Ductus arterioso persistente (DAP)

SEPTIEMBRE 2023 A.SALVADÓ G.

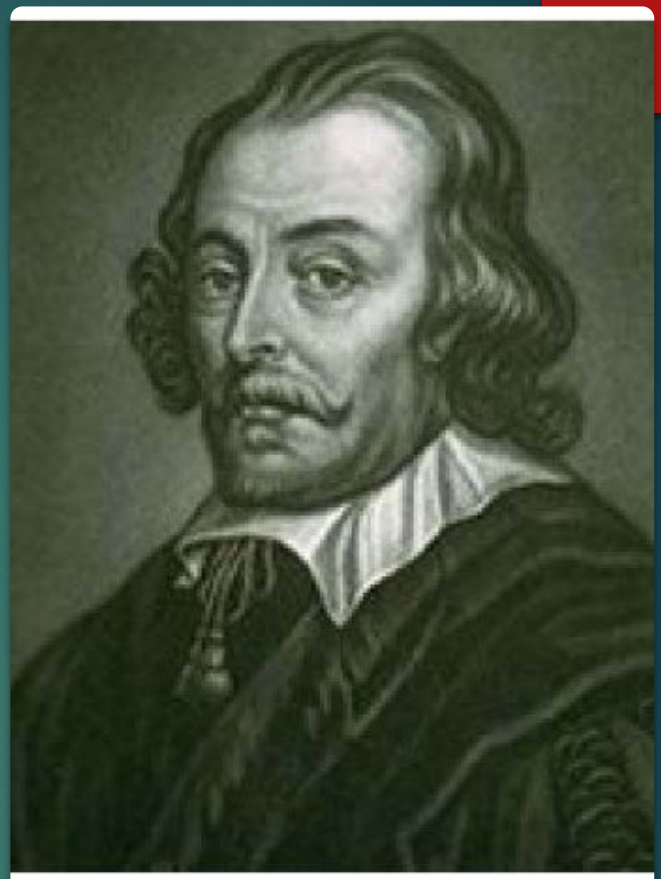
Galen 130-200 AD

LA NATURALEZA NO ES PEREZOSA NI CARECE DE PREVISIÓN. ELLA LO SABE DE ANTEMANO QUE EL PULMÓN DEL FETO NO REQUIERE LAS MISMAS DISPOSICIONES DE UN PULMÓN PERFECCIONADO Y DOTADO DE MOVIMIENTO. POR LO TANTO, SE HA ANASTOMOSADO LA ARTERIA PULMONAR CON LA AORTA……

“Exercitatio anatomica de motu cordis et sanguinis in aminalibus”

“De la arteria pulmonar sale una especie de canal arterial que se dirige oblicuamente hacia la gran arteria o aorta.

El canal se encoge tras el nacimiento y después del tiempo se marchita”



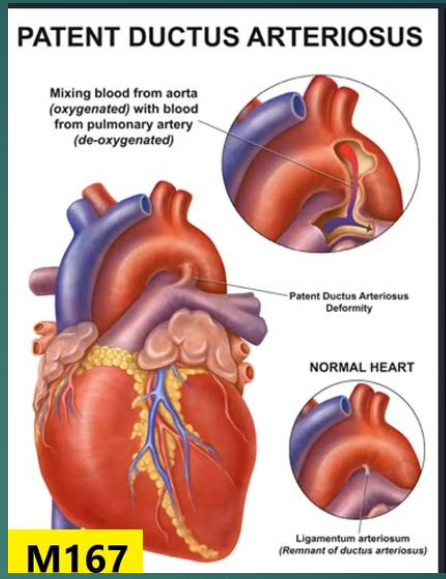
William Harvey
1558-1657

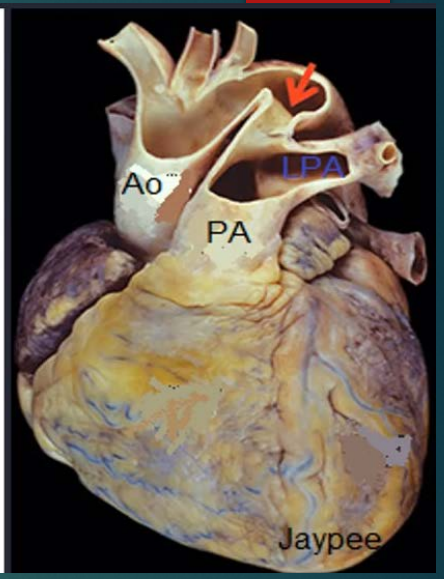
CONTENIDOS

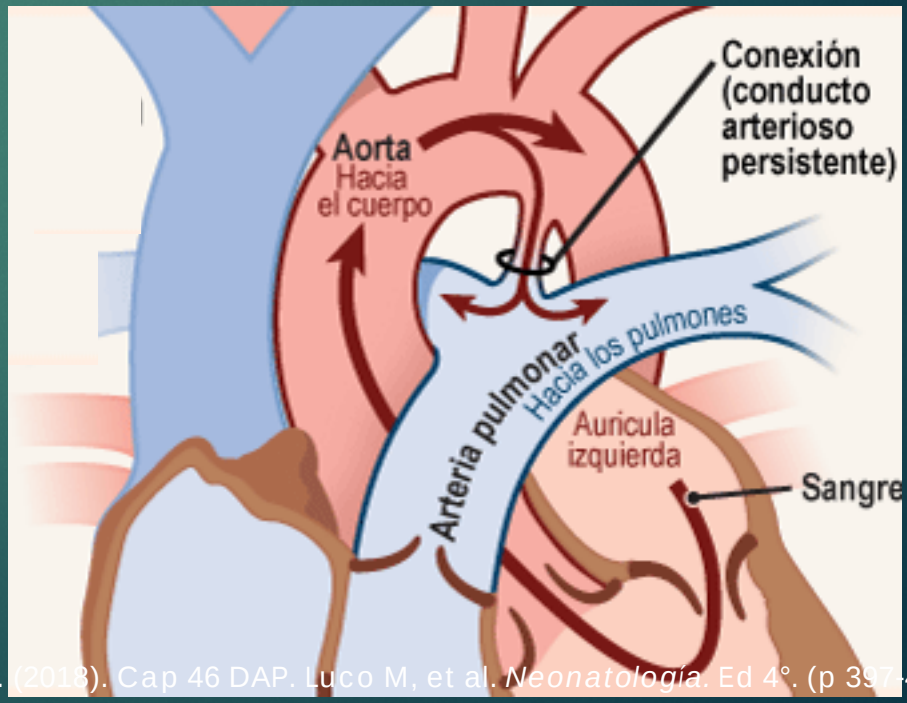
- Introducción
- Epidemiología
- Fisiología y Fisiopatología
- Diagnóstico
- Tratamiento
- Conclusiones
- Bibliografía

