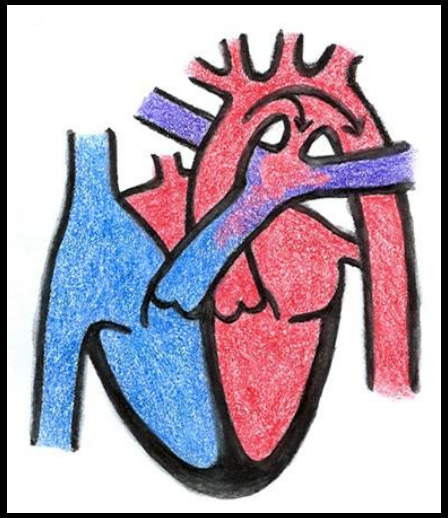


Physiopathologie / traitement du canal artériel

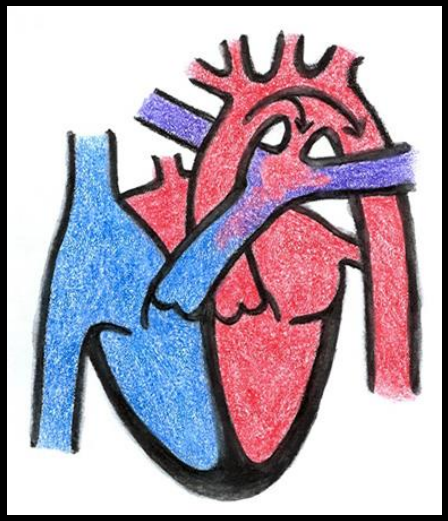
L Storme, S Mur, F Flamein, E Caron-Lesenechal, R Boukhris, M El Hajjar, J De Buyst, C Hocq, A Bouissou, T Dzukou, T Rakza

Hôpital Jeanne de Flandre, CHRU de Lille, FRANCE

Université de Lille

Centre Hospitalier Régional Universitaire de Lille

Outline



1. **Role of the ductus arteriosus:**
   - During the transition at birth
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   - Left-to-Right shunting across the DA in preterm babies
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   - Benefit from fluid restriction ?
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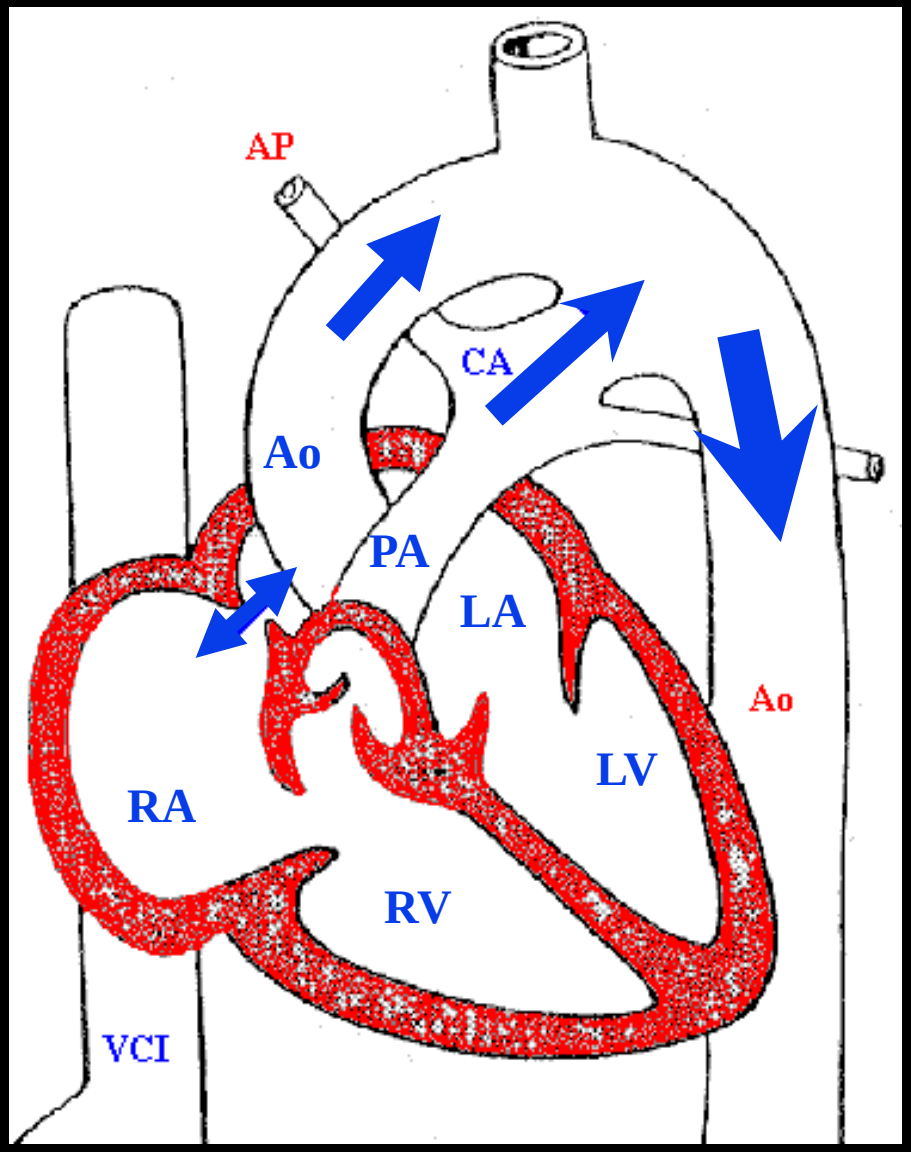
   - Do we need to treat hypotension in babies with DA ?
   - Benefit of red blood cells transfusion ?
   - Impact of IUGR ?

Fetal oxygenation



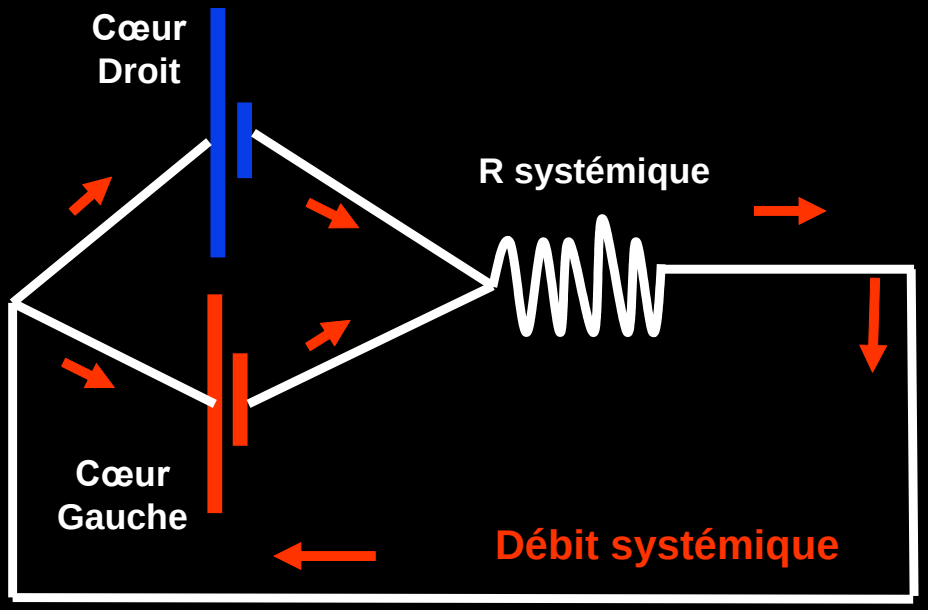
Hypoxemia without hypoxia !

