreated controls left with persistent PDA to compare to varies treatment strategies

Treatment of Symptomatic PDA

Gersony, *et al*: J Pediatr 1983, 102:895

- There were no differences among the 3 treatment groups:
  - in mortality
  - in duration of mechanical ventilation
  - in length of hospital stay
  - nor in the occurrences of IVH or NEC
- There were more pneumothoraces and grades III & IV ROP in the surgical ligation group

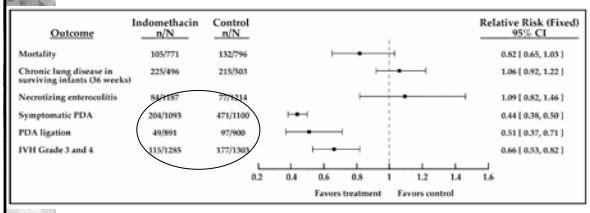
Conclusions

Gersony, et al: J Pediatr 1983, 102:895

- "Walk, don't run to the pharmacy for indomethacin" *Henry Wagner*
- Try to avoid surgical ligation associated morbidities with fluid restriction and indocin if clinical signs of congestive failure persist beyond 48 hours; and pursue surgery by or before 14 days if clinical signs persist

Treatment of PDA

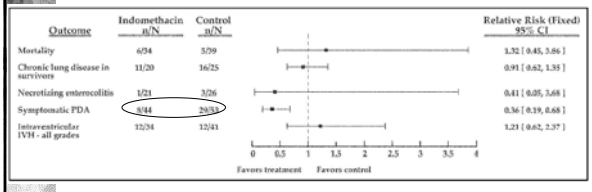
PROPHYLACTIC INDOCIN for all premies on day 1
COCHRANE REVIEW 2002:CD 000174



- **19 studies, total over 2,872 randomized subjects**
- **Symptomatic PDA halved with indocin**
- **Fewer by half required PDA ligation**
- **Also ↓IVH with indocin prophylaxis**
- **No differences in CLD, NEC, later developmental disabilities**

Treatment of PDA

INDOCIN FOR ASYMPTOMATIC DUCTUS (ECHO ONLY): COCHRANE REVIEW 2003:CD 003745



- **Total 97 VLBW subjects PDA reduced to < 20%**
- **Only subjects <1,000 gms had less time in O_2**
- **But no difference in CLD >36 wks, NEC, or ROP**

Prolonged *vs* Short Course Indocin

COCHRANE REVIEW 2005, ISSN 1464-780X

- Indocin ineffective in 40%, PDA re-opens 35%
- Long 4 or more doses *vs* short ≤3 doses
- Prolonged indocin
  - Less severe grades III&IV IVH
  - Less re-opening PDA
  - Less renal impairment with ↓creatinine
  - More CLD
- No difference
  - PDA closure rates
  - Surgical ligation rates

Ibuprofen for PDA

- Effectively treats PDA
- One trial out of many reported PPHN
- ↓Creatinine
- Had no effect on
  - Mortality
  - Severe IVH
  - NEC/or GI bleeds
  - Time to full feeds
  - Need for surgical ligation

Lasix to prevent indocin morbidity

Cochrane Review 2005, ISSN 1464-780X

- Did result in increased urine flow, but
- Did not reduce occurrence rate oliguria
- May dehydrate already dry babies with BUN/creatinine ratios≥20

Dopamine to prevent indocin morbidity

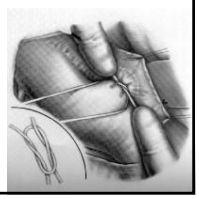
Cochrane Review 2005, ISSN 1464-780X

- Improved urine output, but
- No effect on serum creatinine
- Doesn't prevent oliguria (<1mL/kg/hr)

AN OBSERVATION:
These studies suggest that we're looking for alternatives to treat indocin toxicity and to avoid surgery

Surgical ligation of PDA, a Gold Standard?

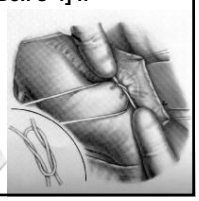
- **Should be 100% effective [well duh!]**
- **Presently reserved only for those failing medical intervention**
- **Associated morbidities:**
  - **Vocal cord paralysis**
  - **Hemorrhage**
  - **Air leaks**
  - **Wound infection**
  - **High grade ROP**



Only Evidence in favor of Surgical ligation for PDA

Cassady, *et al*: N Engl J Med 1989; 320:1511

- **44 babies <1,000 gms randomized to usual therapy without indocin**
- ***versus* 40 babies ligated by 24 hours:**
  - **3/44 (8%) significant NEC [Bell 3-4] if ligated**
  - ***versus* 13/44 (30%) if not**



Surgical ligation *vs* indocin

Gersony, 1983;
COCHRANE REVIEW 2005, ISSN 1464-780X

- <37 wks, <2500 gms
- Symptomatic PDA
- 154 randomized infants
  - No difference in mortality
  - No difference in CLD
  - No difference in NEC
  - No difference in IVH or other bleeding
- Surgical ligation group had
  - More pneumothoraces
  - More ROP grades III-IV
- Indocin group had more PDA failures [well duh!]