INTRODUCCIÓN

- **Definición:** vaso sanguíneo que comunica el tronco de la arteria pulmonar con la aorta descendente.
- **Embriológicamente:** porción distal del sexto arco aórtico.
- **Histológicamente:** Túnica media pobre en fibras elásticas y rica en fibras musculares lisas en forma de doble capa helicoidal → contracción y dilatación.





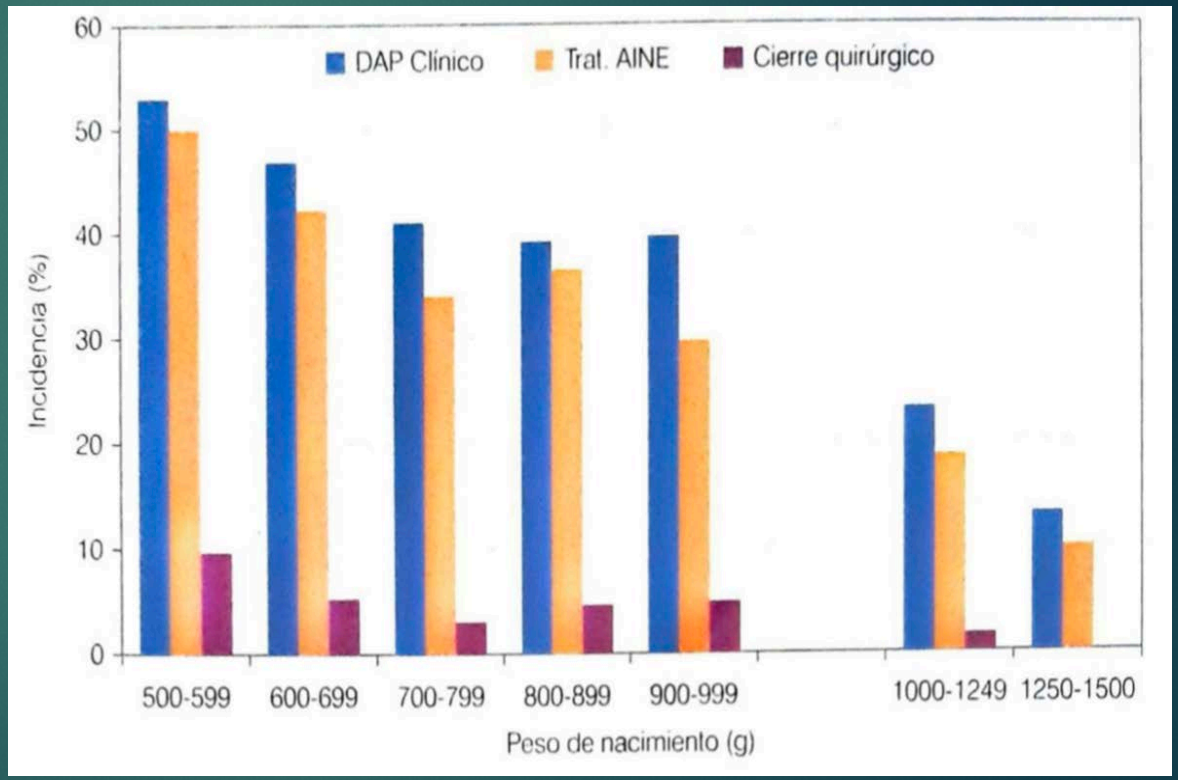


Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología*. Ed 4°. (p 397-406)

INCIDENCIA

- **Incidencia DAP:** 20-40%<1500 gr y 35-70% <1000 gr.
- Hasta 60-70% puede requerir manejo médico o quirúrgico, con los criterios actuales
- **Factores de riesgo DAP:**
  - Edad gestacional y PN.
  - SDRA (>EDS).
  - Infecciones.
  - Trombocitopenia.
  - Altura sobre nivel del mar.

Fig 46-1. Incidencia DAP clínico y tratamiento en 1770 RN <1500 gr en 16 unidades de la red Neocosur 2010-2011.



Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)

FACTORES QUE INFLUYEN EN DAP

Factors Promoting Postnatal DA Closure	Factors Promoting Preterm DA Patency
Molecular Factors	
Increased O_2 tension Decreased vasodilating prostaglandins Activation of cytochrome P450 Increased endothelin-1 levels Production of isoprostanes (8-iso-PGF2α) Inhibition of potassium channels (K_{ATP}, Kv, BK_{Ca}) Activation of transient receptor potential channels Decrease in intracellular cAMP and/or cGMP levels Angiotensin II Bradykinin Acetylcholine Norepinephrine Activation of RhoA, RhoB, Rock1, and Rock2	Hypoxia Increased nitric oxide signaling Increased prostaglandin signaling
Physiologic Factors	
Decreased pulmonary vascular resistance Increased systemic vascular resistance	Prolonged bidirectional or right-to-left blood flow Low-velocity blood flow
Structural Factors	
Mature contractile smooth muscle cells Prominent intimal cushions Vasa vasorum Zone of ischemia and/or necrosis Platelet adherence to lumen	Thin layer or immature smooth muscle Insufficient intimal cushion development Thrombocytopenia or platelet dysfunction

PEDIATRICS Volume 146, number 5, November 2020:e20201209. State Of the Art Review Article. Patent Ductus Arteriosus of the Preterm Infant.