O_2 delivery =

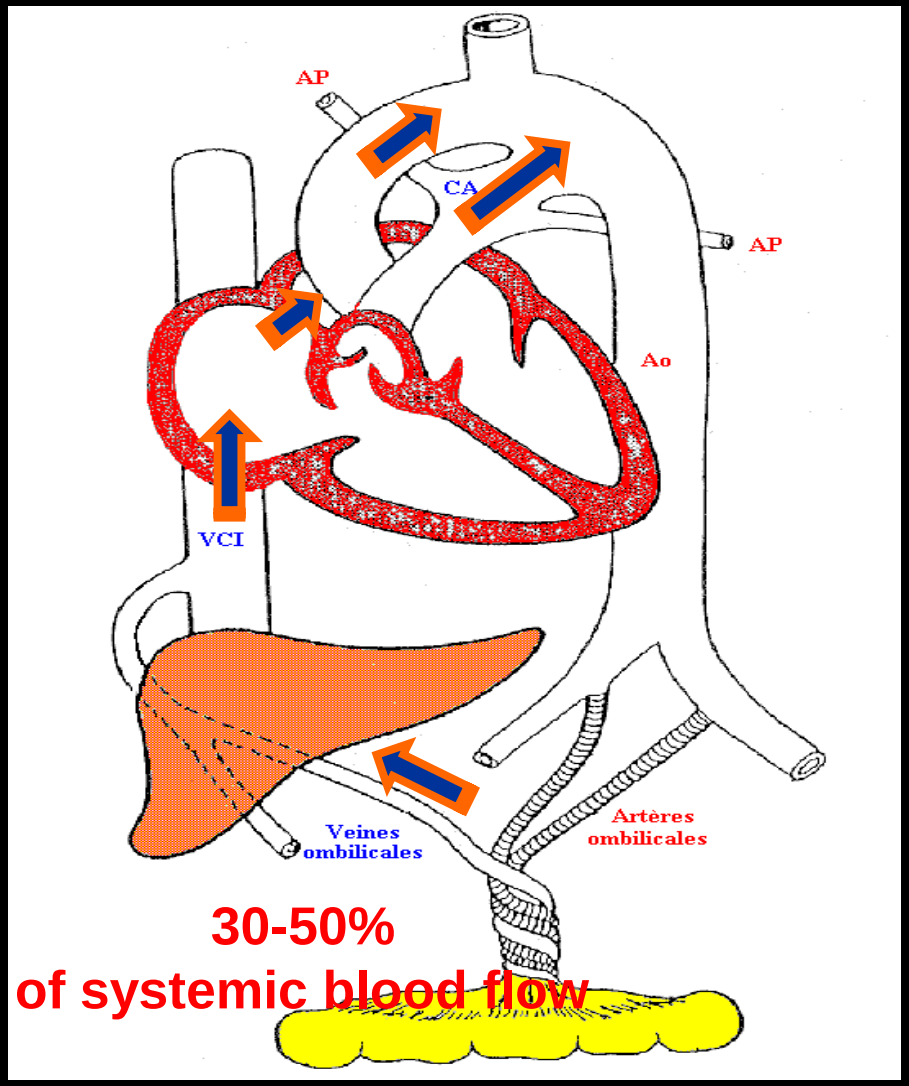
1.3x **Qc** x SaO_2 x Hb

Systemic blood flow =

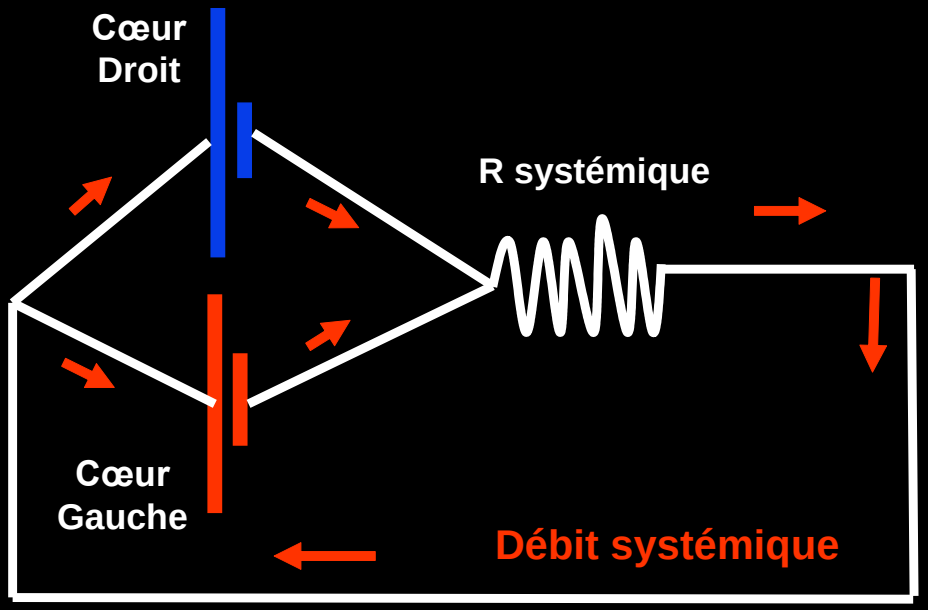
$Q_{LV} + Q_{DA}$



Circulation foetale

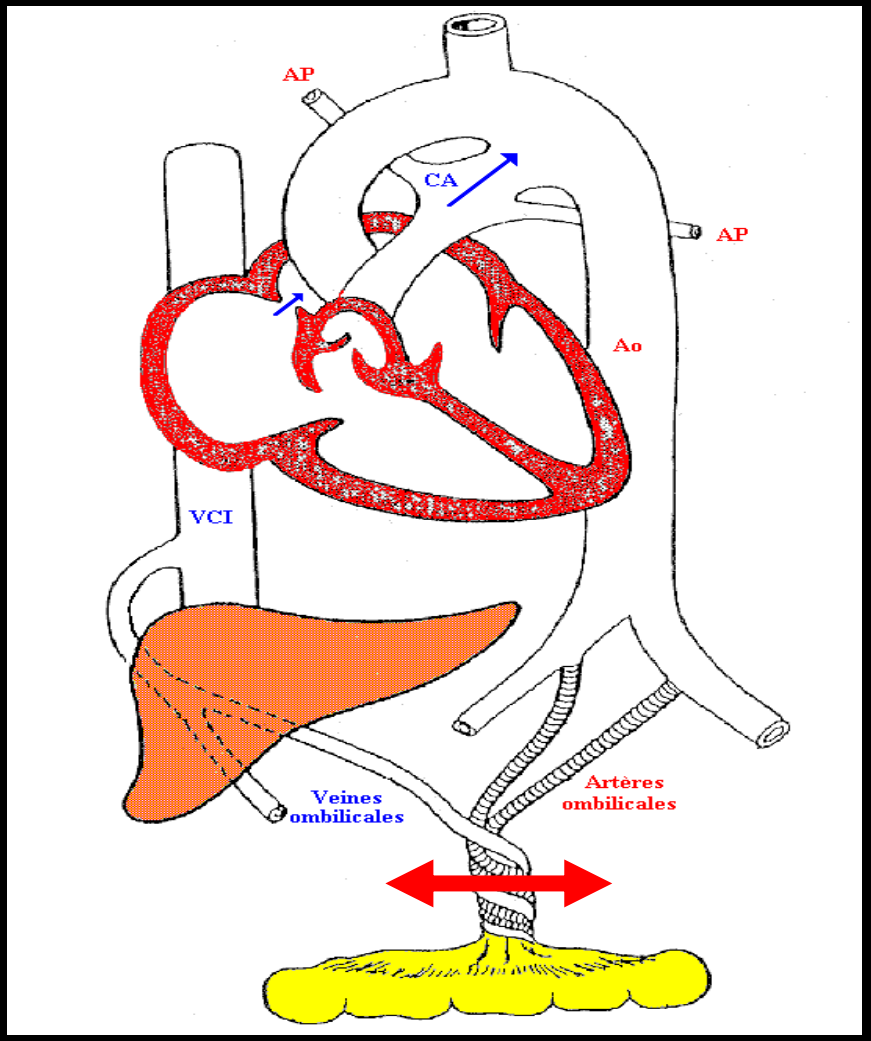


Débit systémique = $Q_{LV} + Q_{DA}$



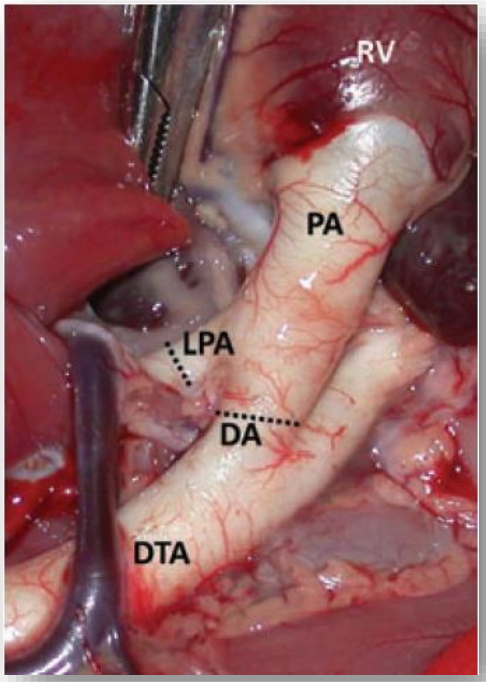
Effets du clampage du cordon

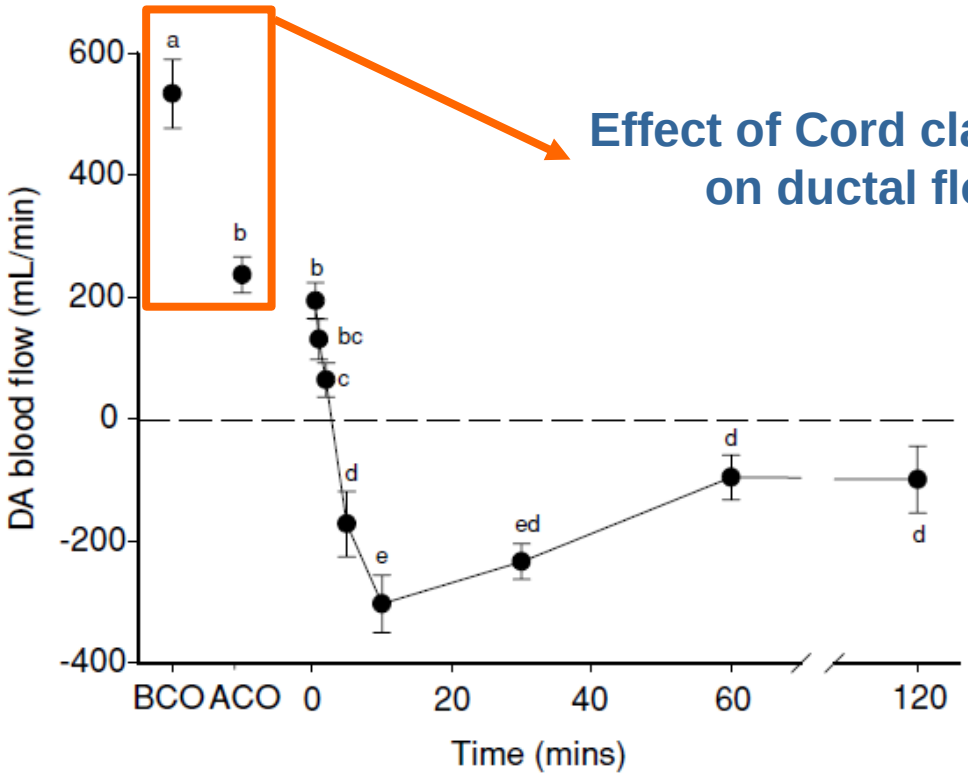
⇓ précharge VG



⇑ postcharge VG et VD

S Bhatt, J Physiol 2013



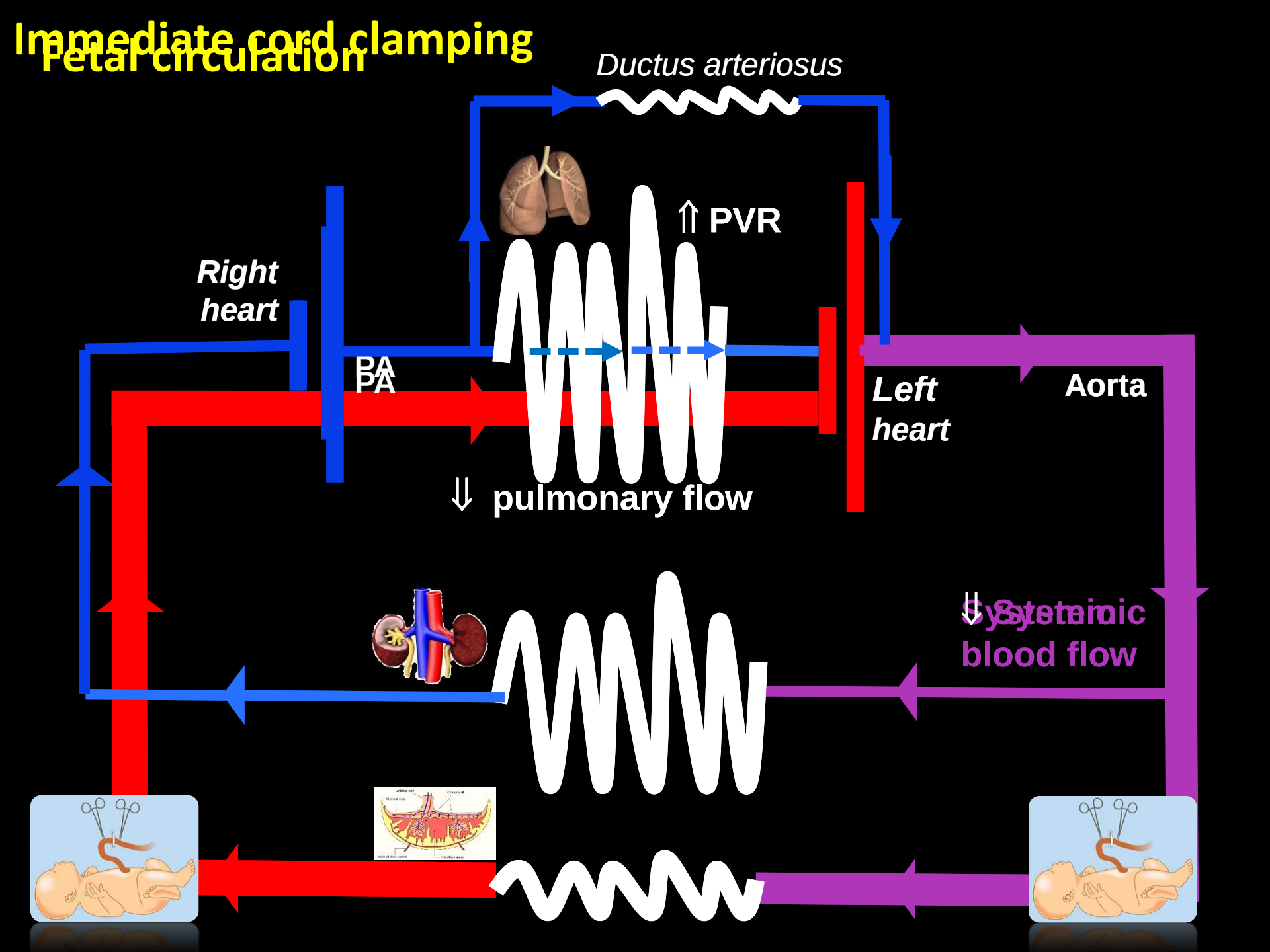


Effect of Cord clamping on right ventricle output

Time	HR (beats min^{-1})	RVO (ml min^{-1})
BCO	167 ± 9	623 ± 55^{a}
ACO	166 ± 18	315 ± 14^{b}

Crossley J, J Physiol 2009

Immediate cord clamping
Fetal circulation

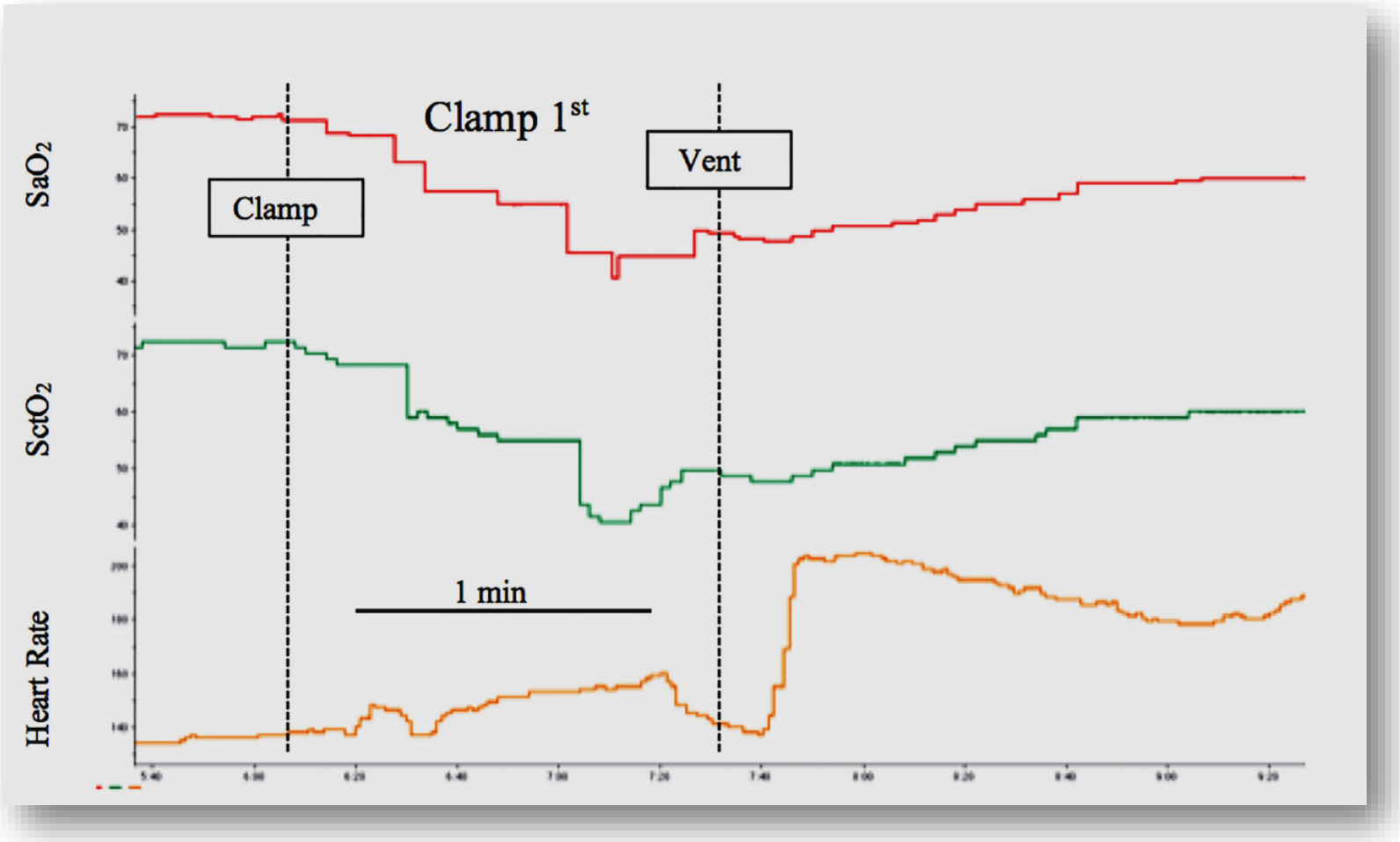


Effet du clampage immédiat du cordon avant le début de la ventilation

SaO2

ScO2

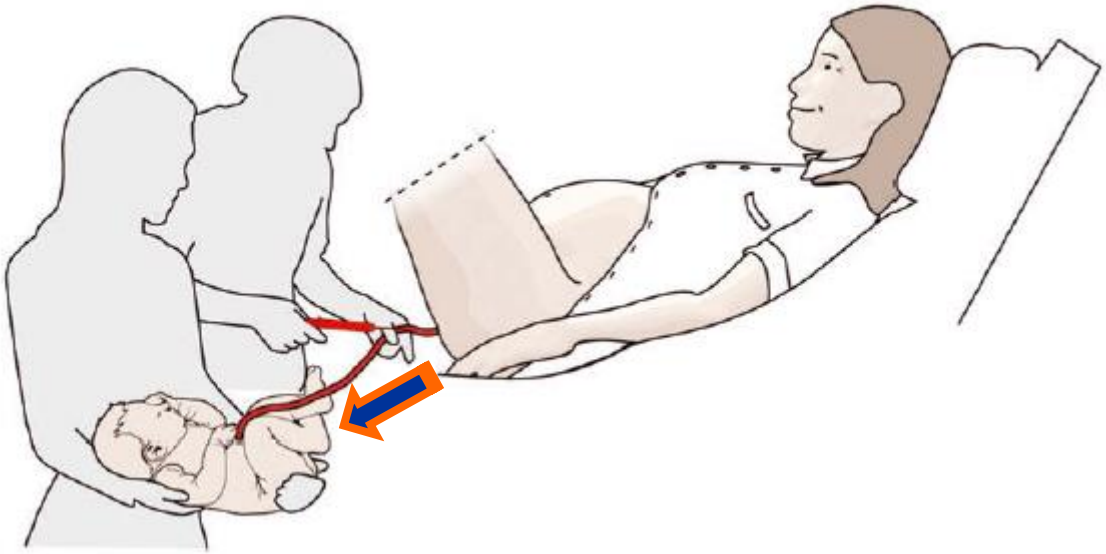
FC



Polglase, Plos One 2015

Delayed vs immediate cord clamping

120 ml/kg of blood
with 40-50 ml/kg
in the placenta and cord



- **Placental transfusion;**
- **« Smooth » hemodynamic transition**

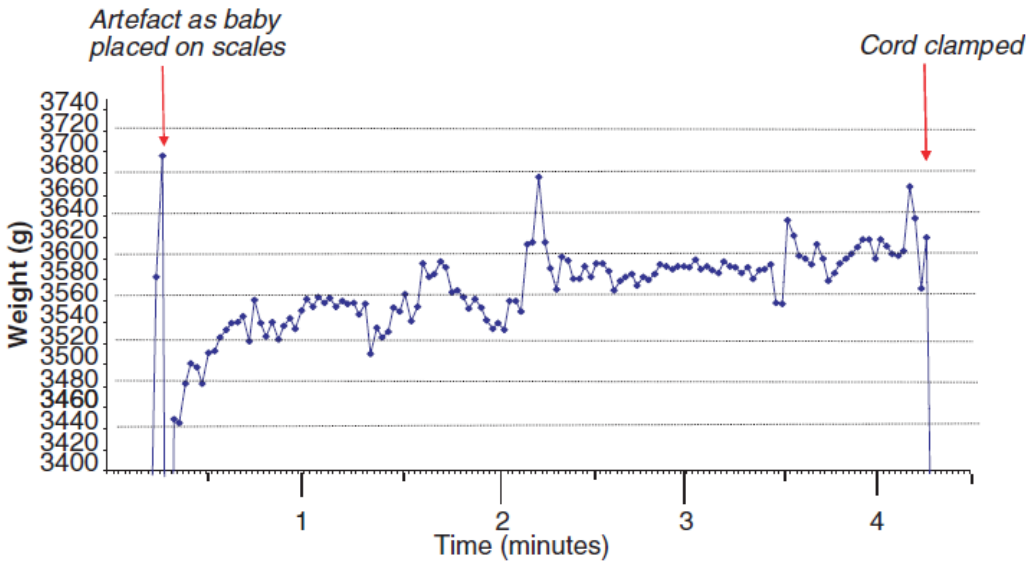


Figure 1. Weight change from birth to cord clamping.

Table 2. Weight and weight change at birth using a B-spline and inspection of the graphs

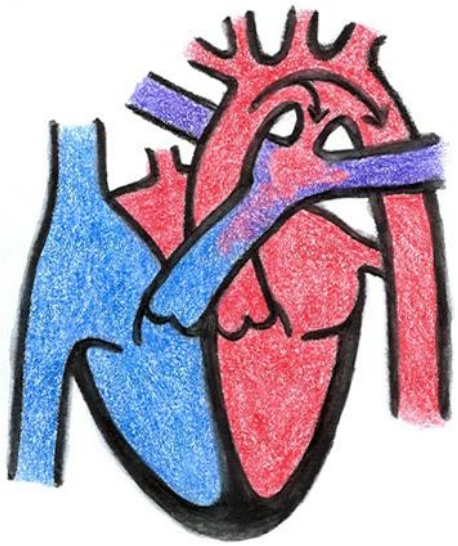
	n	Start mean weight (g)	End mean weight (g)	Mean difference in weight (g) (95% CI)	t (*df*)*	*P*
B-spline						
Total	26	3295	3411	116 (72–160)	5.44 (25)	<0.001
Mode of birth						
caesarean section	13	3466	3597	131 (64–198)	0.69 (24)	0.5
Vaginal	13	3124	3225	101 (36–167)		
Position of baby						
Above bed	14	3235	3332	96 (38–154)	−0.99 (22)	0.3
On bed	12	3364	3504	139 (64–214)		
Uterotonic drug**						
Yes	21	3408	3530	122 (69–174)	−0.60 (8)	0.6
No	5	2820	2913	93 (-17–204)		

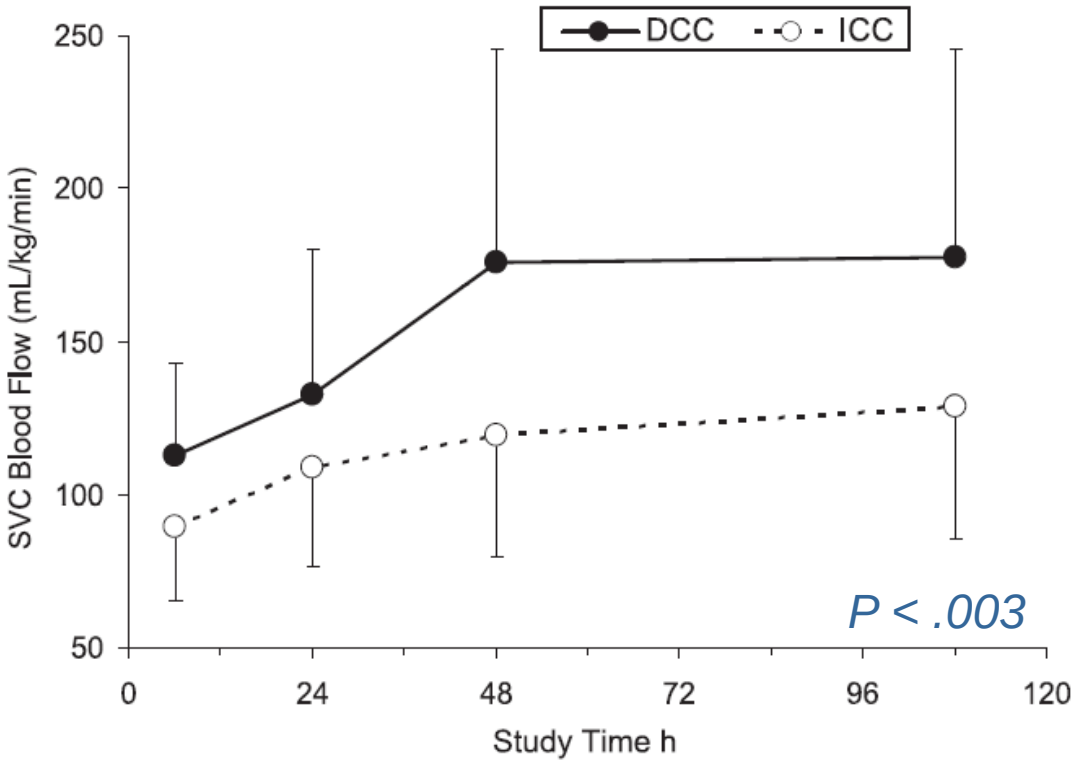
Farrar D, BJOG 2011

TABLE 2 Infants' Demographic and Clinical Characteristics after Delivery

	DCC, $n = 25$	ICC, $n = 26$	P
Gestation wk, mean (SD)	28.3 (2.3)	27.7 (2.0)	.4
Birth weight, g, mean (SD)	1204 (394)	1116 (467)	.5
Cesarean delivery, n (%)	9 (36.0)	14 (53.9)	.3