Reported risks of PDA ligation include:

[1] Pneumothoraces
[2] Vocal cord paralysis
[3] Hemorrhage
[4] Infection
[5] Higher grades ROP

CONCLUSIONS: Attendings 1 and 2

[1] Aggressive treatment of PDA does not attenuate CLD or NEC; failure to treat significant PDA may increase the risk

[2] No randomized trial compares a fluid restriction approach to indocin and/or surgical treatment of PDA: with large PDAs, who would take the risk?

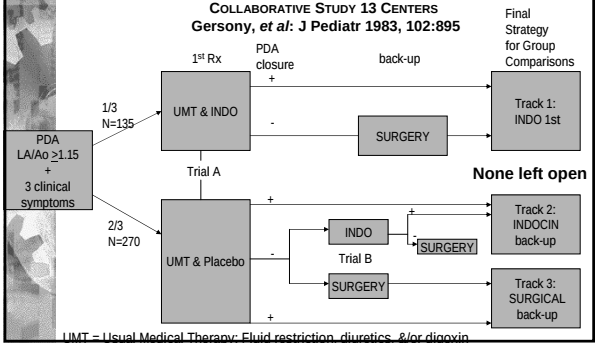
[3] There are no recent human trials investigating the risks *versus* the benefits of surgical PDA ligation; likely to be institution dependent

Treatment of Symptomatic PDA

- When and how to treat PDAs is controversial and excellent institutions with good outcomes have different approaches.
- Two extremes
  - Prophylactic pharmacologic closure
  - Treat only if in persistent CHF
- Middle paths still derived from Multi-Centered Trial of Gersony et. al. 1983

Does Timing or Mode of Treatment of Symptomatic PDA Affect Morbity?

Effects Of Indomethacin In Premature Infants With PDA: A National Collaborative Study 13 Centers
Gersony, *et al*: J Pediatr 1983, 102:895



UMT = Usual Medical Therapy: Fluid restriction, diuretics, &/or digoxin

Alternative to Routinely Aggressive Treatment of PDA

- PDA in severe lung disease may be an adaptive pop-off, and physiologic, maintaining PBF despite 👍👍👍PVR
- 👍👍👍PVR is present when F_IO_2@ >0.50
- Avoid fluid overload (CHF & NEC)
- Observe for signs of left ventricle failure, and
- Treat PDA only if intractable congestive heart failure >at least 48 hours

Cochrane Reviews

- Fowlie PW, Davis PG 2002 Prophylactic IV indomethacin for preventing mortality and morbidity in preterm infants
- Prophylactic treatment with indomethacin has a number of immediate benefits
  - A reduction in symptomatic patent ductus arteriosus
  - Reduction of duct ligation and severe intraventricular haemorrhage
  - There is no evidence to suggest either benefit or harm in longer term outcomes including neurodevelopment.
  - Depending on clinical circumstances and personal preferences, there may be a role for prophylactic indomethacin in some infants on some neonatal units.

Cochrane Reviews

- Malviya M, Ohlsson A, Shah S 2003 Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants.
- The data regarding net benefit/harm are insufficient to make a conclusion as to whether surgical ligation or medical treatment with indomethacin is preferred as initial treatment for symptomatic

Cochrane Reviews

- Ohlsson A, Walia R, Shah S 2005 Ibuprofen for the treatment of patent ductus arteriosus in preterm/LBW infants
- We found no statistically significant difference in the effectiveness of ibuprofen compared to indomethacin in closing the PDA. Ibuprofen reduces the risk of oliguria. However, ibuprofen may increase the risk for CLD, and pulmonary hypertension has been observed in three infants after prophylactic use of ibuprofen.

Cochrane Reviews

Shah SS, Ohlsson A 2005 Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

- Prophylactic use of ibuprofen reduces the incidence of PDA, the need for rescue treatment with cyclo-oxygenase inhibitors & surgical closure.
- In the control group, the PDA had closed spontaneously by day three in 60% of the neonates.
- Prophylactic treatment exposes a large proportion of infants unnecessarily to a drug that has important side effects (mainly involving the kidneys) without conferring any important short term benefits.
- Prophylactic treatment with ibuprofen is not recommended. Until long-term follow-up results are published from the trials included in this review, no further trials of prophylactic ibuprofen are recommended.

Cochrane Reviews

Herrera C, Holberton J, Davis P 2007 Prolonged versus short course of indomethacin for the treatment of patent ductus arteriosus in preterm infants

- Prolonged indomethacin course does not appear to have a significant effect on improving outcomes, (PDA treatment failure, CLD, IVH, or mortality).
- The reduction of transient renal impairment does not outweigh the increased risk of NEC associated with the prolonged course.
- A prolonged course cannot be recommended for the routine treatment of PDA in preterm infants.

THE END