ALTERACIONES GENÉTICAS ASOCIADAS A DAP

TABLE 1 Genetic Factors Associated With PDA

Human Syndromes (Gene)	Nonsyndromic SNPs (Accession Number)
22q11.2 deletion	Increased Risk of PDA
Char (*TFAP2B*)	*TFAP2B* (rs987237)
Cantu (*ABCC9*, *KCNJ8*)	*TRAF1* (rs1056567)
Noonan (*PTPN11*)	*AGTR1* (rs5186)
Mowat-Wilson (*SMADIP1*)	Decreased Risk of PDA
DiGeorge (*TBX1*)	*PTGIS* (rs493694, rs693649)
Holt-Oram (*TBX5*)	*ESR1* (rs2234693)
Loeys-Dietz (*TGFBR1* and *TGFBR2*)	*IFN-γ* (rs2430561)
Rubinstein-Taybi (*CREBP*)	
Periventricular heterotopia (*FLNA*)	

PDA is associated with several genetic syndromes. Several SNPs have also been associated with cases of nonsyndromic PDA. *ABCC9*, ATP binding cassette subfamily C member 9; *AGTR1*, angiotensin II receptor type 1; *CREBP*, cyclic adenosine monophosphate–response element binding protein; *ESR1*, estrogen receptor 1; *FLNA*, filamin A; *IFN-γ*, interferon-γ *KCNJ8*, potassium inwardly rectifying channel subfamily J member 8; *PTGIS*, prostaglandin I2 synthase; *PTPN11*, protein tyrosine phosphatase nonreceptor type 11; *SMADIP1*, SMAD-interacting protein 1; SNP, single-nucleotide polymorphism; *TBX1*, T-box transcription factor 1; *TBX5*, T-box transcription factor 5; *TFAP2B*, transcription factor AP-2-β; *TGFBR1*, transforming growth factor-β receptor type 1; *TGFBR2*, transforming growth factor-β receptor type 1; *TRAF1*, tumor necrosis factor receptor associated factor 1.

PEDIATRICS Volume 146, number 5, November 2020:e20201209. State Of the Art Review Article. Patent Ductus Arteriosus of the P
Infant

International Journal of *Molecular Sciences*

MDPI

Review

The Association of Patent Ductus Arteriosus with Inflammation: A Narrative Review of the Role of Inflammatory Biomarkers and Treatment Strategy in Premature Infants

Yu-Jen Wei [1,2,†], Rosie Hsu [3,†], Yung-Chieh Lin [1], Tak-Wah Wong [4,5,6], Chung-Dann Kan [7] and Jieh-Neng Wang [1,*]

Método:

- 5883 artículos iniciales→ N° 77 validos

Conclusiones:

- **Corioamnionitis** →proceso inflamatorio fetal → citoquinas y DAP: remodelación vascular o dilatación vasos del conducto.
- **Esteroides prenatales**: ↓ incidencia y gravedad DAP en RN con corioamnionitis.

Table 2. Potential biomarkers involved in PDA pathogenesis.

Biomarker	Potential Pathological or Clinical Role That May Relate to Perinatal Inflammation and PDA
TNF-α	Mediators in the early inflammatory response
IL-1	Mediators in the early inflammatory response Risk of preterm birth
IL-6	Mediators in the early inflammatory response Risk of preterm birth Clinically related to persistent PDA
IL-8, IL-10, MIP-1α	Related to persistent PDA Clinical risk of preterm birth
IL-15	Attenuates smooth muscle cell proliferation Involved in atherogenesis
IL-17	Risk of preterm birth Involved in vascular remodeling and prostaglandin expression Increases platelet aggregation
GDF-15	Related to persistent PDA Associated with tissue hypoxia, inflammation, acute injury, and oxidative stress.
MCP-1	Clinically related to persistent PDA Regulates migration and infiltration of monocytes and macrophages Risk of preterm birth Related to thrombus formation
PGDH	Risk of preterm birth

Yu-Jen Wei, et al. *Int. J. Mol. Sci.* 2022, *23*, 13877.

FISIOLOGÍA

Cierre Funcional

- Vasocontricción DA 1° 48 hrs RNT.
- Vasocontricción 2°↑PaO2, ↓PG y cambios hemodinámicos.

Cierre Anatómico

- Se completa 2-8 sem.
- Contricción → hipoxia pared ductal → disrrupcion endotelial→ muerte celulas musculares → reacción inflamatoria local → fibrosis y cierre definitivo

Vasocontrictores

- Oxígeno → ↑Ca intracel
- Endotelina 1

Vasodilatadores

- Prostaglandinas (PGE1-PGI2)

+

Alta resistencia pulmonar fetal

Circulación fetal

Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)