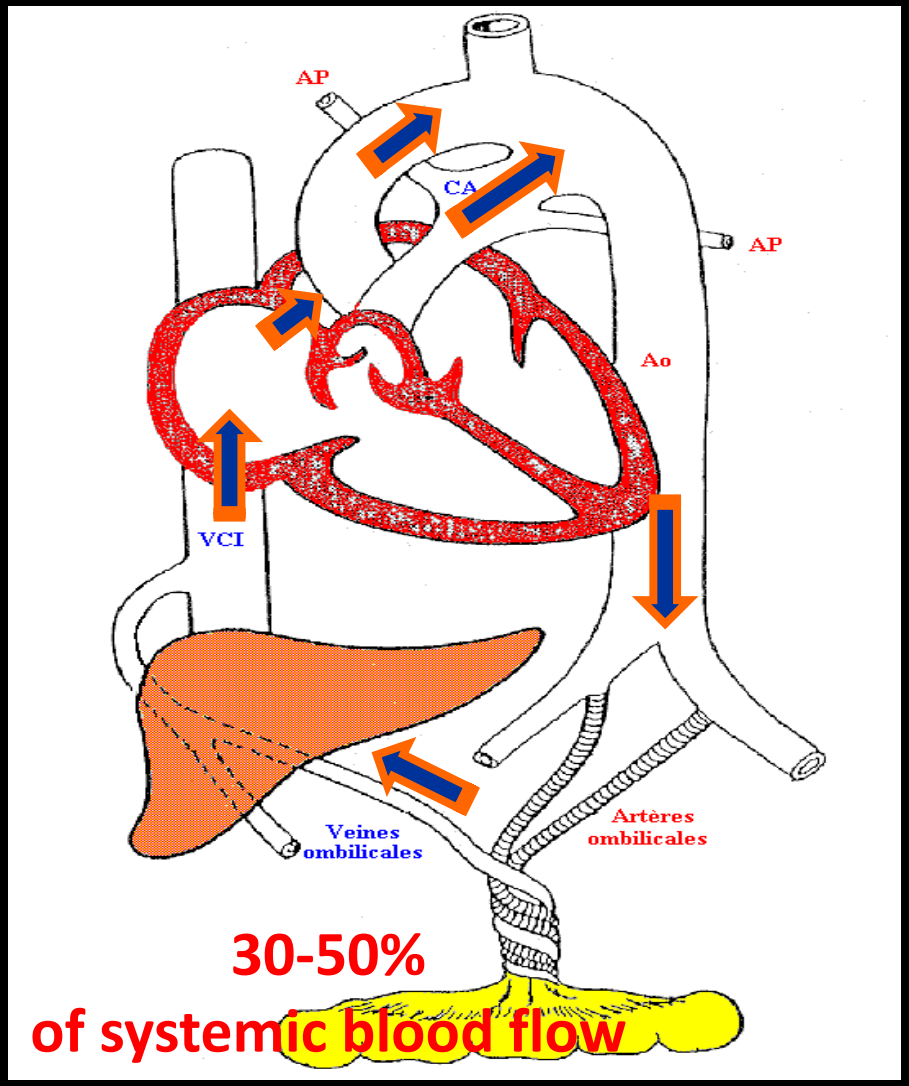
Superior
Vena cava
Blood flow



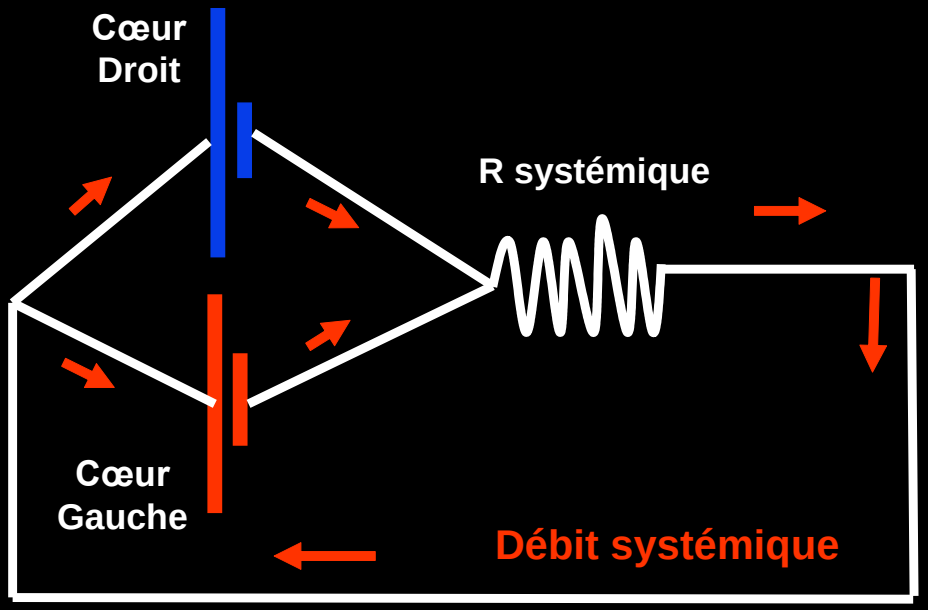


Sommers R, Pediatrics 2012

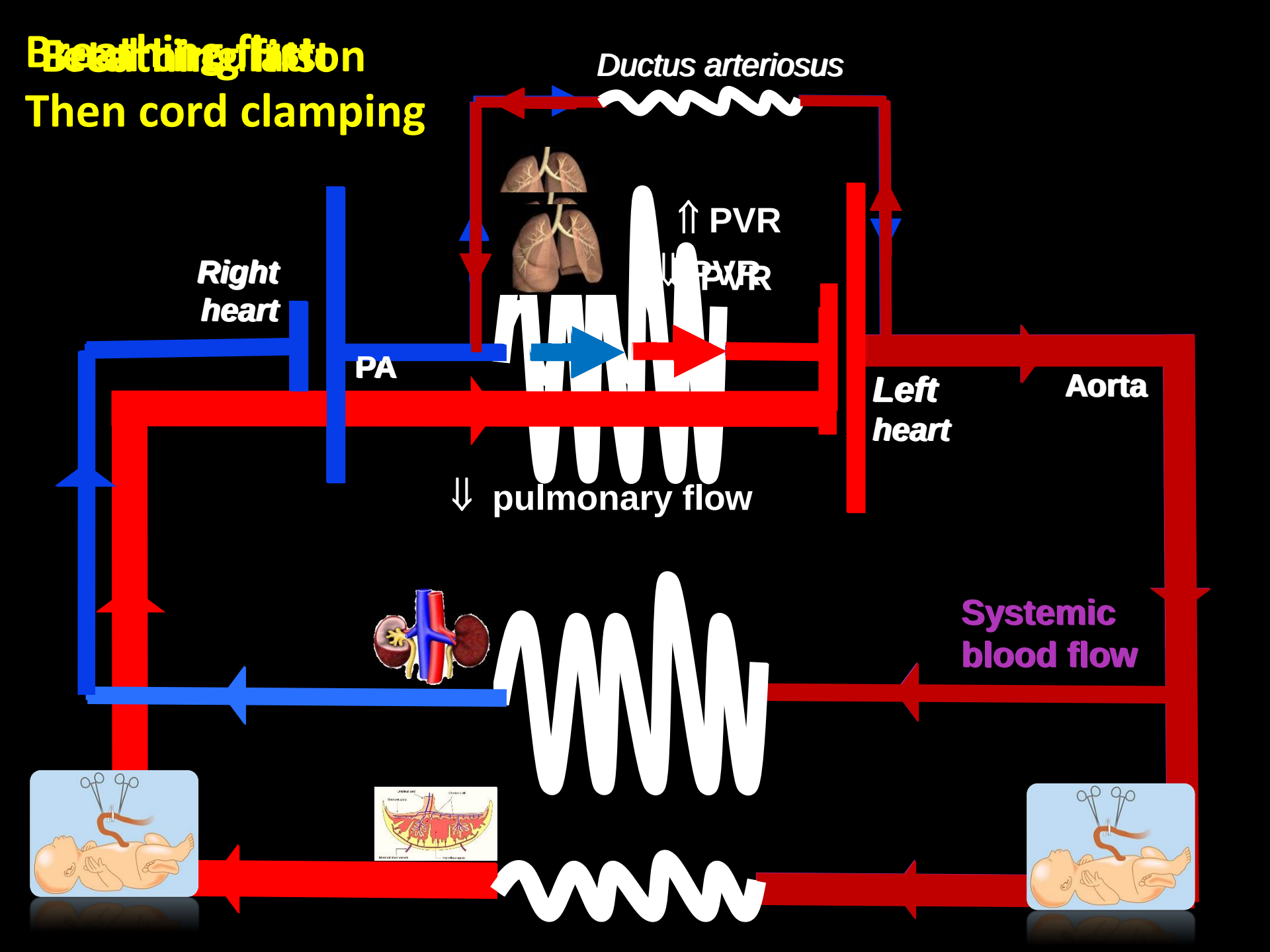
Fetal circulation



Systemic blood flow = $Q_{LV} + Q_{DA}$

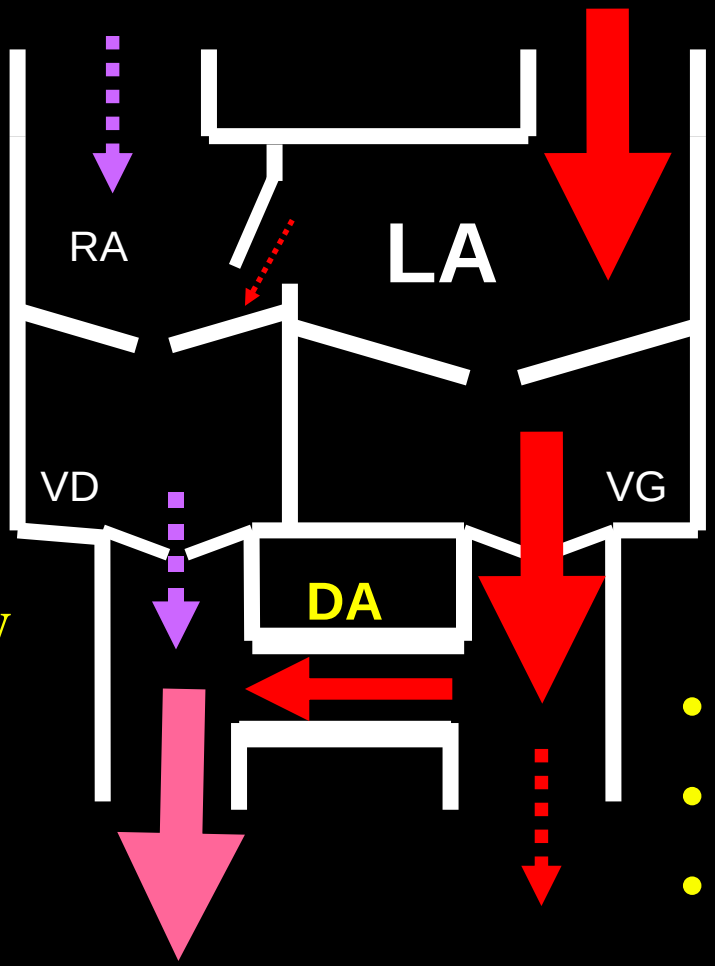


Breathing first
Then cord clamping

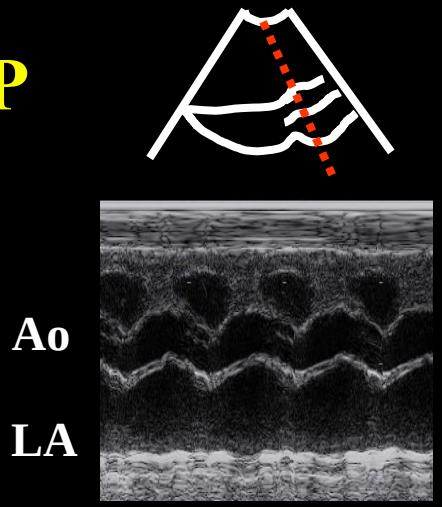


Effects of DA in the preterm baby

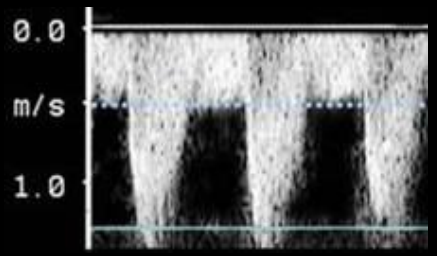
- ↓ SVC flow



- ↑ LAP



- ↑ Flow
- ↑ PAP



LPA flow

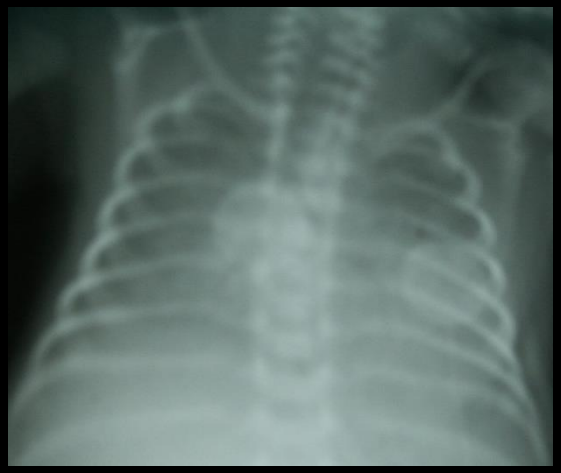
- ↑ Resistance Index
- ↓ AoP
- ↓ Flow

Severity of the ductal shunt: a comparison of different markers

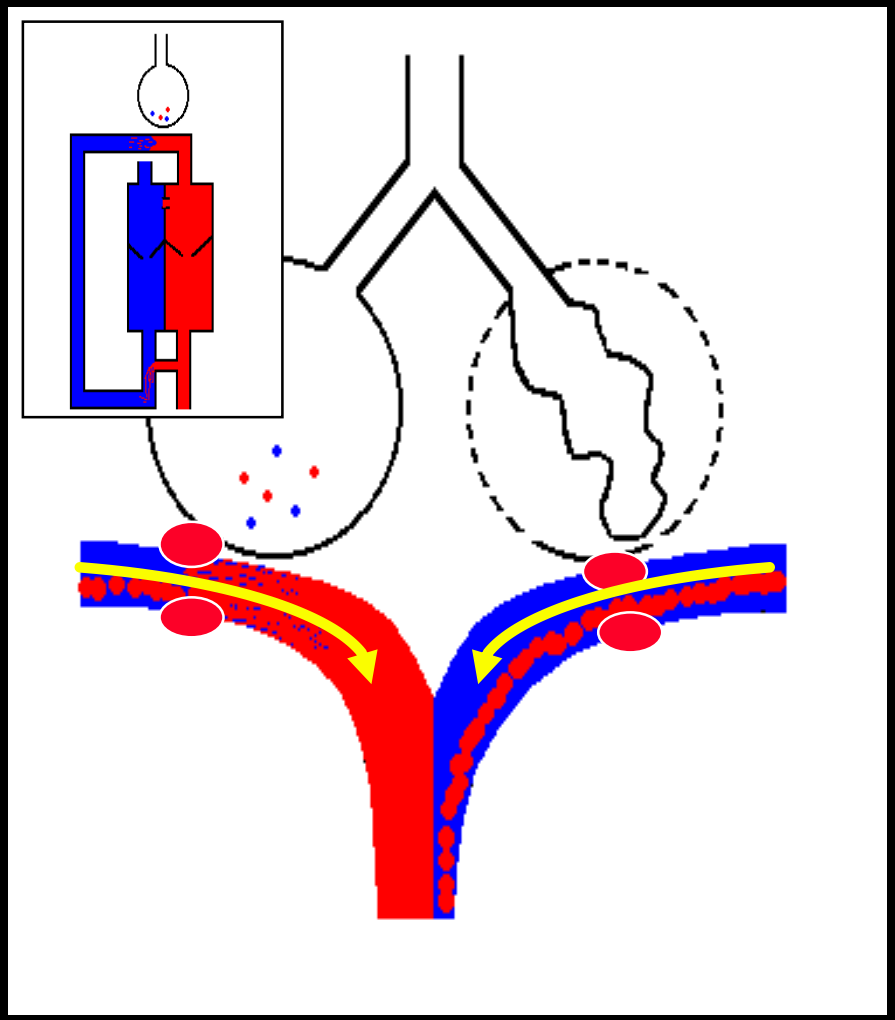
M El Hajjar, G Vaksmann, T Rakza, G Kongolo, L Storme

Arch Dis Child Fetal Neonatal Ed 2005;90:F419–F422. doi: 10.1136/adc.2003.027698

Left-to-Right shunting through DA

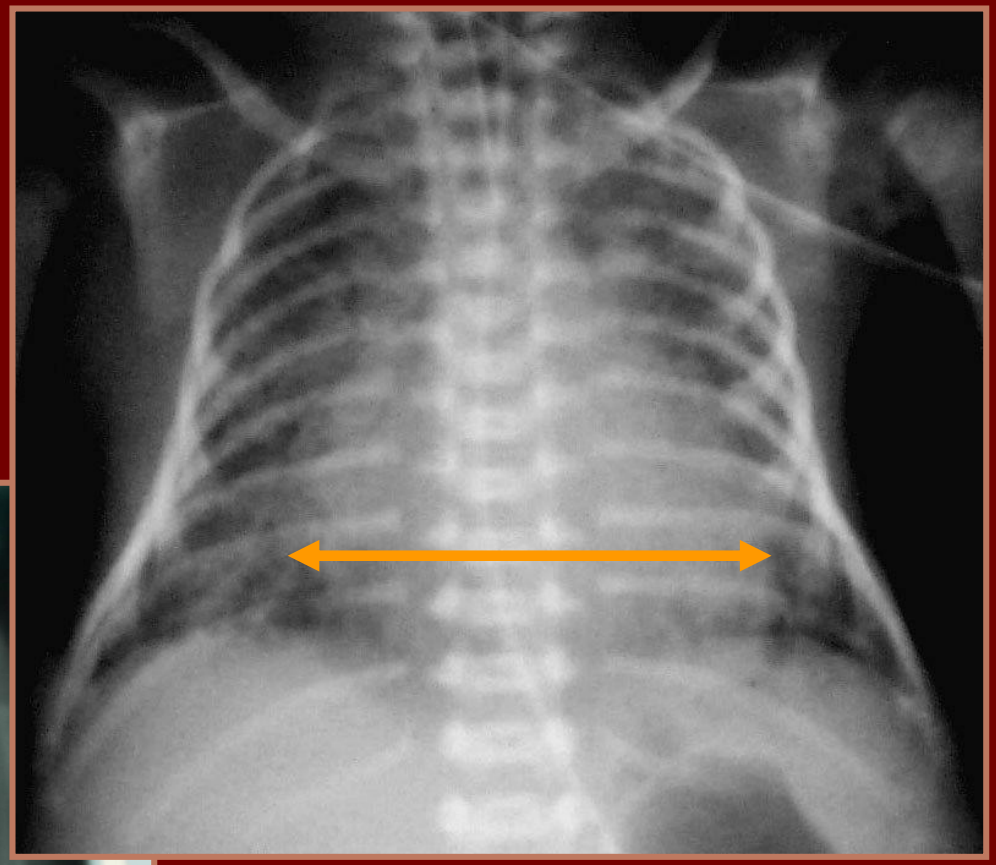


O2 need = 21% !