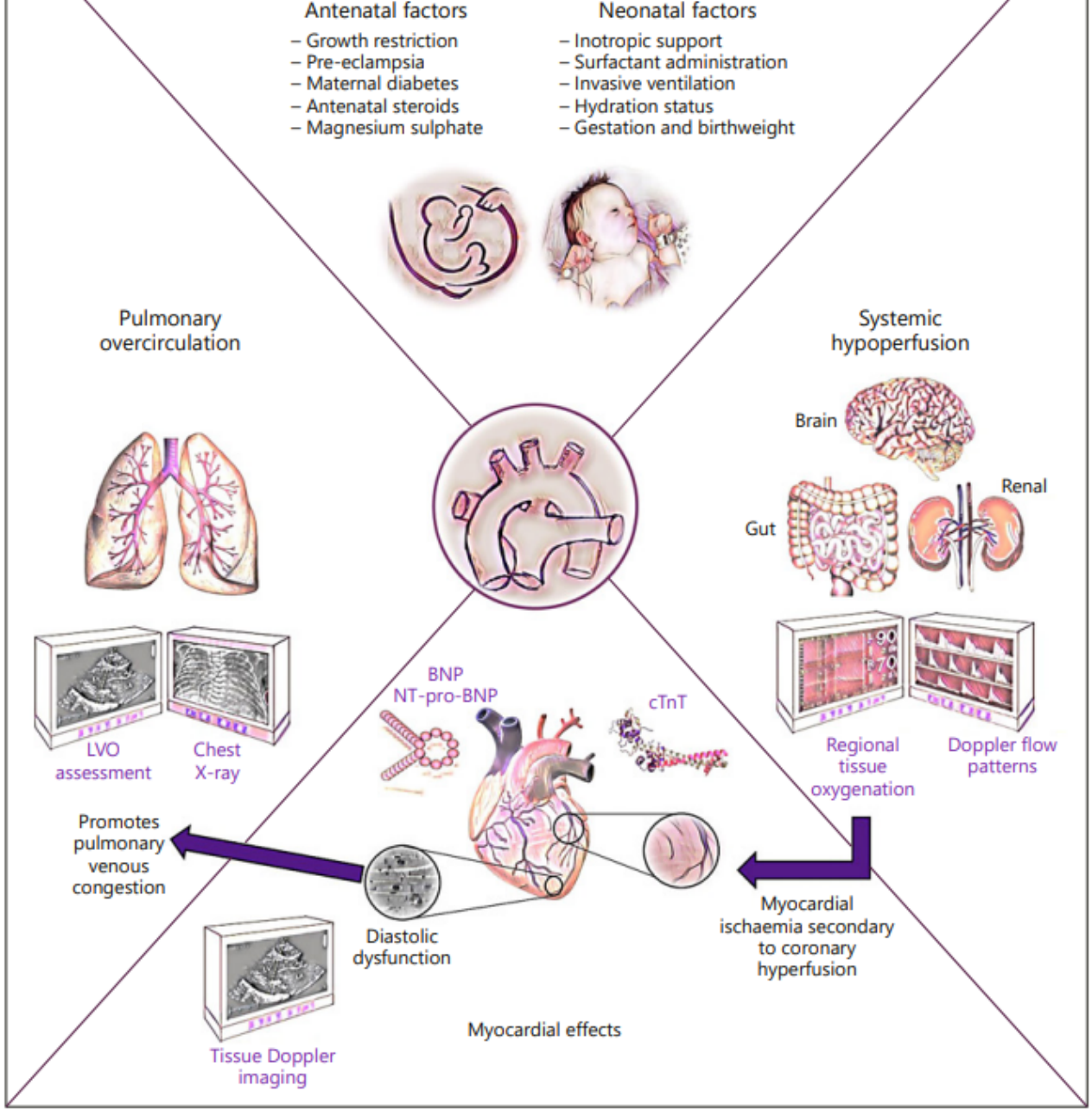


Fig. 2. Determinants of haemodynamic significance. The concept of haemodynamic significance is a complex one made of several interconnected components. A holistic approach to determine significance is needed. LVO, left ventricular output; BNP, B-type natriuretic peptide; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; cTnT, Cardiac troponin T.

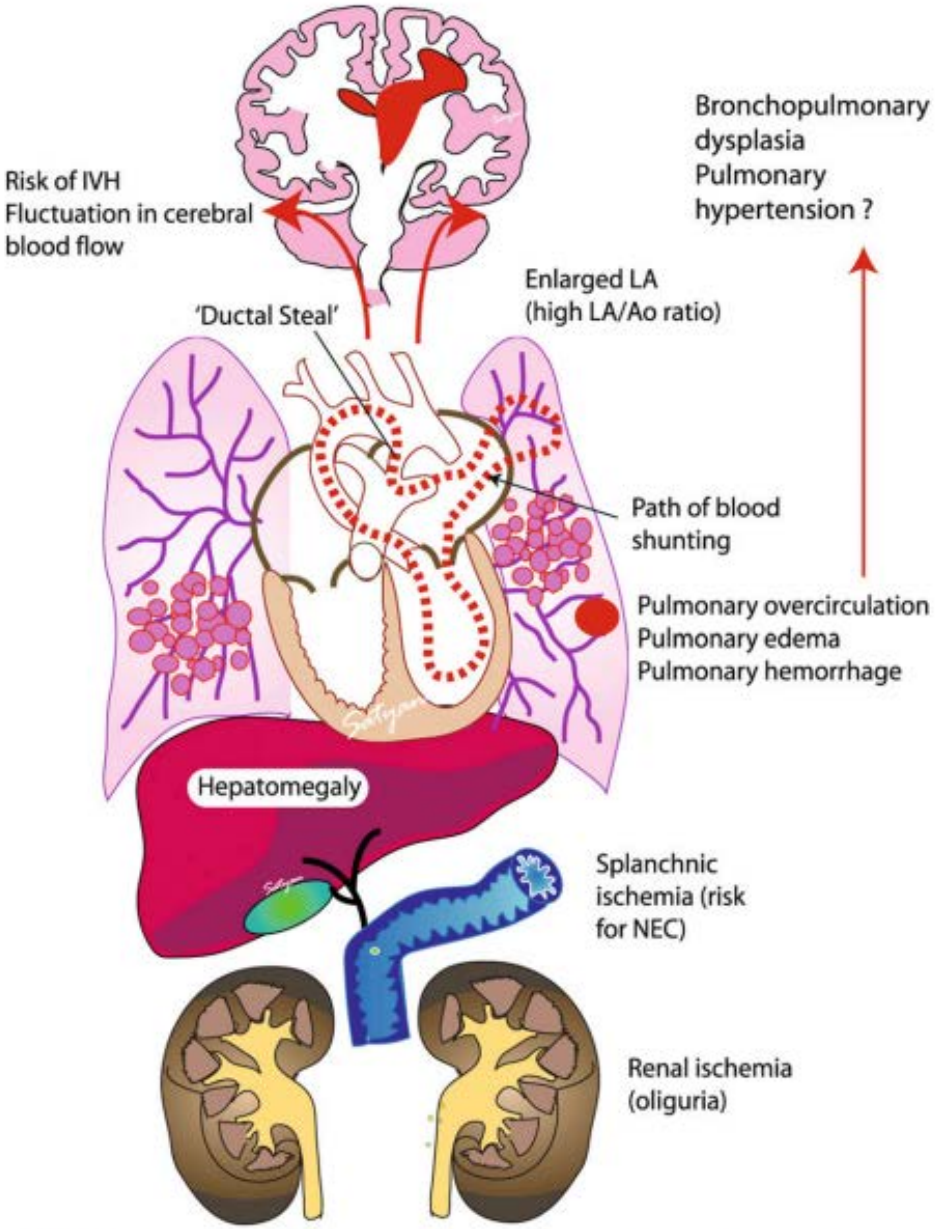
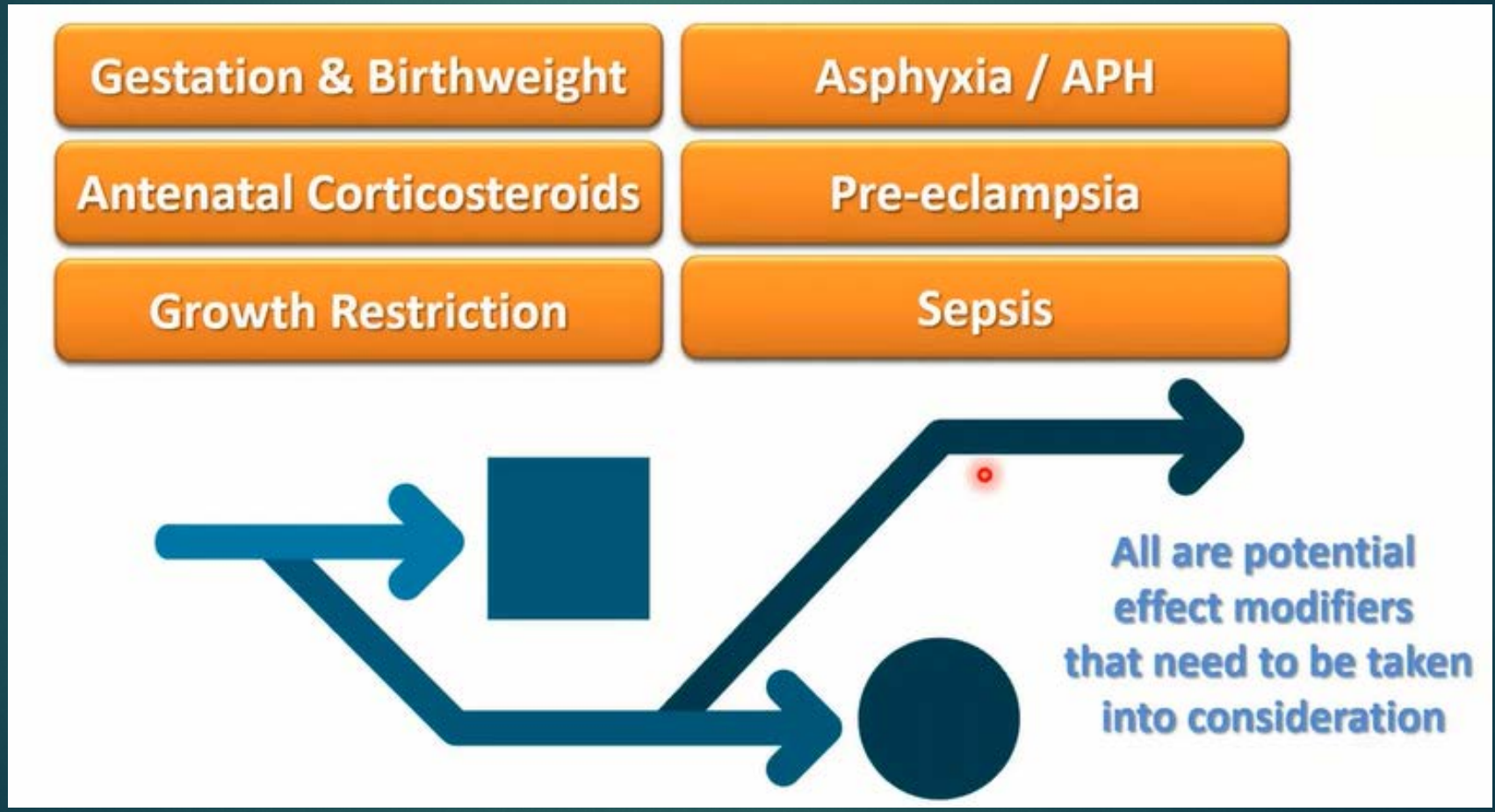


Figure 1. Hemodynamically significant patent ductus arteriosus pathophysiology. LA=left atrium; Ao=Aorta; IVH=intraventricular hemorrhage; NEC=necrotizing enterocolitis. Reprinted with permission from SpringerNature and copyright holder Satyan Lakshminrusimha, MD. (4)