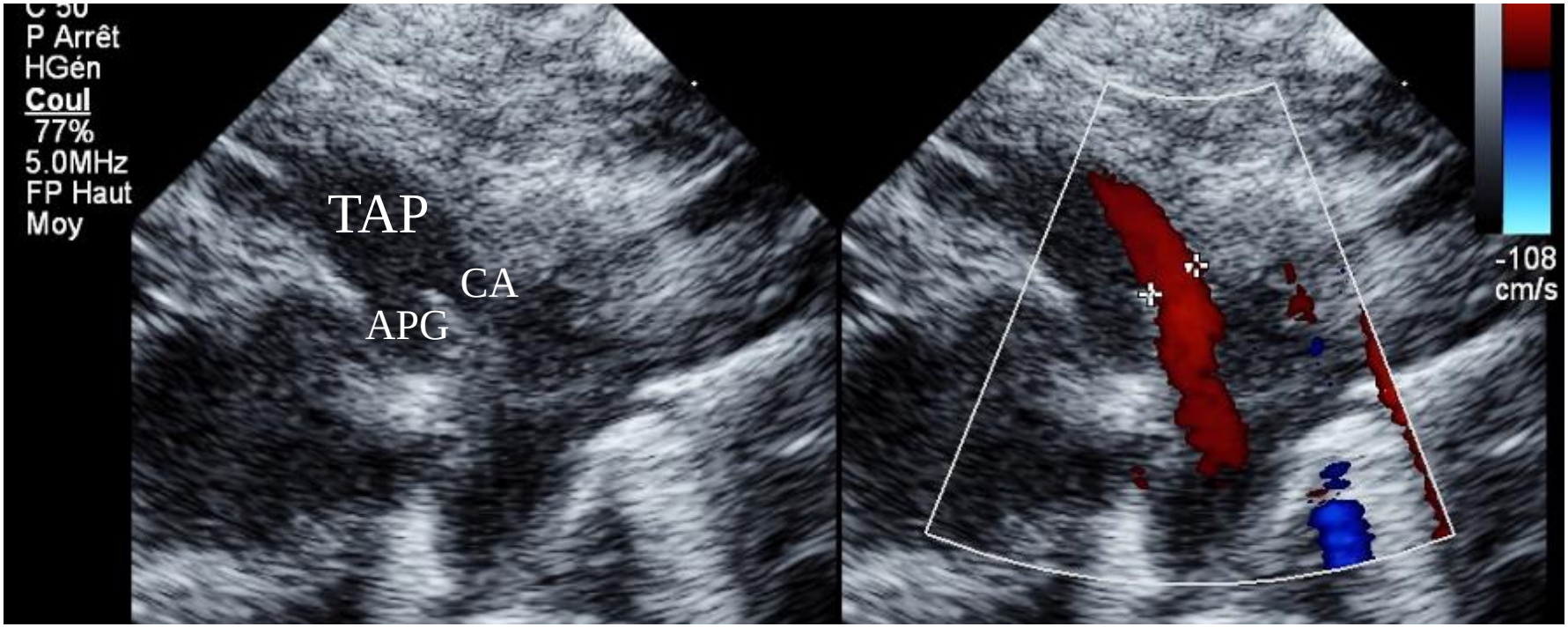
± Hypoxemia

Signes radiologiques



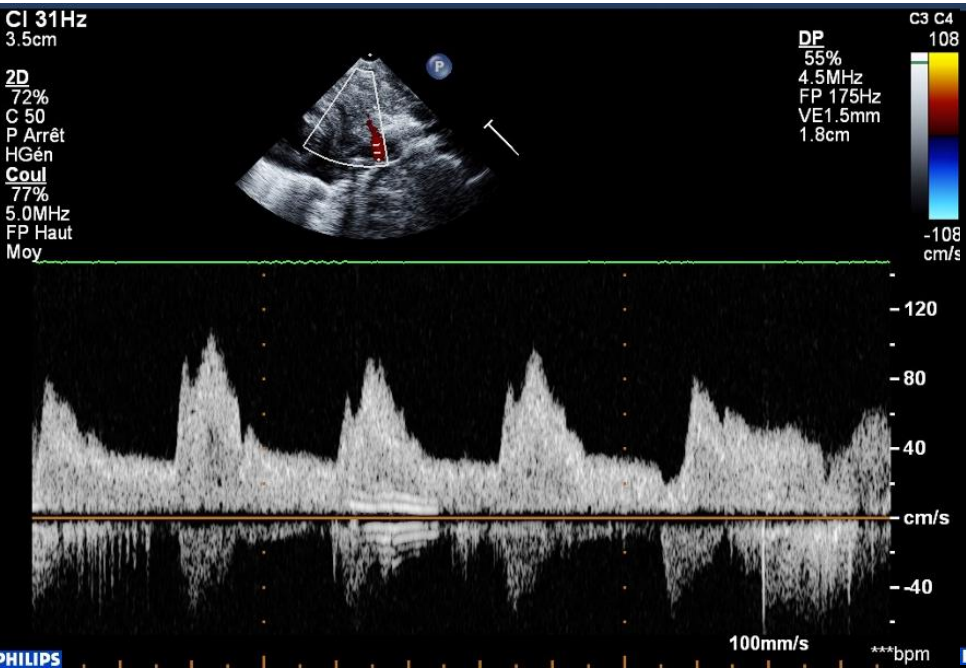
Cardiomégalie ICT > 60%,
surcharge pulmonaire

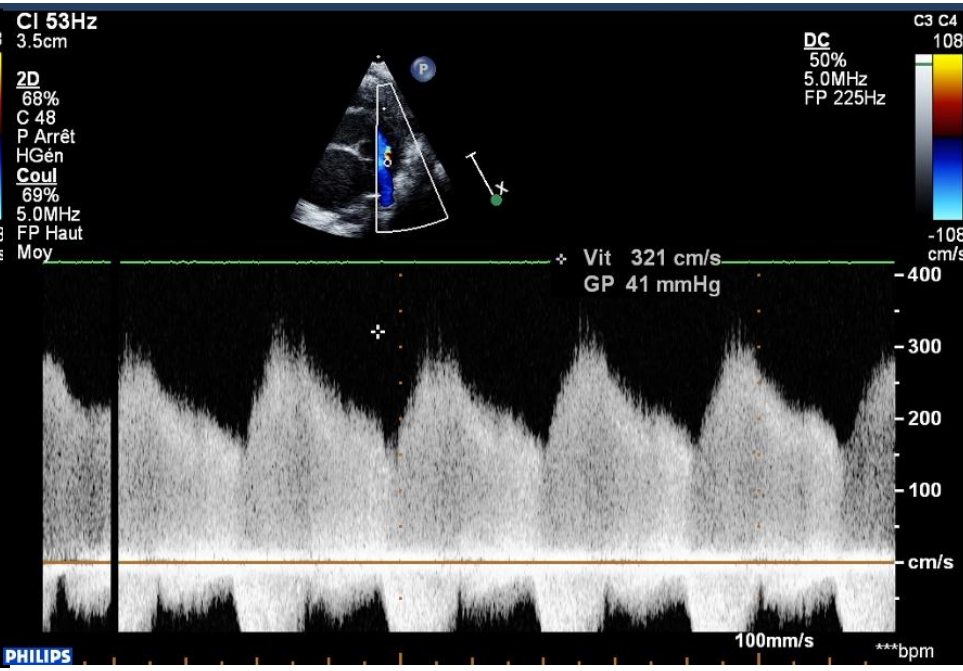
Significant PDA :
Débit systémique = $Q_{VG}/2$



DA > 1,4 mm/kg

Significant PDA

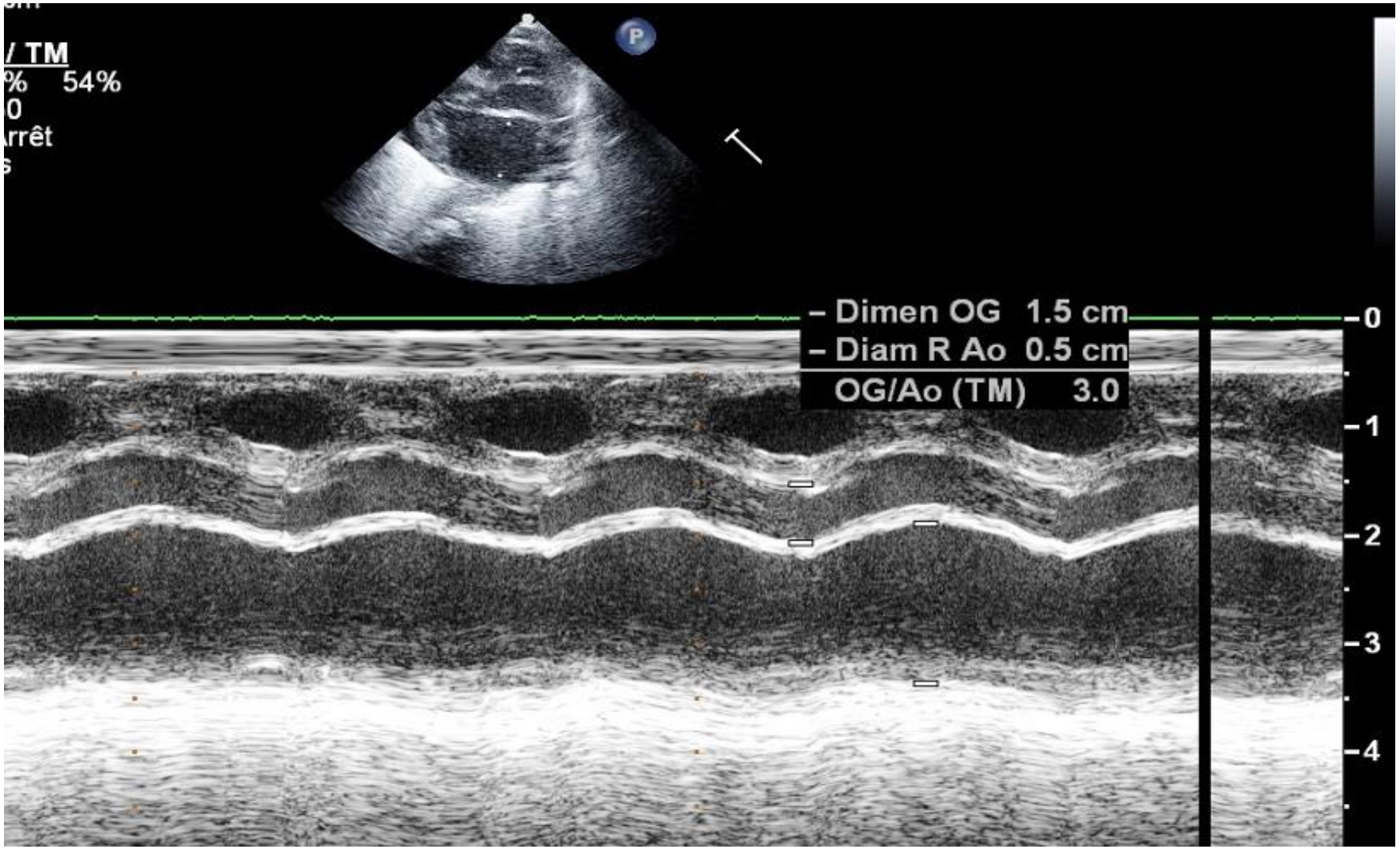




↑ PAP:

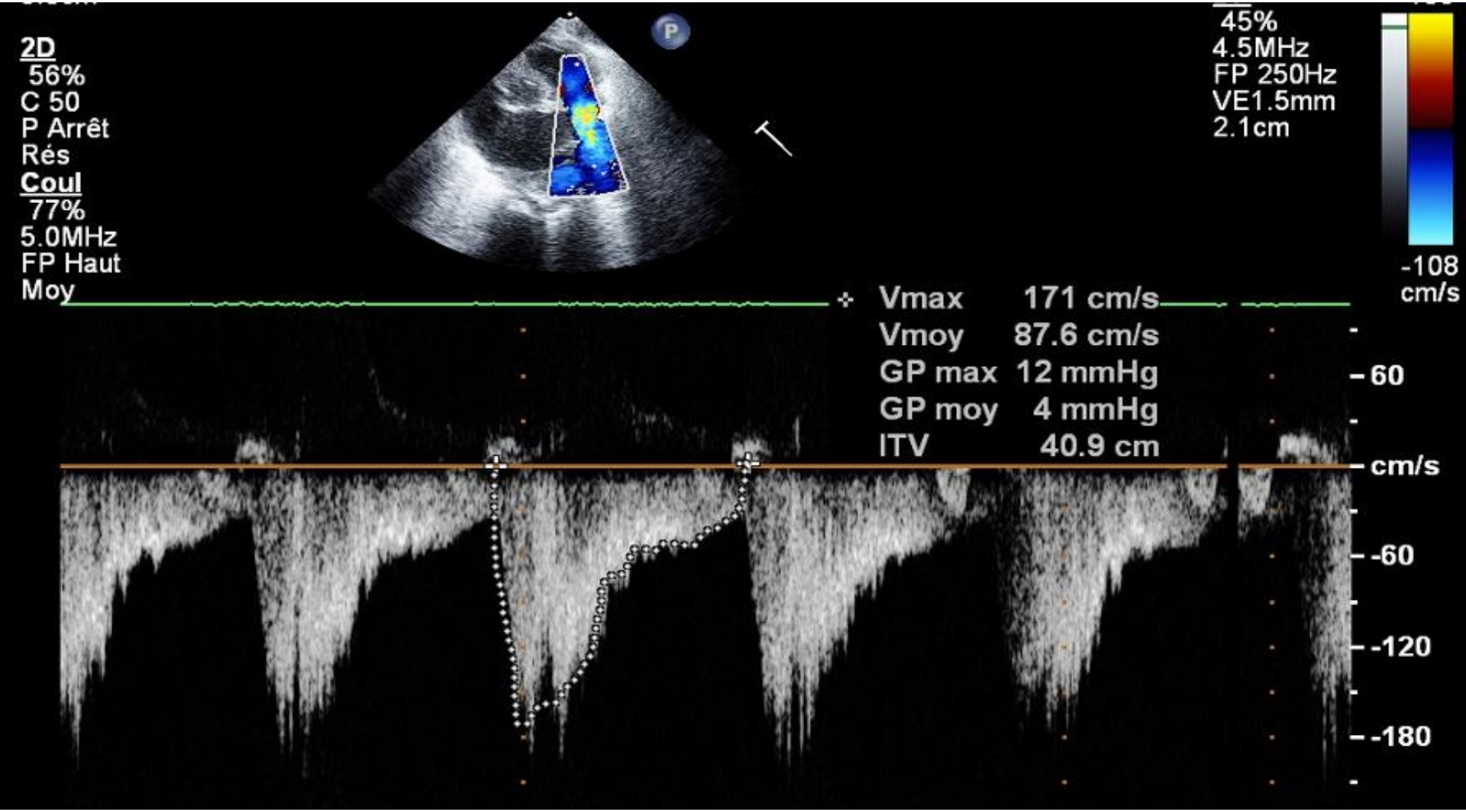
- Low flow velocities
- Pulsatile flow

Significant PDA



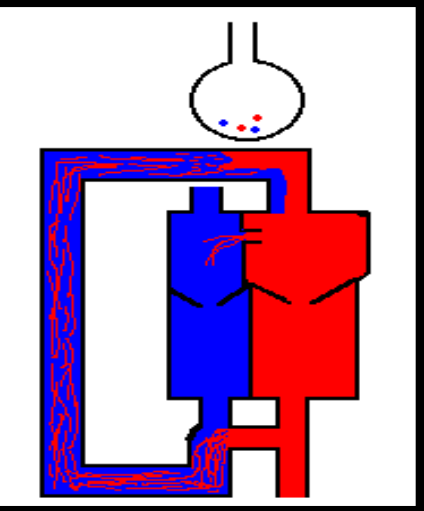
LA/Ao ratio > 1,4

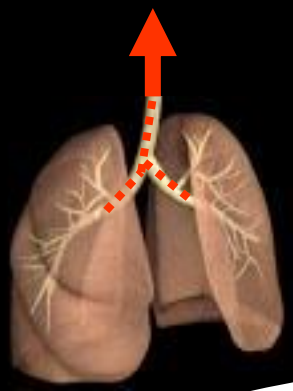
Significant PDA

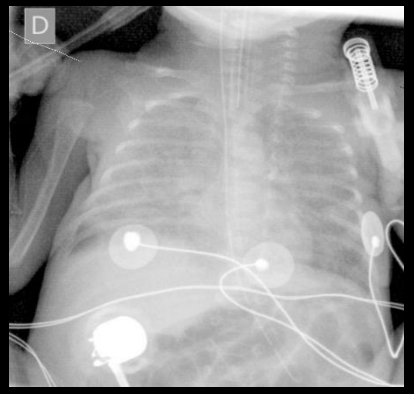


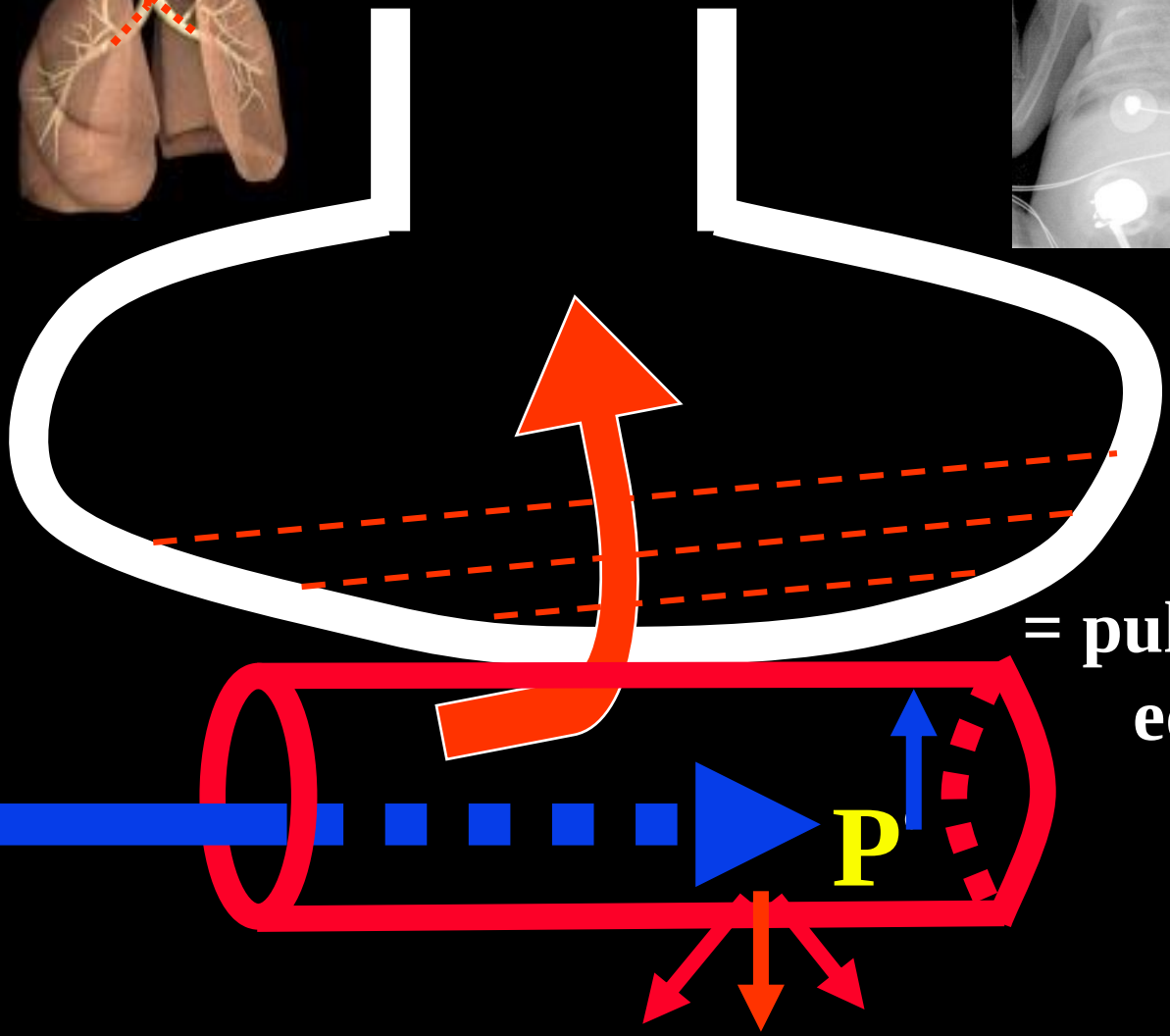
- Mean velocities in the LPA > 0,40 m/s
- Diastolic velocities in the LPA > 0,2 m/s