Consideraciones clínicas relevantes



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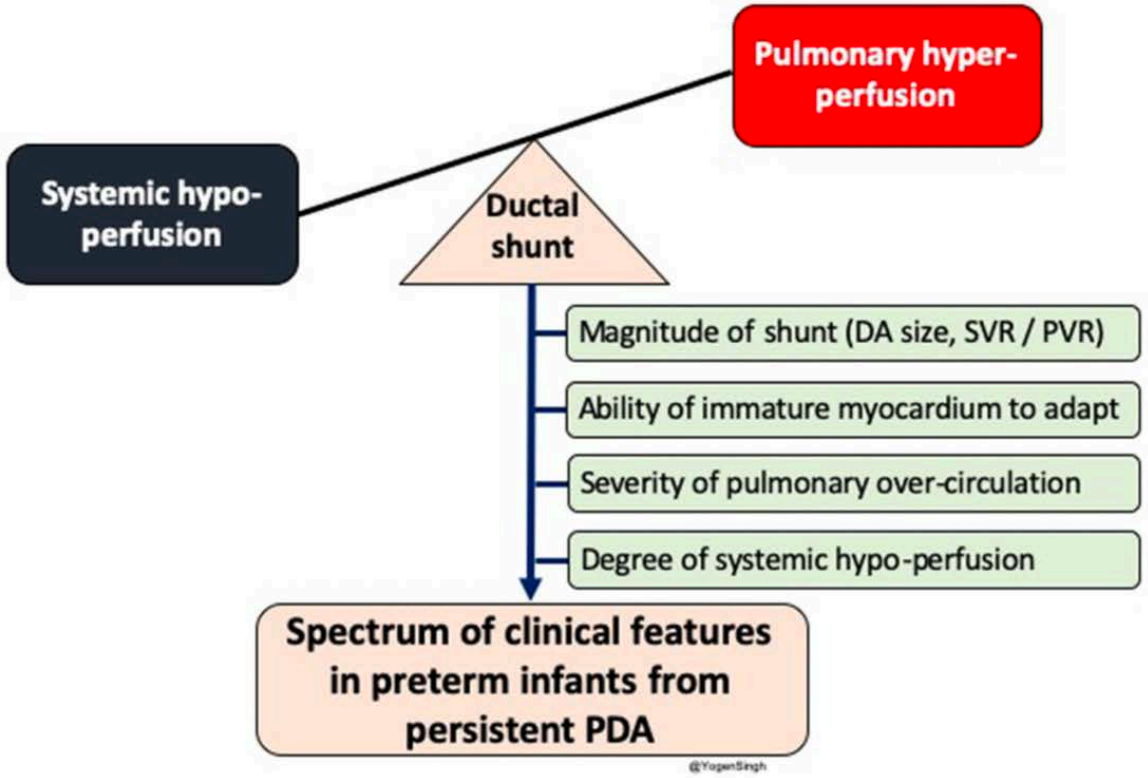


FIGURE 1 | Diagram showing impact of significant left to right shunt across ductal arteriosus (DA) leading to pulmonary over-circulation and systemic hypoperfusion. Spectrum of clinical features in preterm infants depends upon magnitude of ductal shunt, which depends upon DA size and balance between systemic and pulmonary vascular resistance, and inability of immature myocardium to adpat to circulatory disturbance. PDA, patent ductus arteriosus; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

Singh Y, et al. Front. Pediatr. 8:573627.

DIAGNÓSTICO: CLÍNICO Y MARCADORES BQ…

Triada clínica:

Hipotensión	•Dentro de las 1° 48 hrs.
Soplo sistólico infraclav izq→ dorso	•2° caída de resistencia vascular pulmonar, con aumento velocidad del cortocircuito por el DA
Precordio Hiperactivo	•Pulsos saltones y taquicardia 2° a compensación del "robo sistémico".

Biomarcadores bioquímicos…

- **Marcadores séricos:** Péptido natriurético tipo B (BNP), NT-proBNP y la troponina T cardíaca (cTnT).
- **Marcadores urinarios:** lipocalina asociada a la gelatinasa de neutrófilos y la proteína de unión a ácidos grasos de tipo cardíaco.

Usado para predecir el momento del cierre ductal…

Parkerson S, et al. (2021) Front. Pediatr. 8:590578.
Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)

El uso de biomarcadores en la evaluación del DUCTUS arterioso persistente: péptido natriurético cerebral y propéptido natriurético cerebral N-terminal

- En respuesta a la carga de volumen y presión, los miocitos en ambos ventrículos activan el péptido natriurético cerebral (BNP) en el BNP biológicamente activo y el pro-BNP amino terminal inactivo.(NTpBNP). El BNP promueve la natriuresis y la diuresis para contrarrestar la sobrecarga de volumen del VI secundaria a un DAP significativo

Los estudios han evaluado la confiabilidad de las mediciones de BNP y NTpBNP en varias funciones potenciales en la atención clínica, incluida la sustitución de ecocardiografía para el diagnóstico de DAP, la evaluación de respuesta al tratamiento, la clasificación de los pacientes para la detección del DAP de tratamiento temprano o como complemento a la ecocardiografía. La interpretación e integración de mediciones de BNP y NTpBNP en la práctica clínica, se ha visto obstaculizado por la disponibilidad de múltiples kits de prueba, cada uno con un rango de referencia distinto y con resultados publicados en estudios observacionales que correlacionan estos biomarcadores con el desarrollo de un PDA

El uso de biomarcadores en la evaluación del DUCTUS arterioso persistente: péptido natriurético cerebral y propéptido natriurético cerebral N-terminal

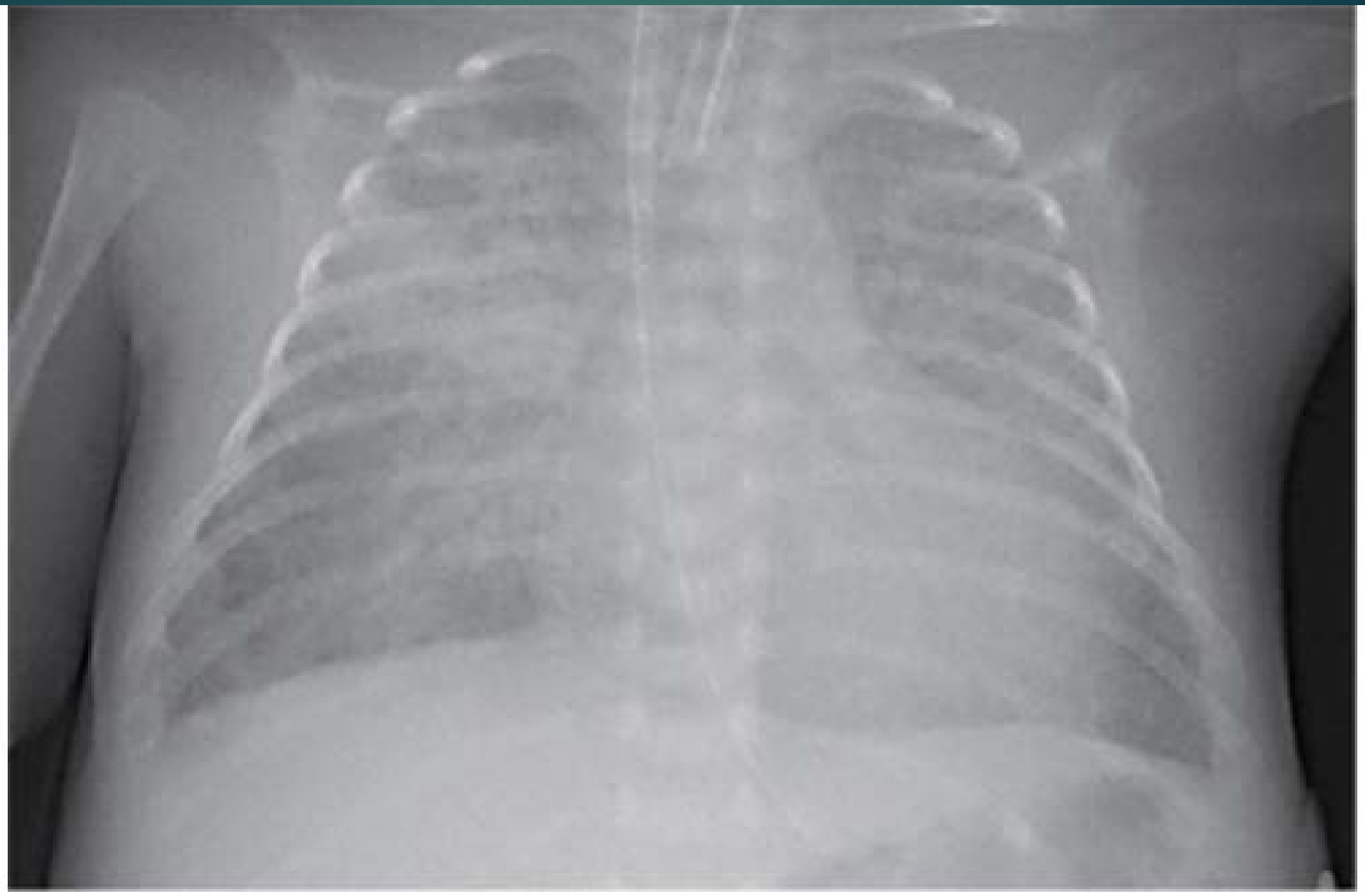
- Tanto el BNP como el NTpBNP predicen un hsPDA después del segundo día de vida y puede usarse para clasificar a los pacientes para evaluación ecocardiográfica o terapia empírica. Existen varios límites en la literatura tanto para BNP como para NTpBNP y diagnóstico de DAP
- Sin embargo, hay superposición significativa en las concentraciones séricas de estos biomarcadores entre los niños que responden y los que no responden, lo que significa que el seguimiento por ecocardiografía no se puede reemplazar de forma fiable

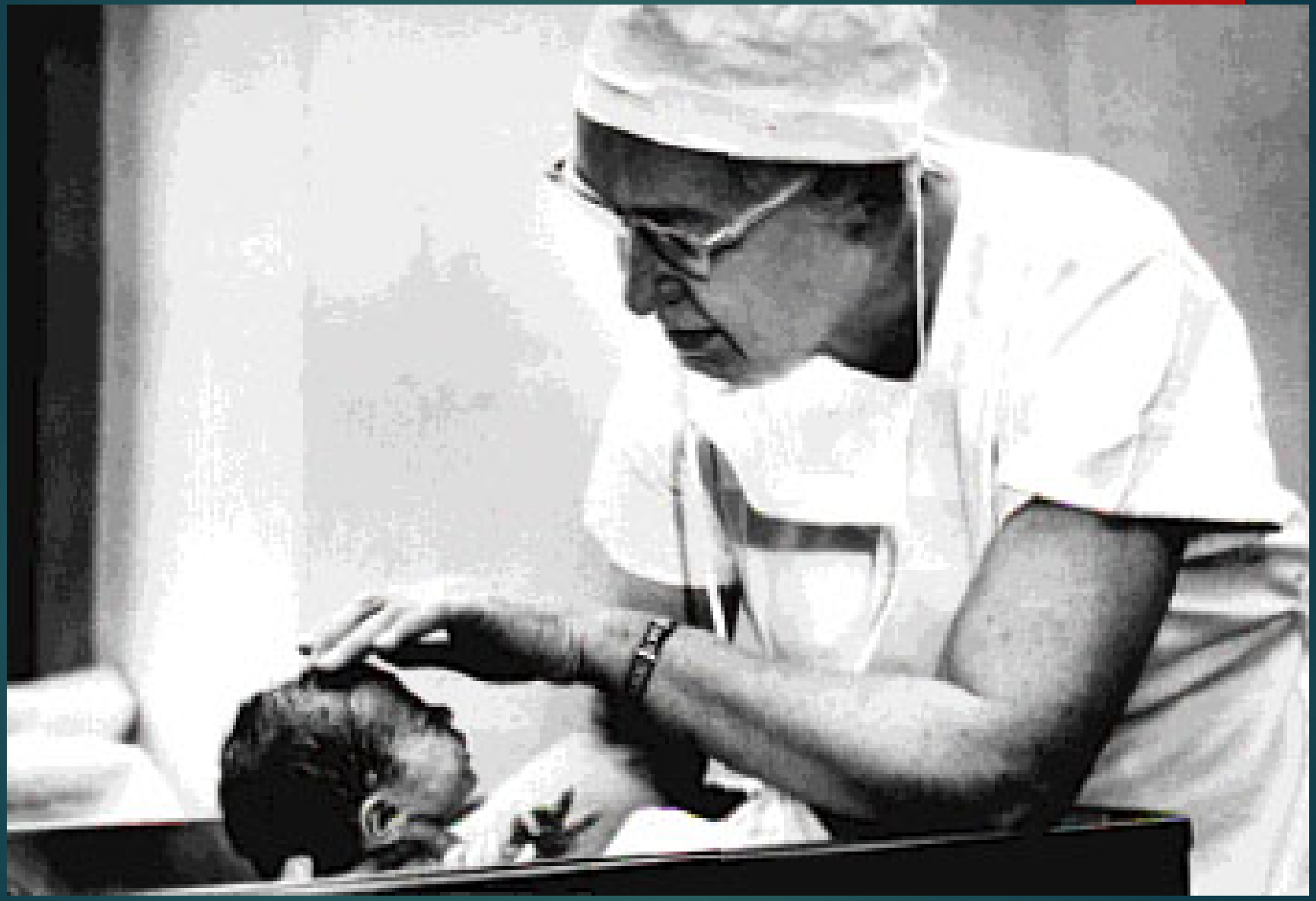
El uso de biomarcadores en la evaluación del DUCTUS arterioso persistente: péptido natriurético cerebral y propéptido natriurético cerebral N-terminal (SENEO 2023)