DA and pulmonary hemorrhage









Q_p

= pulmonary edema

Risque d'hemmoragie pulmonaire et canal artériel

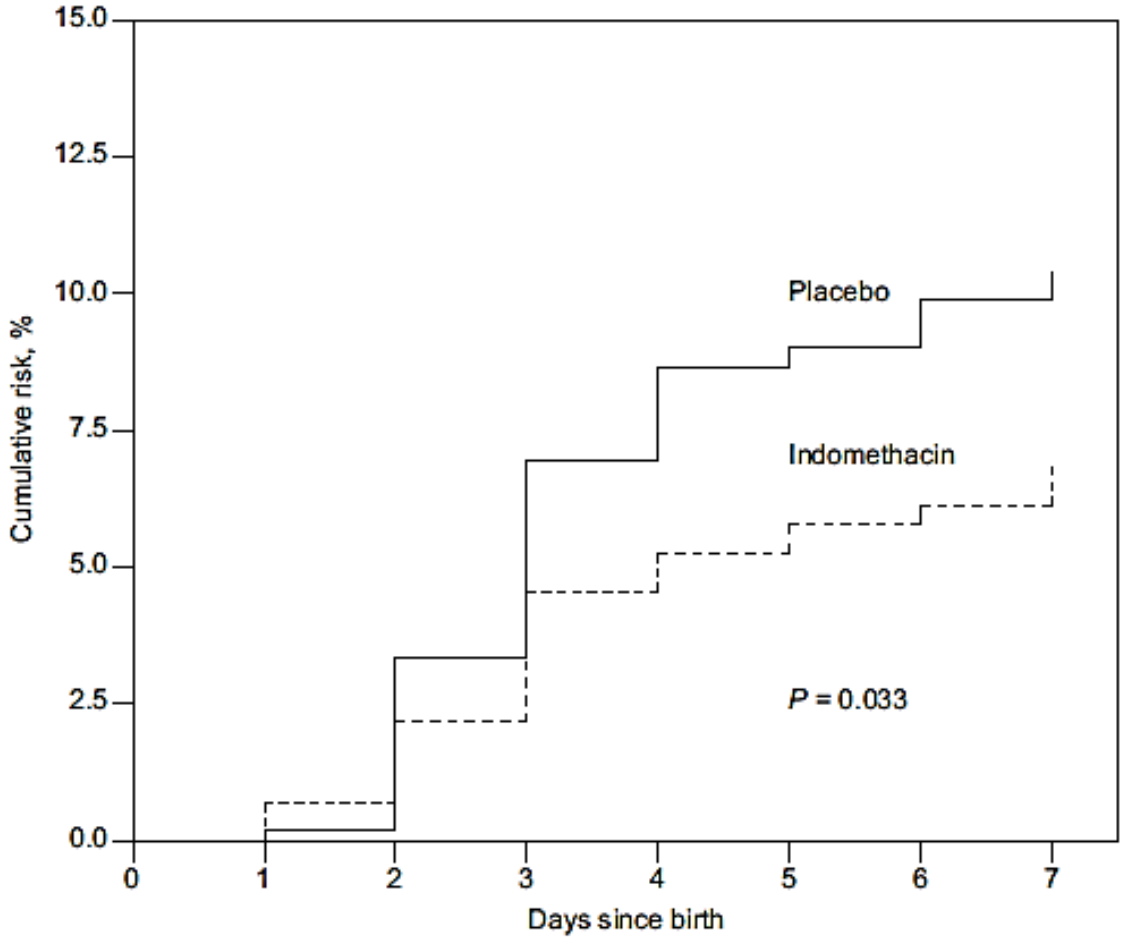


FIGURE 1
Kaplan-Meier estimates of the cumulative risk for serious pulmonary hemorrhage in prophylactic indomethacin and placebo groups during the first week of life.

Alfaleh, Pediatrics 2008

Artère mésentérique supérieure

- ↑ de l'I Résistance
  - Associé à PCA

  41 enfants <35 SA

Freeman–ladd M. J Perinatol. 2005;25:459

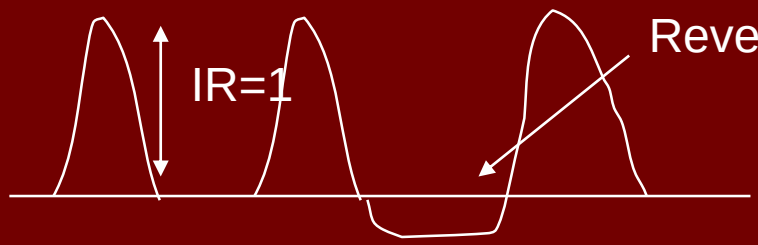
Shimada S. J Ped 1994;125:270

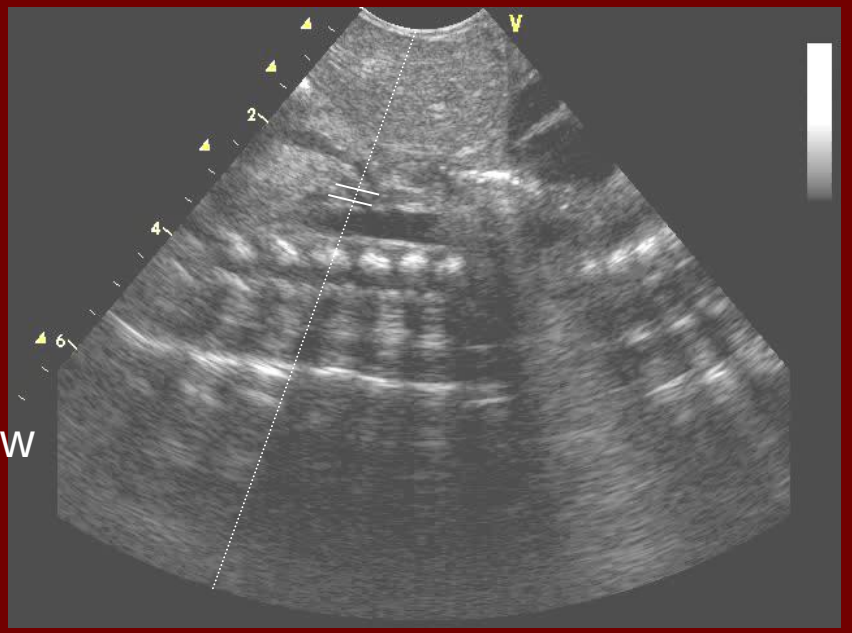
Coupe sous sternale

- ↓ ou inversion du flux en diastole

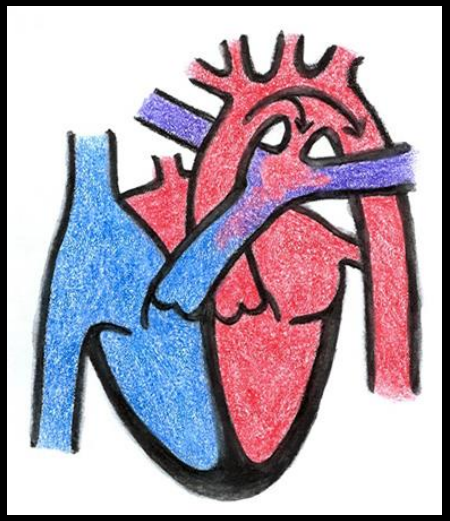
Etude avant après ligature

Wong SN.J Ultrasound Med. 1990 ;9:125





Outline



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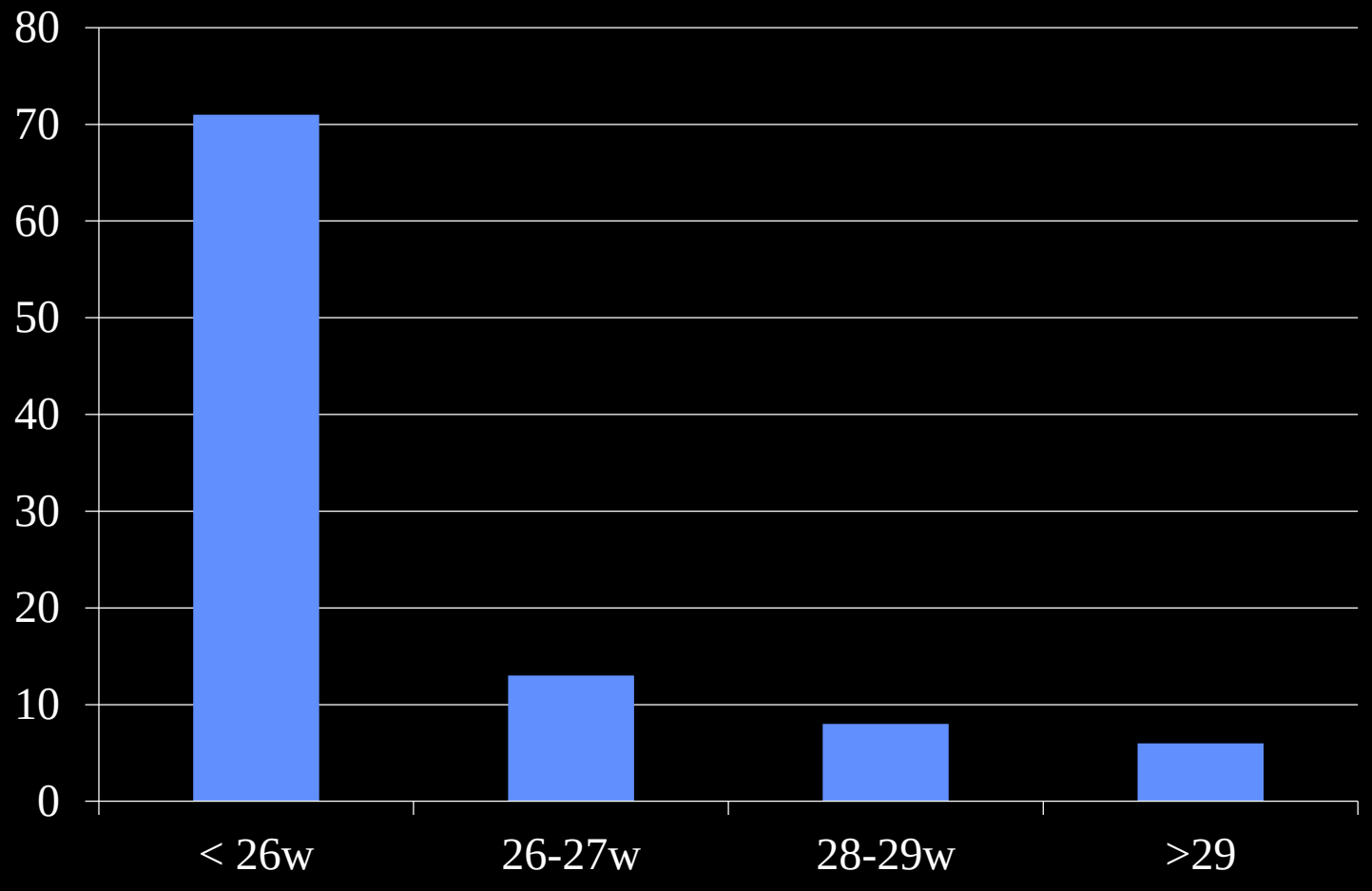
Age médian en jours à la fermeture du canal artériel

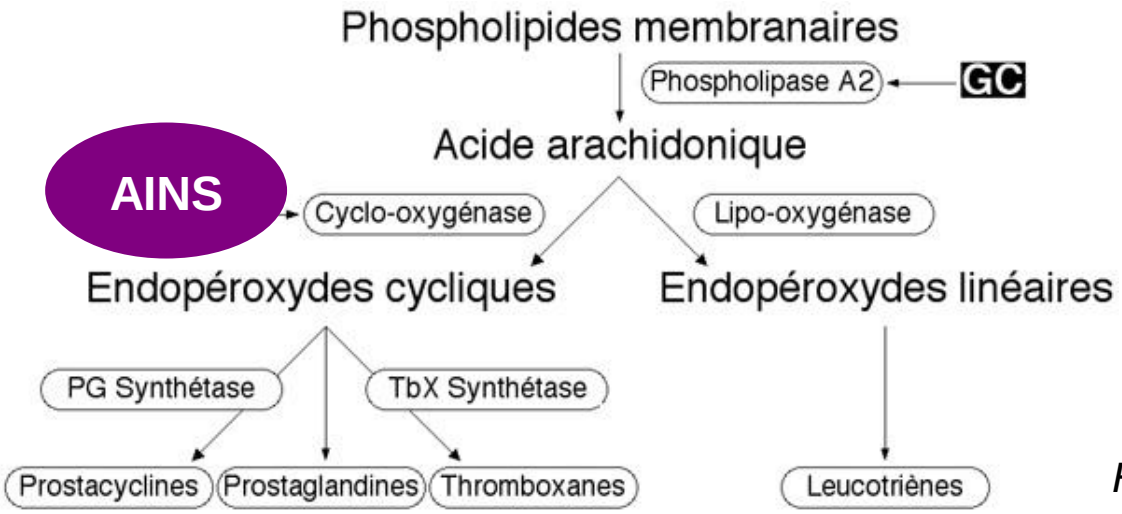


Traitement:

- **Ibuprofene IV 3j:**
  - Effets secondaires : perforation digestive, insuffisance rénale
- Paracétamol IV 6j (PO ?)
  - En cas de CI à Ibuprofen
- Fermeture chirurgicale
- Occlusion par cathétérisme

Ibuprofene

- Inhibiteurs non sélectifs des COX 1 et 2
- Inhibition synthèse prostaglandines
- Contraction cellules ductales
- Fermeture du canal artériel



Heymann, NEJM, 1976
Patel, Lancet, 1995

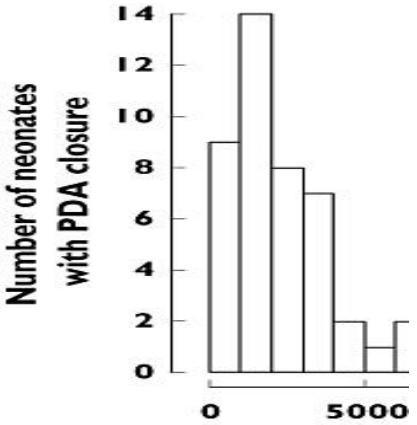
Posologie : Schéma standard

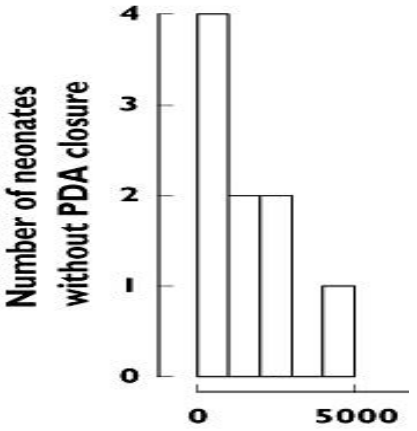
- 3 doses à 24 heures d'intervalle
  - 10 mg/kg J0
  - 5 mg/kg J1 et J2
- Diminution concentrations PG jusqu'à H72
- Efficacité : 40 à 60% fermeture CA
- Bonne tolérance clinico-biologique

Keady, Intensive and Critical Care Nursing, 2005
Ohlsson, Cochrane, 2013

Posologie : Adaptation âge ?

- Etude pharmacologique sur 66 prématurés
- Dosage ibuprofène après schéma standard (10-5-5)
- Relation entre AUC et pourcentage fermeture CA
- Indépendant AG
- Clairance augmente avec âge post-natal
- Modèle ajustement posologie :
  - <70 h : 10/5/5 mg/kg
  - 70-108 h : 14/7/7 mg/kg
  - > 108-180 h : 18/9/9 mg/kg



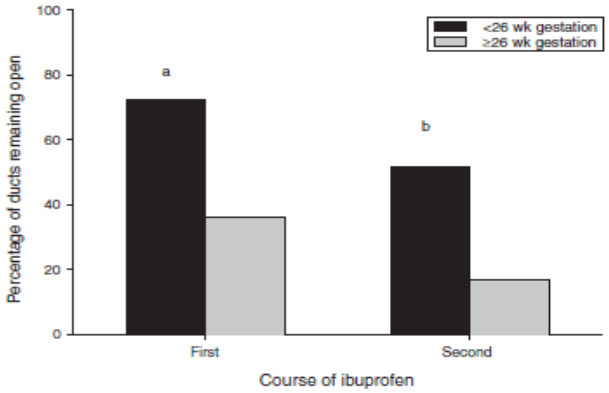


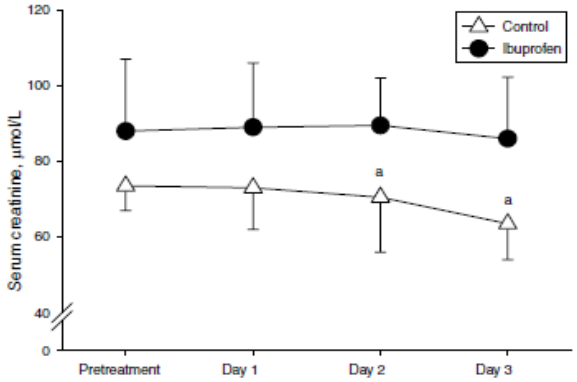
	Actual dosage	Proposed dosage
All neonates	88%	94%
Age <70 h	97.7%	97.7%
Age 70–108 h	83.5%	93%
Age >108 h	50%	80%

Hirt, British Journa Cli Pharm, 2008

Intérêt d'une deuxième cure ?

- 40-60% fermeture après 1è cure
- Taux fermeture 2è cure identique
- Moins bonne réponse chez WLBW
- 1è cure tardive = facteur prédictif 2ècure
- Pas plus d'EI (créatinine augmentée)





Van Der Lugt, European Journal of Pediatrics, 2012
Richards, Pediatrics 2009

Quand traiter ?

- Prophylactique : < H24
  - Diminution risque HIV sans augmentation survie long terme
  - Effets secondaires et traitement inutiles
- Traitement curatif CA pré-symptomatique : H24/48
  - Diagnostic échographique CA
  - Diminution traitement inutiles
- Traitement CA significatif : > H72
  - Augmentation risque effets secondaires
  - Majoration bas débit mésentérique, rénal, cérébral
  - Augmentation risque échec

Golombeck, SIBEN's clinical consensus, Anales de Padiatria, 2008
Clyman, The Journal of Pediatrics, 1996

En pratique : en France

- Dépistage échographique précoce <28 SA (24-72 h de vie)
- Traitement curatif :
  - Détresse respiratoire (VM ou VNI)
  - CA hémodynamiquement significatif
- Cure de 3 jours d'Ibuprofène (AMM depuis 2004)
  - 10 mg/kg J0
  - 5 mg/kg J1 et J2
- Deuxième cure si persistance du CA
- Traitement chirurgical si échec ou CI traitement médical

Gournay, Archives de Pédiatrie, 2011

Traitement:

- Ibuprofene IV 3j:
  - Effets secondaires : perforation digestive, insuffisance rénale
- Paracétamol IV 6j (PO ?)
  - En cas de CI à Ibuprofen
- Fermeture chirurgicale
- Occlusion par cathétérisme

… mais questions non résolues :

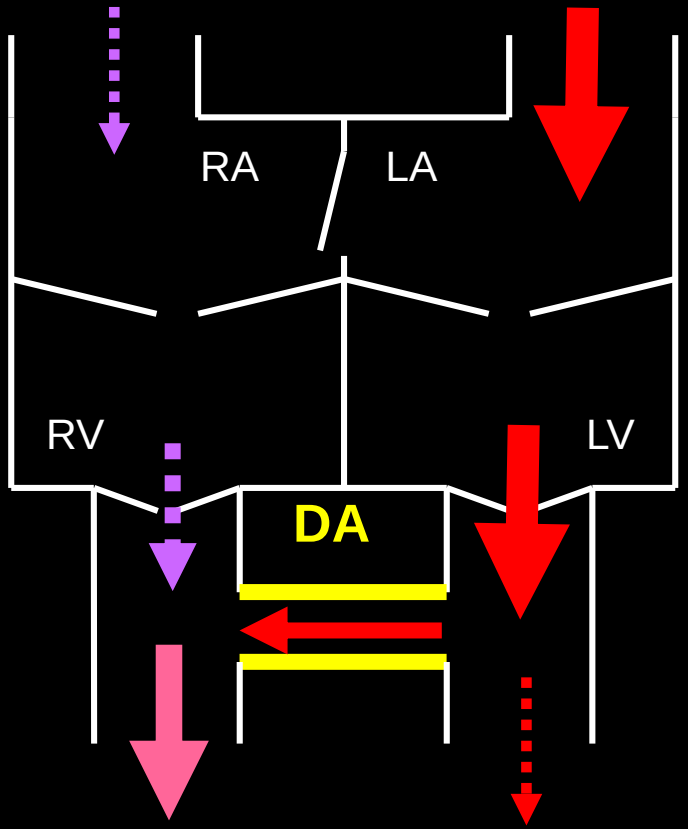
- Quand débuter le traitement ?
- Ibuprofene vs Paracétamol ?
- Doses ?
- Timing chirurgie ? Indication ?
- Place du cathétérisme ?

Symptomatic treatment ?

(excluding Ibuprofen/paracetamol)

↓ Left heart overload

- **Fluid restriction ?**



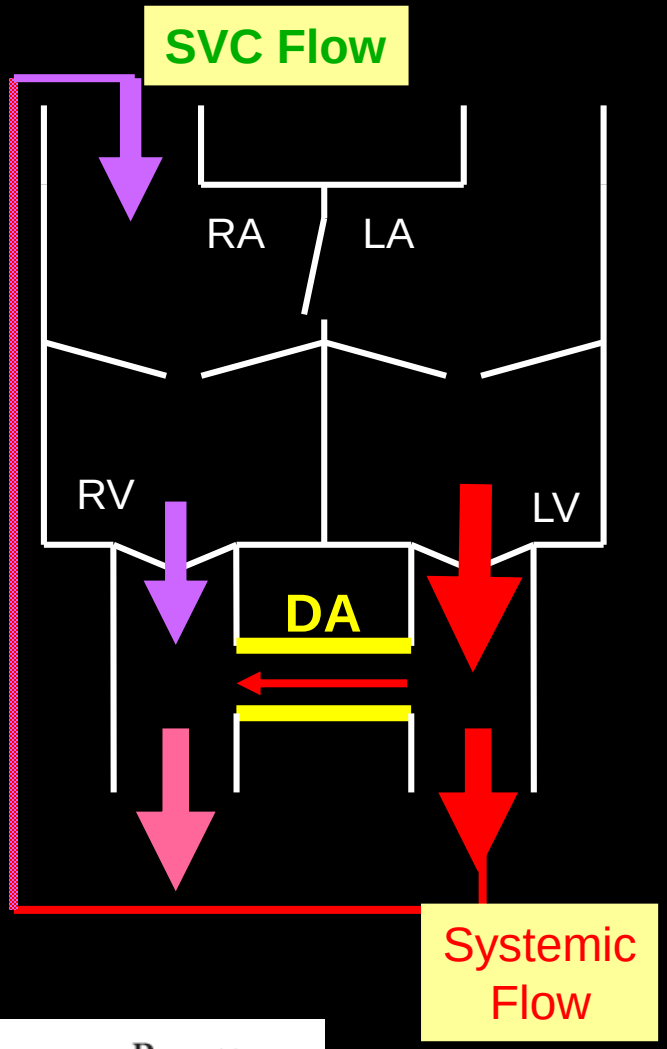
⇑ PVR ?

- **FiO_2**
- **Vasoactive drugs**
- **⇑ Hb**
- **Mechanical ventilation**

Do we need to decrease fluid intake ?

- GA = 25±1 w, PN = 850±150 w
- n = 18
- Clinical and echocardiographic symptoms
- Mean postconceptional age = 27±1SA

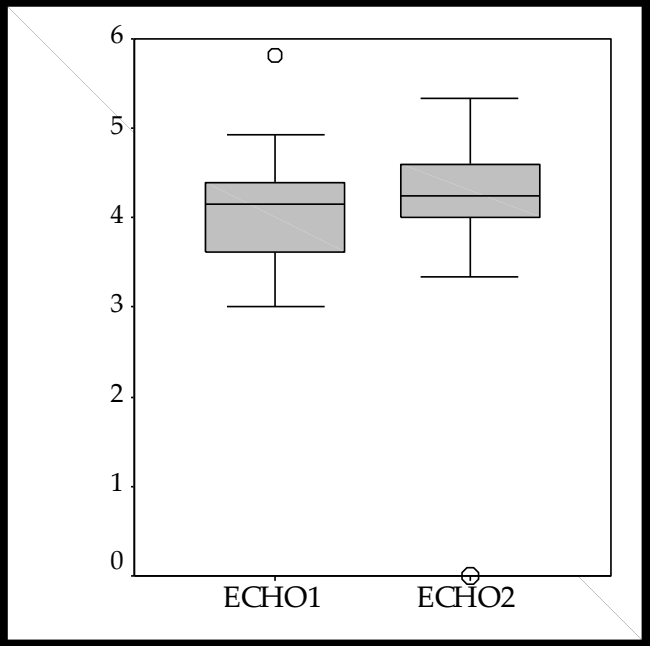
- Fluid restriction : **from 145 ml/kg to 100 ml/kg**
- Assessment before and 24Hr after fluid restriction

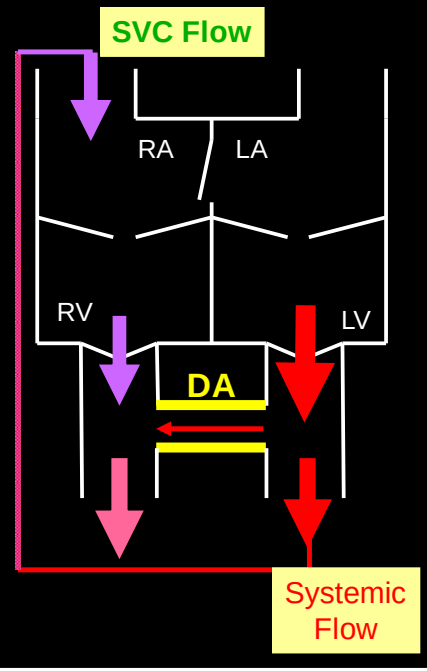


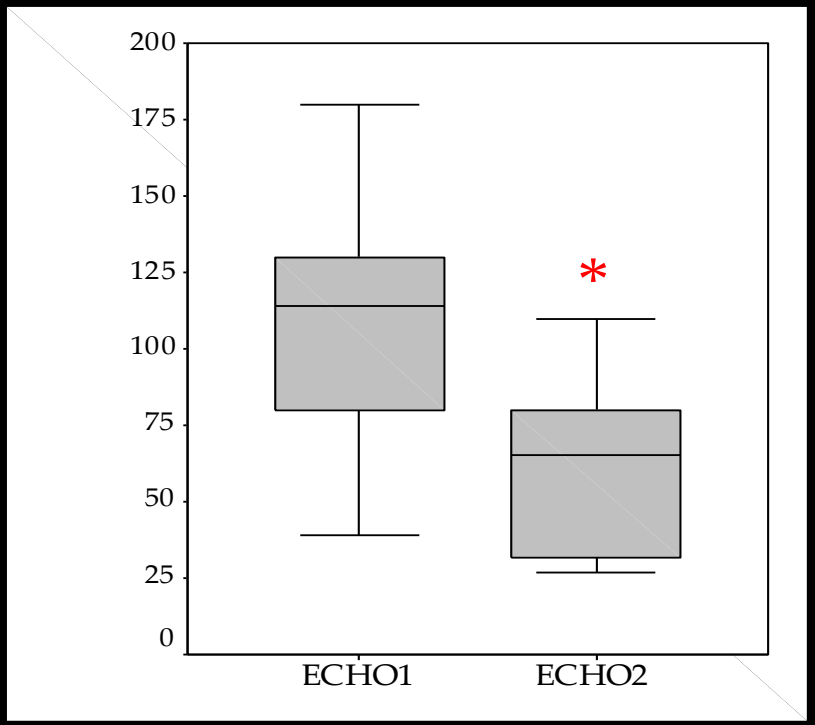
ORIGINAL ARTICLES
www.jpeds.com • The Journal of Pediatrics

Hemodynamic Effects of Fluid Restriction in Preterm Infants with Significant Patent Ductus Arteriosus

Julie De Buyst, MD[1], Thameur Rakza, MD[2,3], Thomas Pennaforte, MD[2], Anne-Britt Johansson, MD[1], and Laurent Storme, MD[2,3]







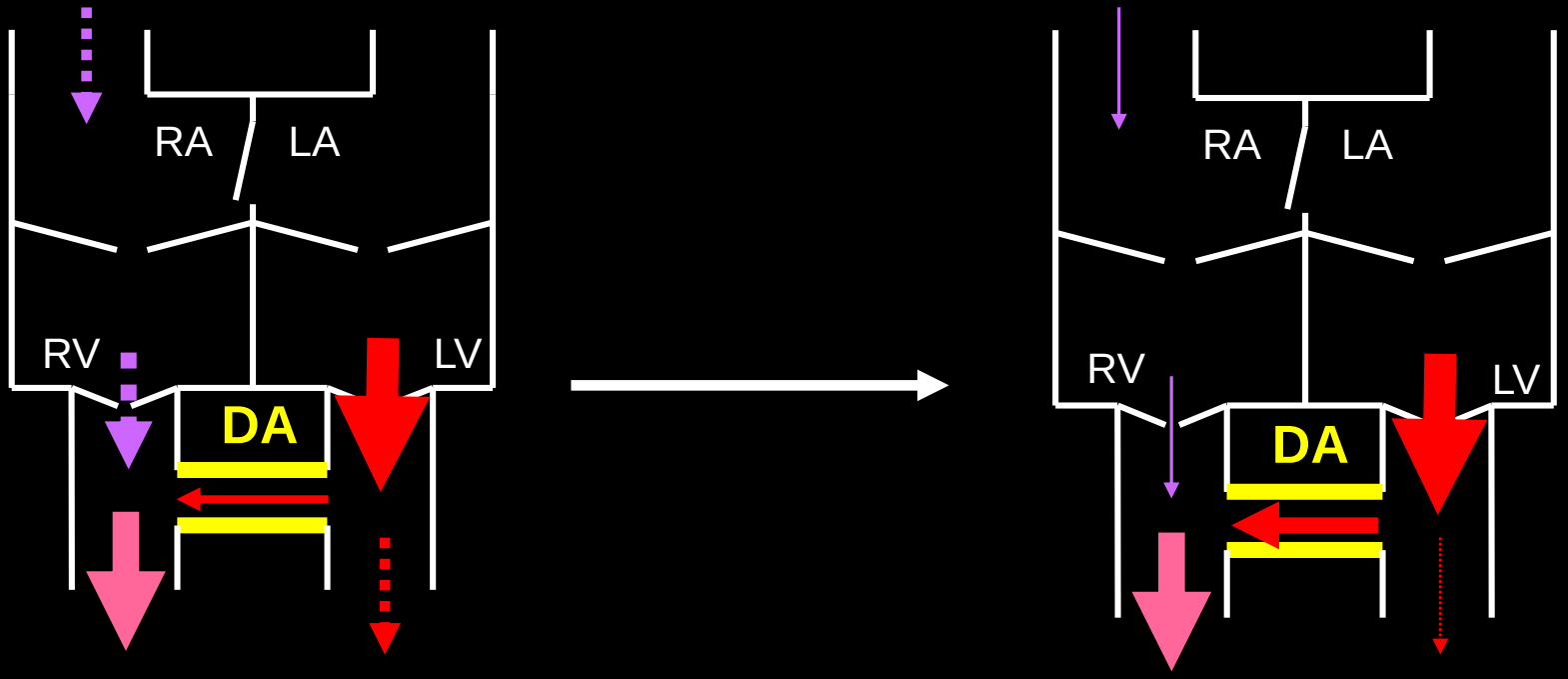
J De Buyst, J Pediatr 2011

Table II. Comparison between the echocardiographic variables for ECHO 1 and ECHO 2 (N = 18)

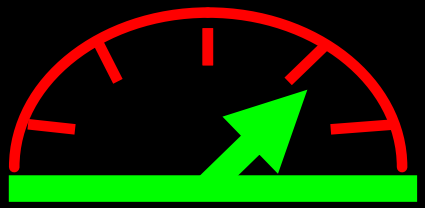
	ECHO 1	ECHO 2
Maximal flow-velocity in DA (m/s)	1.18 ± 0.38	1.23 ± 0.58
Mean flow-velocity in LPA (m/s)	0.58 ± 0.14	0.60 ± 0.12
End-diastolic flow-velocity in LPA (m/s)	0.22 ± 0.04	0.26 ± 0.04
LA:Ao	1.68 ± 0.28	1.65 ± 0.21
Mean flow-velocity in ascending aorta (m/s)	0.46 ± 0.10	0.43 ± 0.08
LVSF (%)	54 ± 9	51 ± 8
Mean blood flow-velocity in the MCA (m/s)	0.17 ± 0.05	0.13 ± 0.04
RI in the MCA	0.92 ± 0.09	0.98 ± 0.04
Mean blood flow-velocity in the SMA (m/s)	0.24 ± 0.04	0.15 ± 0.03*
RI in the SMA	0.79 ± 0.08	0.96 ± 0.09*

J De Buyst, J Pediatr 2011

Effects of decreased fluid intake



↓ PVR



⇑⇑ SVR

Sympathetic activation

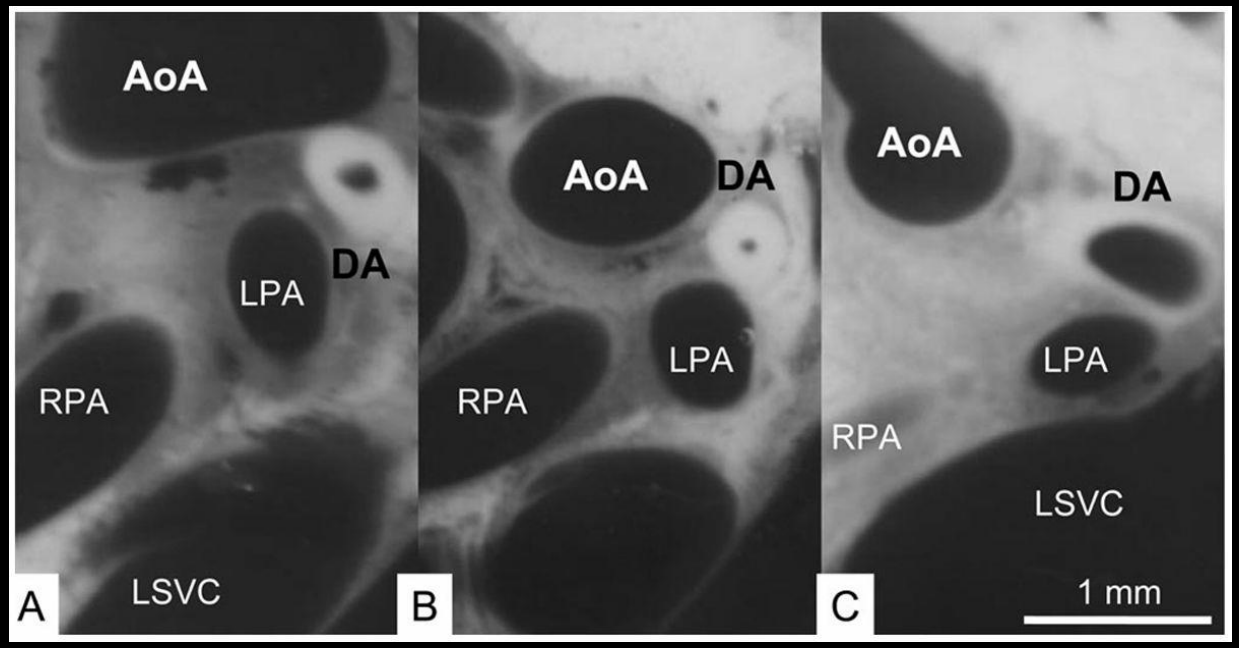
J De Buyst, J Pediatr 2011

Acta Paediatr. 2012 August ; 101(8): 835–845. doi:10.1111/j.1651-2227.2012.02699.x.

Unexpected Extra-renal Effects of Loop Diuretics in the Preterm Neonate

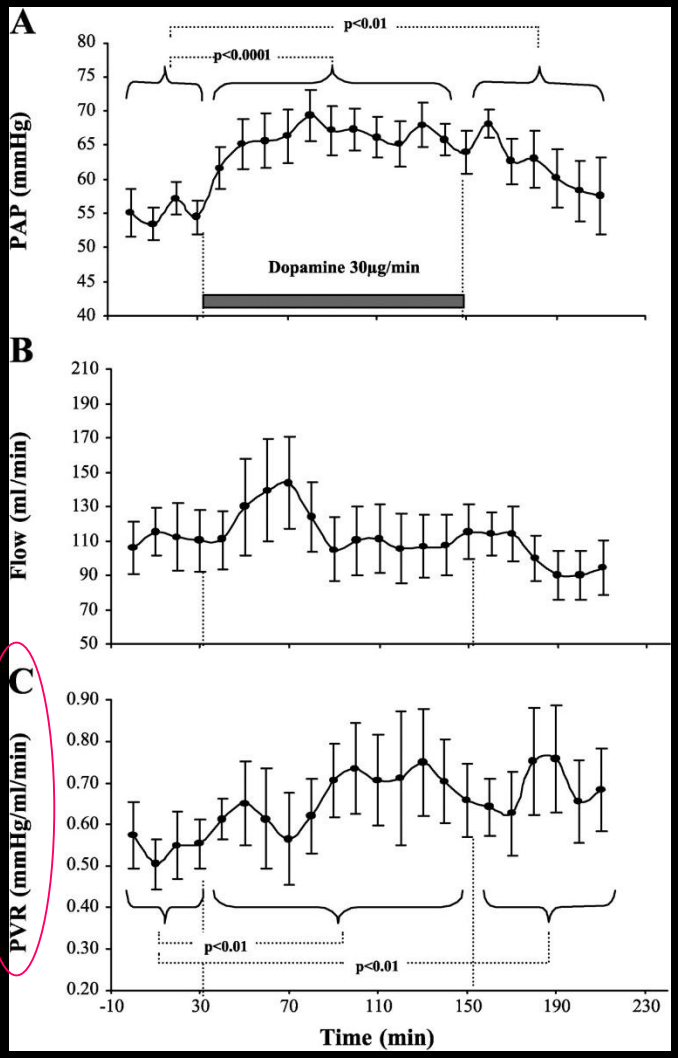
Robert Cotton[1], Sandra Suarez, and Jeff Reese

- Diurétique expose aux mêmes risques que restriction hydrique;
- Lasilix : ⇑ PDA through ⇑ PGE1 release

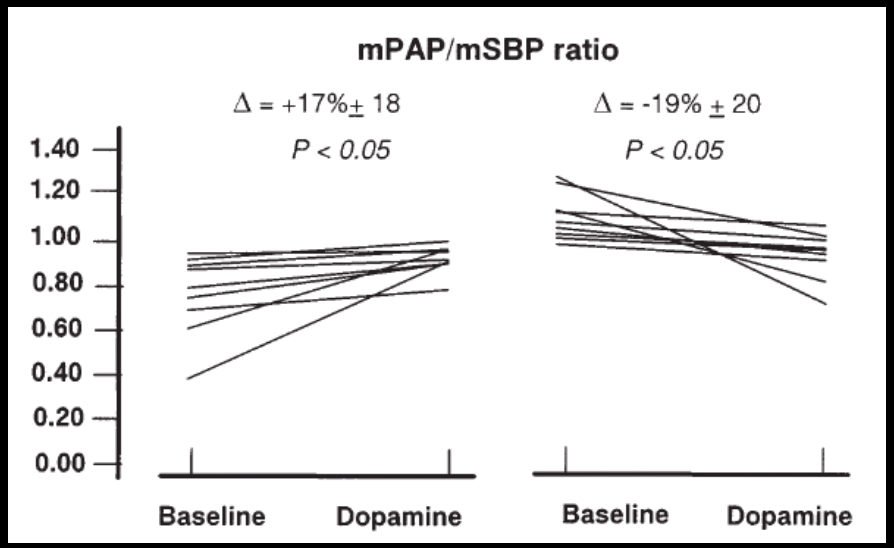


At 60 min At 120 min After lasilix

Dopamine for hypotension ?



Jaillard S, *Am J Physiol*. 2001 ;281:R607



Liet JM, *J Pediatr* 2002;140:373-5

Population

17 infants

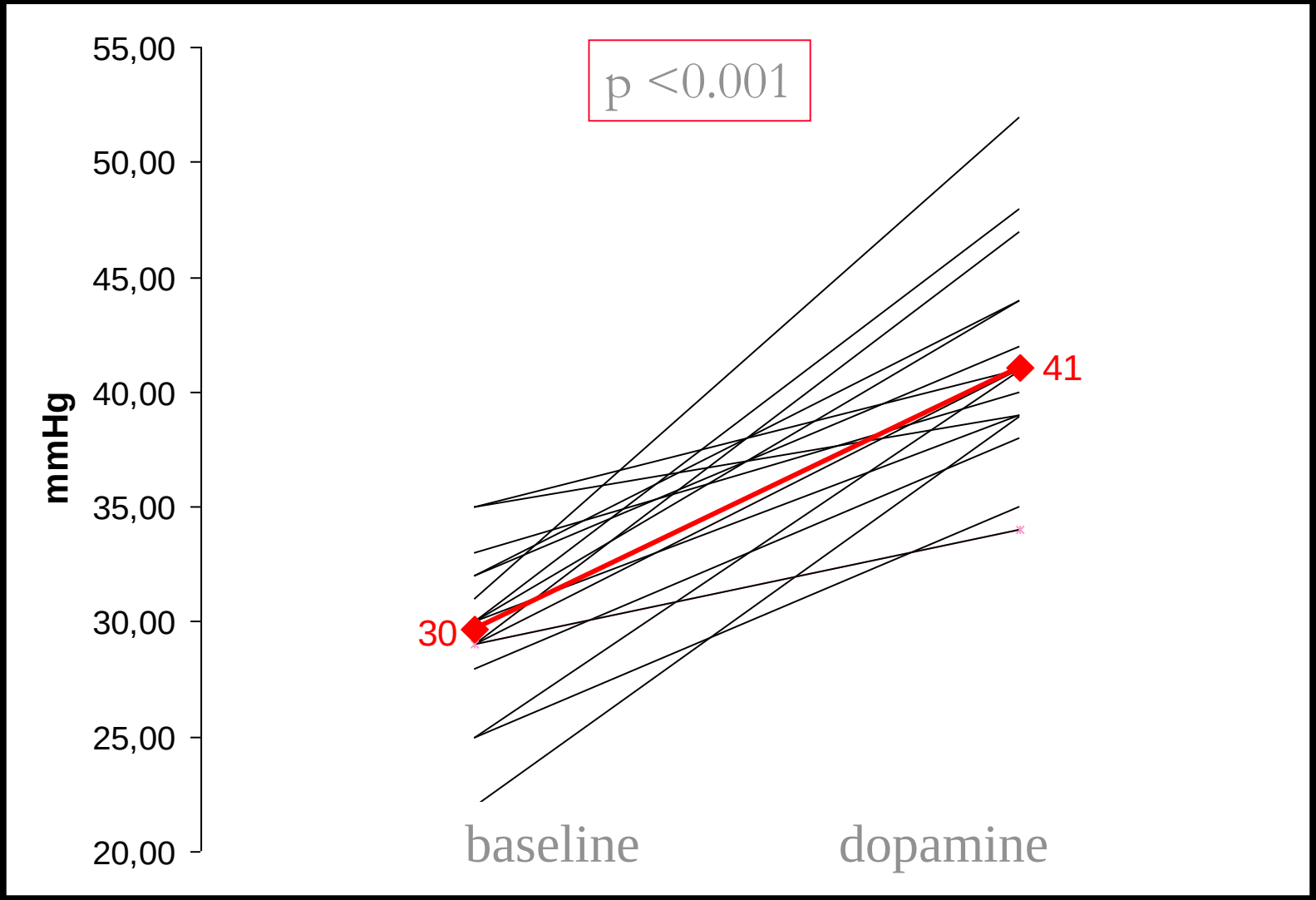
Gestational age	28 ± 2 weeks
Weight	1050 ± 400 g
Age at treatment	5 days [2 – 13]
Ibuprofen course	1 or 2
Dopamine	8 ± 2,5 µg/Kg/min

Hypotension in Preterm Infants with Significant Patent Ductus Arteriosus: Effects of Dopamine

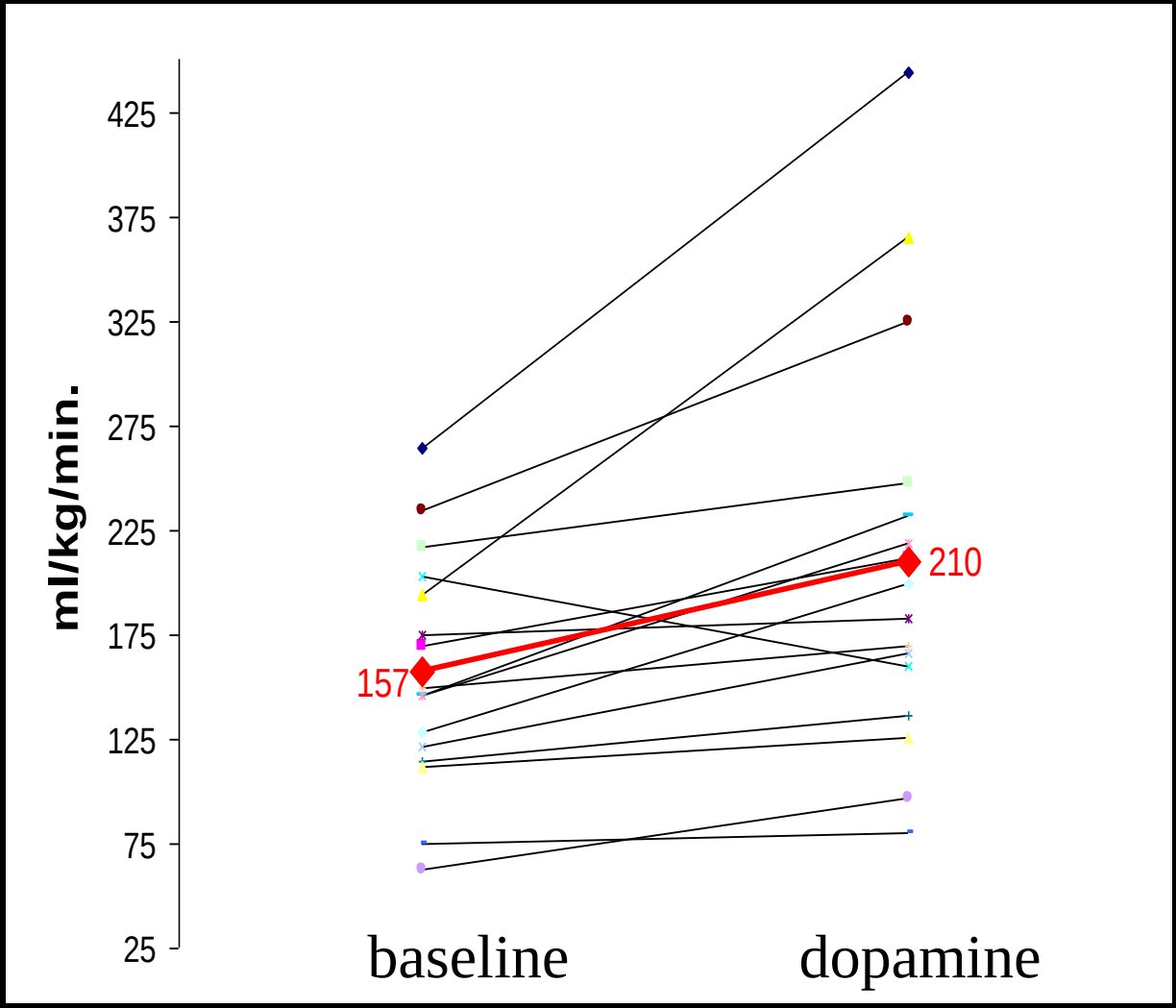
ANTOINE BOUISSOU, MD, THAMEUR RAKZA, MD, SERGE KLOSOWSKI, MD, PIERRE TOURNEUX, MD, MARIE VANDERBORGHT, MD, AND LAURENT STORME, MD, PHD

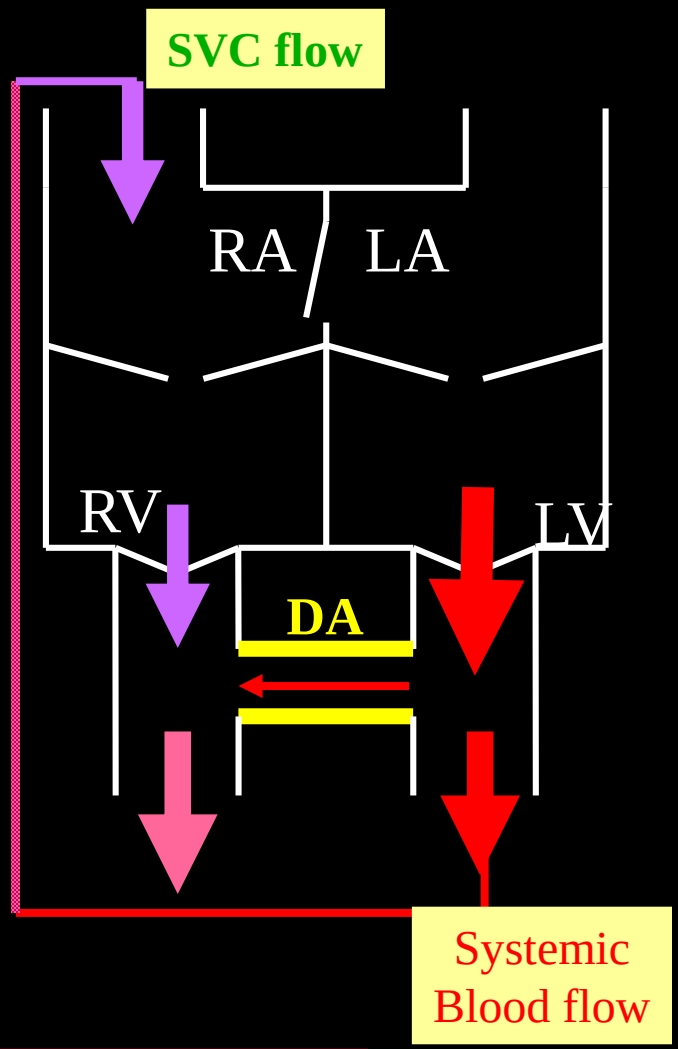
(J Pediatr 2008;153:790-4)

Arterial pressure



Superior vena cava flow





Increased by 31 %[14 - 54] (p= 0.002)

Results

Parameters	baseline	dopamine	p
DA diameter (cm)	**0.24 ± 0.05**	**0.24 ± 0.05**	**0.74**

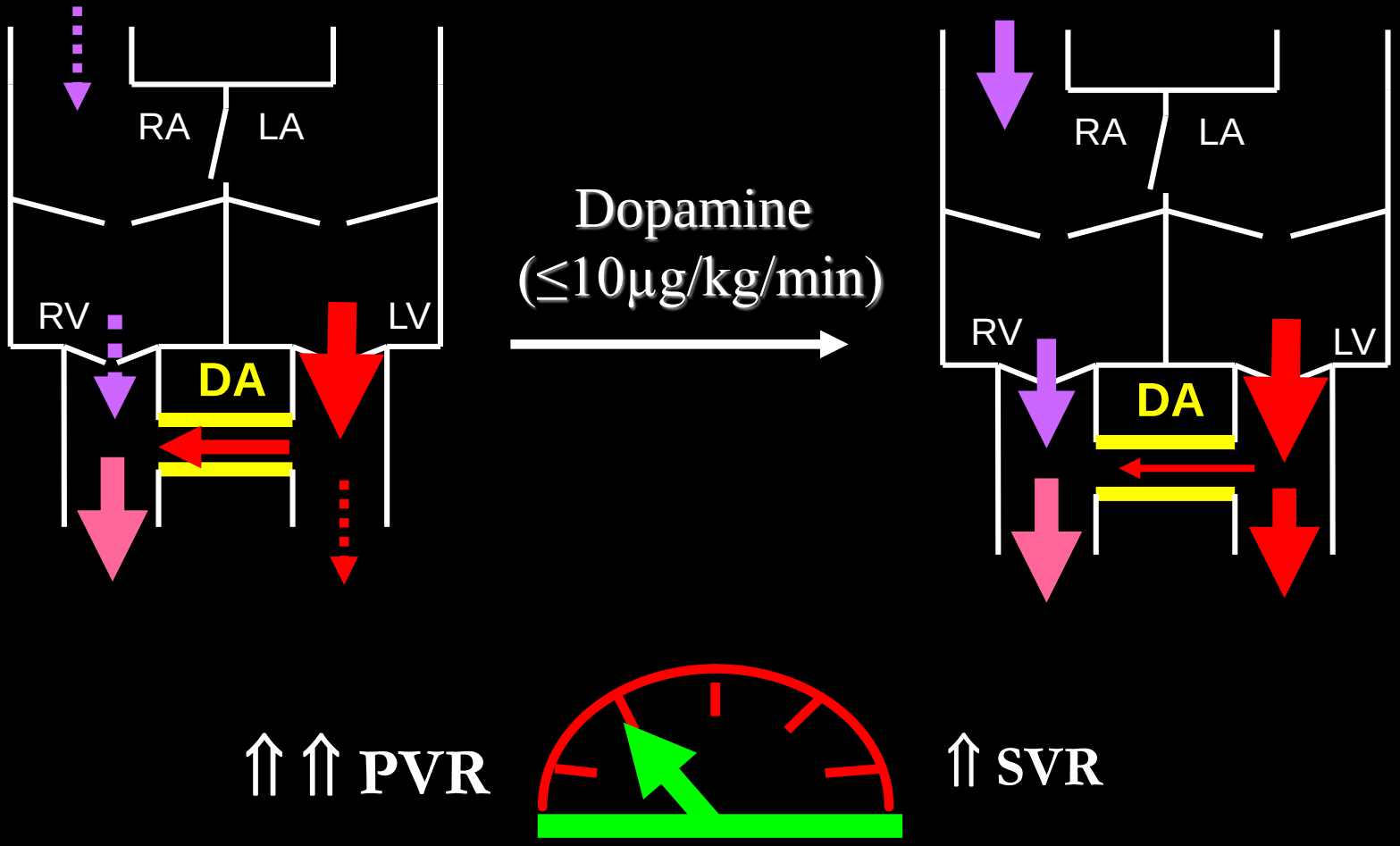
A Bouissou, J Pediatr 2008

Tissue perfusion

Parameters	baseline	dopamine	p value
Mesenteric Art. RI	0.96 ± 0.15	0.82 ± 0.17	0.03
Cerebral Art. RI	0.93 ± 0.19	0.76 ± 0.18	0.001
Blood lactate (mmol/l)	1,82 ±1,55	1,38 ±1,12	0,056

A Bouissou, J Pediatr 2008

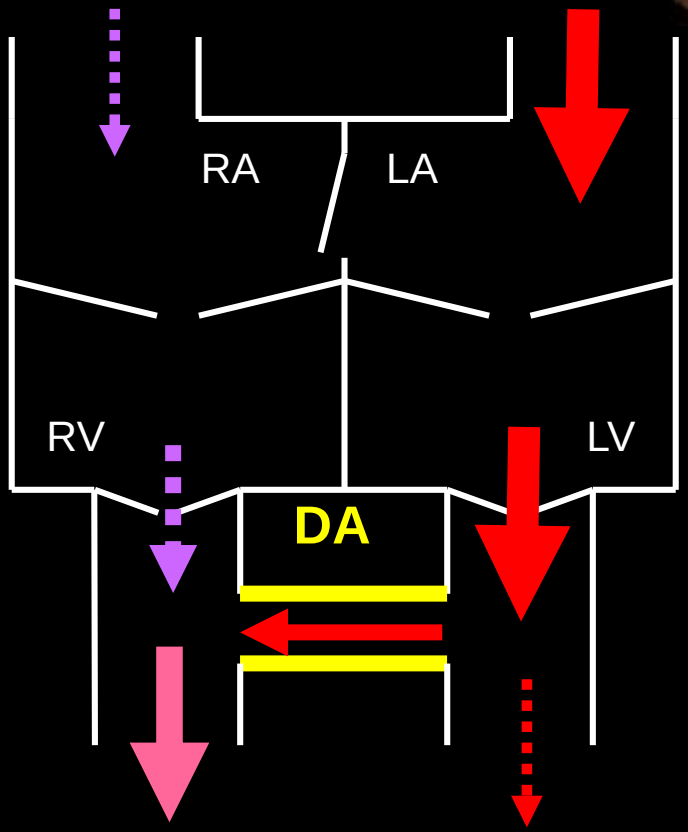
Dopamine decreases DA shunting



Bouissou A, J Pediatr 2008

Best ventilatory mode ?

↓ pulmonary Edema ?



⇑ LAP ?

⇓ PVR ?

Impaired Lung Function After Intubation and Mechanical Ventilation for Surgical Ligation of the Ductus Arteriosus in Preterm Infants

Thierry Dzukou, MD,* Thameur Rakza, MD,*† Antoine Bouissou, MD,* Ceneric Alexandre, MD,* Serge Dalmas, MD,†‡ and Laurent Storme, MD*†

Journal of Cardiothoracic and Vascular Anesthesia, Vol 25, No 6 (December), 2011: pp 1000-1004

Results

- 18 newborn infants
  - Gestational age: 25 - 30 weeks (27 ± 1 SA)
  - Weight: 700 - 1180 g (930 ± 160 g).

Dzukou T, J Cardiothorac Vasc Anesth. 2011

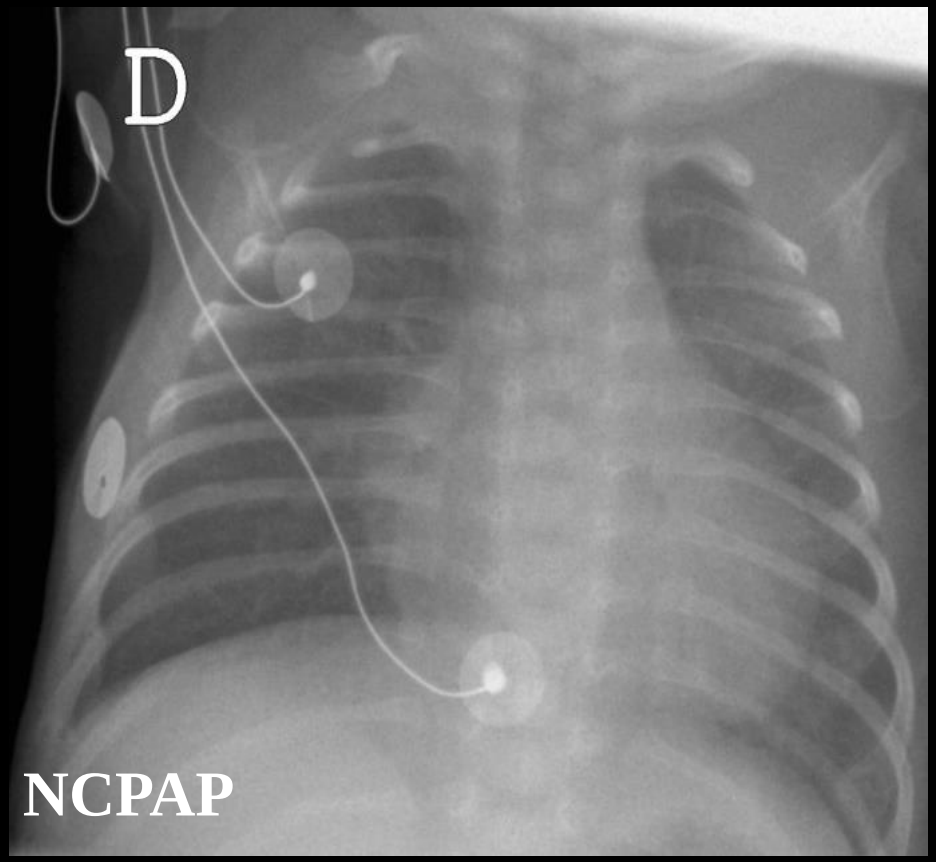
	1 Hr before	1 Hr after
FiO_2 (%)	21	27± 4*
Airway pressure (cmH_2O)	4	12±3*
SpO_2 (%)	97±2	92±3*
pH	7.32±0.06	7.25±0.05*
PCO_2 (mmHg)	43±4	63±8*

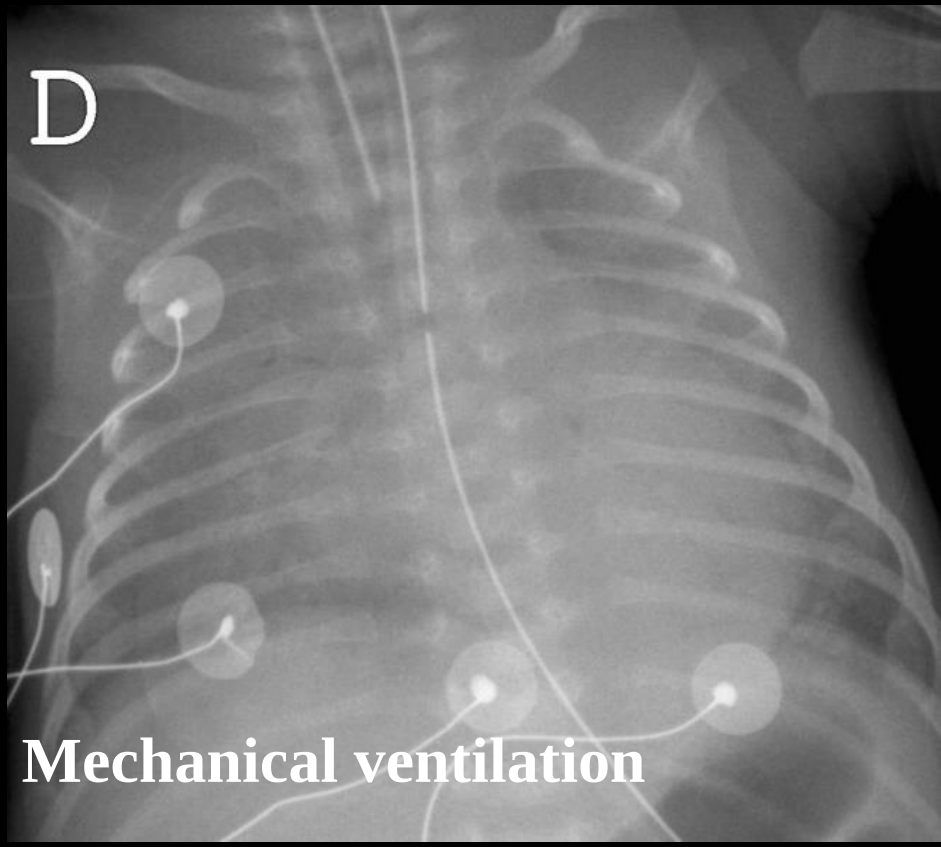
* = p<0.05

Dzukou T, J Cardiothorac Vasc Anesth. 2011

1 Hr avant

1 Hr après



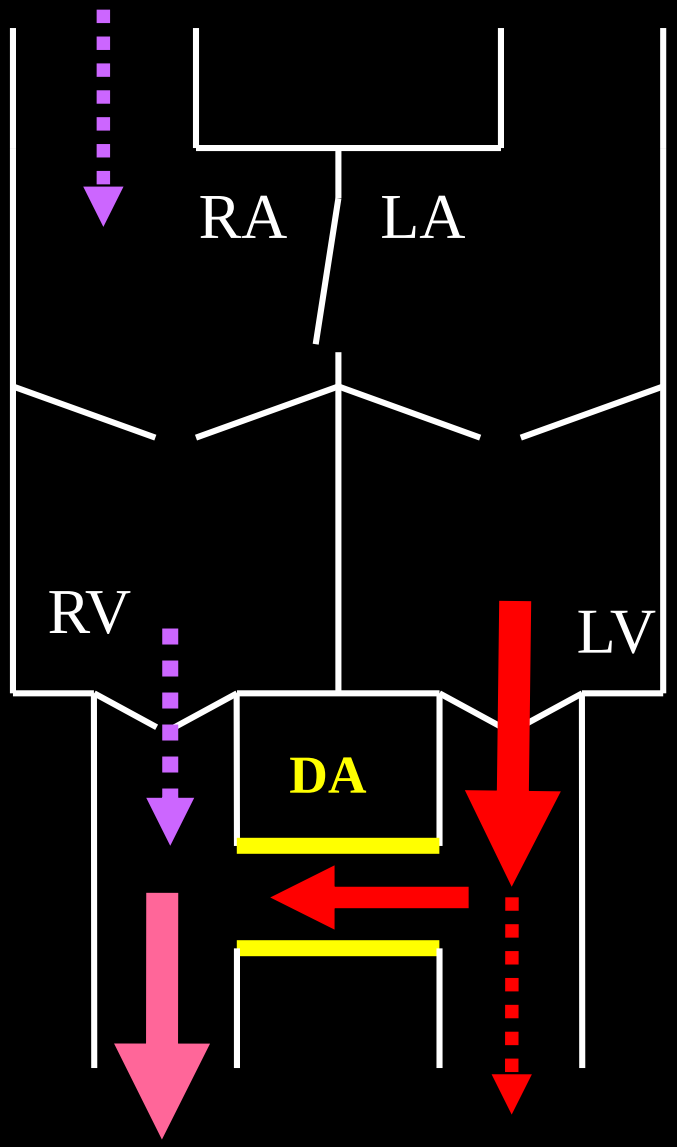


CPAP

Mechanical ventilation

Dzukou T, J Cardiothorac Vasc Anesth. 2011

PARAMETRE	1 hr AVANT	1 hr APRES
Diamètre du CA (mm)	2.8±0.6	2.7±0.6
Vitesse télédiastolique artère pulmonaire gauche (m/s)	0.3±0.07	0.3±0.1
Vitesse moyenne APG (m/s)	0.5±0.1	0.47±0.1
OG/AORTE	1.9±0.2	1.8±0.2
Fraction de raccourcissement du VG (%)	34.6±3.8	34.3±4
Débit du VG (ml/kg.min)	350.3±95	379±85
Débit de la veine cave supérieure (ml/kg.min)	131±22	175±33



DA in IUGR

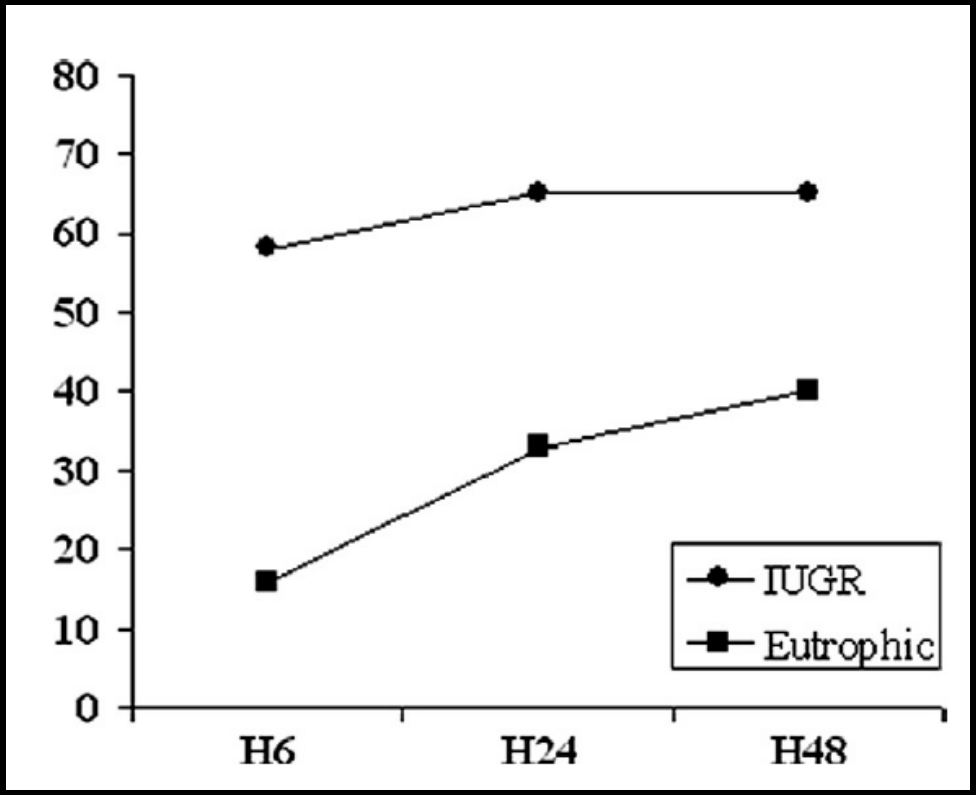
Table I. General characteristics of the studied population

	Eutrophic (n = 31)	IUGR (n = 17)	*P*
Gestational age (weeks)	29 ± 1.4	29.3 ± 1.5	NS
BW (g)	1300 ± 160	810 ± 140	<.01
Birth height (cm)	39 ± 1	33 ± 1	<.01
Head circumference (cm)	27.2 ± 0.5	24.4 ± 0.5	<.01
Antenatal corticosteroids	27 (87%)	16 (94%)	NS
RDS	20 (64%)	9 (52%)	NS
CRIB score	2.5 ± 0.6	4.5 ± 0.7	<.05

Early Hemodynamic Consequences of Patent Ductus Arteriosus in Preterm Infants with Intrauterine Growth Restriction

T. Rakza, MD, E. Magnenant, MD, S. Klosowski, MD, P. Tourneux, MD, A. Bachiri, MD, and L. Storme, MD

(J Pediatr 2007;151:624-8)



Rakza T, J Pediatr 2007

Table II. Comparison, at 6 hours of age, of the echocardiographic markers of patent ductus arteriosus between growth-restricted and eutrophic preterm infants

	Eutrophic (n = 31)	IUGR (n = 17)	*P*
DA diameter (mm)	2.1 ± 0.6	2.7 ± 0.7	<.05
LA:Ao	1.2 ± 0.06	1.5 ± 0.08	<.01
SF (%)	35 ± 9	45 ± 8	=.06
ED-LPA (m/s)	0.16 ± 0.03	0.23 ± 0.02	<0.05
MRI	0.7 ± 0.05	0.86 ± 0.08	<.05

Effects of PEEP level on DA flow

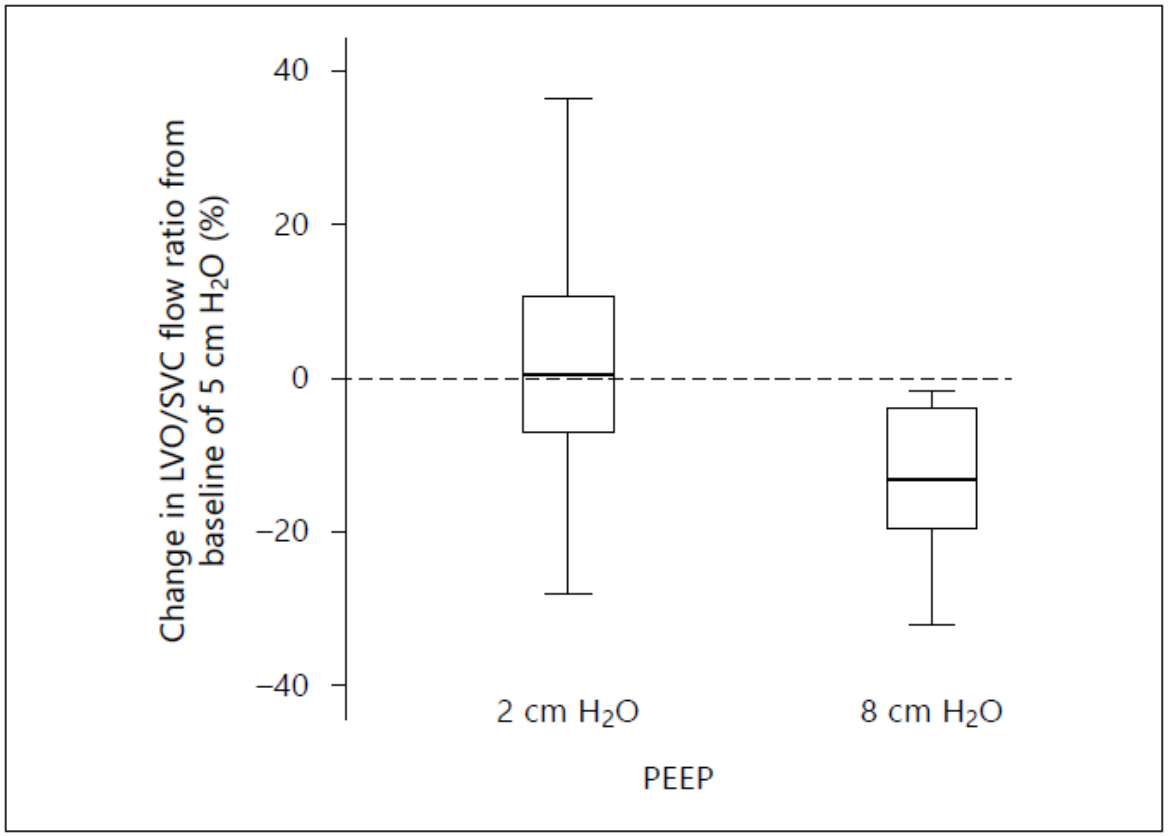


Fig. 1. Changes in the LVO/SVC flow ratio at PEEP of 2 and 8 cm H_2O with respect to the baseline PEEP of 5 cm H_2O. A consistent decline in the LVO/SVC flow ratio was observed at the higher PEEP.

Fajardo, Neonatology 2014

Take home message !

1. DA is required at birth for normal transition, …. but also in conditions with PPHN !!!
2. In preterm babies with significant DA:
   - FiO2 and SpO2 have little impact on the DA shunting;
   - Dopamine increase systemic pressure and systemic flow;
   - Fluid restriction and mechanical ventilation worsen the consequences of significant DA;
   - Red blood cells transfusion decreases pulmonary flow in signicant DA;
   - IUGR is associated with earlier and increased PDA