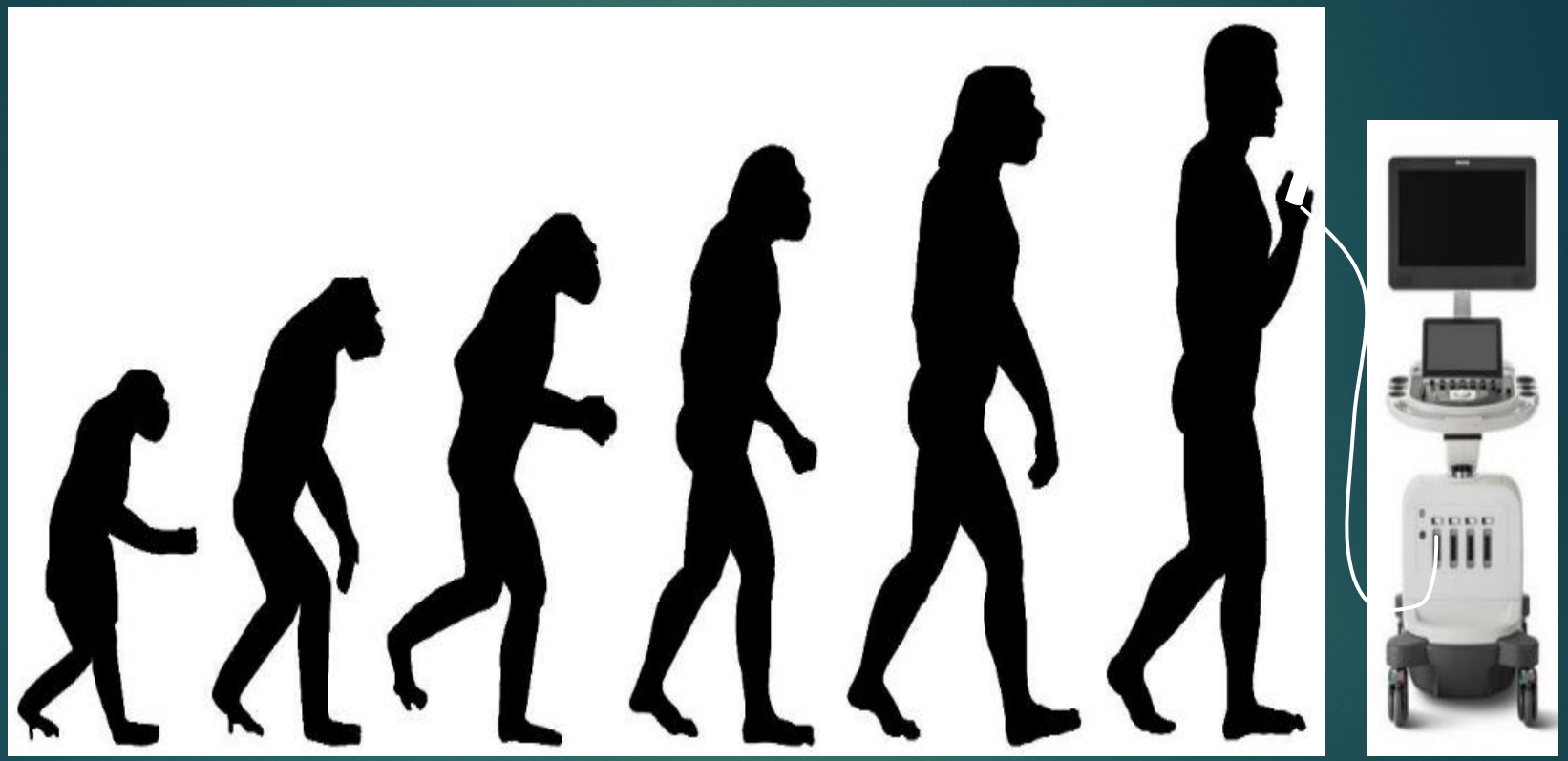
Repercusión hemodinámica y probabilidad de cierre espontáneo

Al no existir una definición universalmente aceptada de DA hemodinámicamente significativo (DAhs), dicha valoración se basa en datos clínicos, ecocardiográficos y biomarcadores, combinados de distintas maneras en los llamados "scores de estadiaje ductal", que intentan estimar dicha repercusión de la forma más objetiva posible. En todo caso, **la ecocardiografía es la base de la valoración** y permite clasificar el cortocircuito (tabla 1).

El NT-proBNP es el biomarcador más utilizado. Se trata de una determinación ya introducida en la mayoría de centros, idónea en RN por precisar muestras muy pequeñas, que ha demostrado clara asociación con la repercusión hemodinámica y respuesta al tratamiento, pero con puntos de corte variables entre 10000-20000 ng/mL, según los distintos trabajos.





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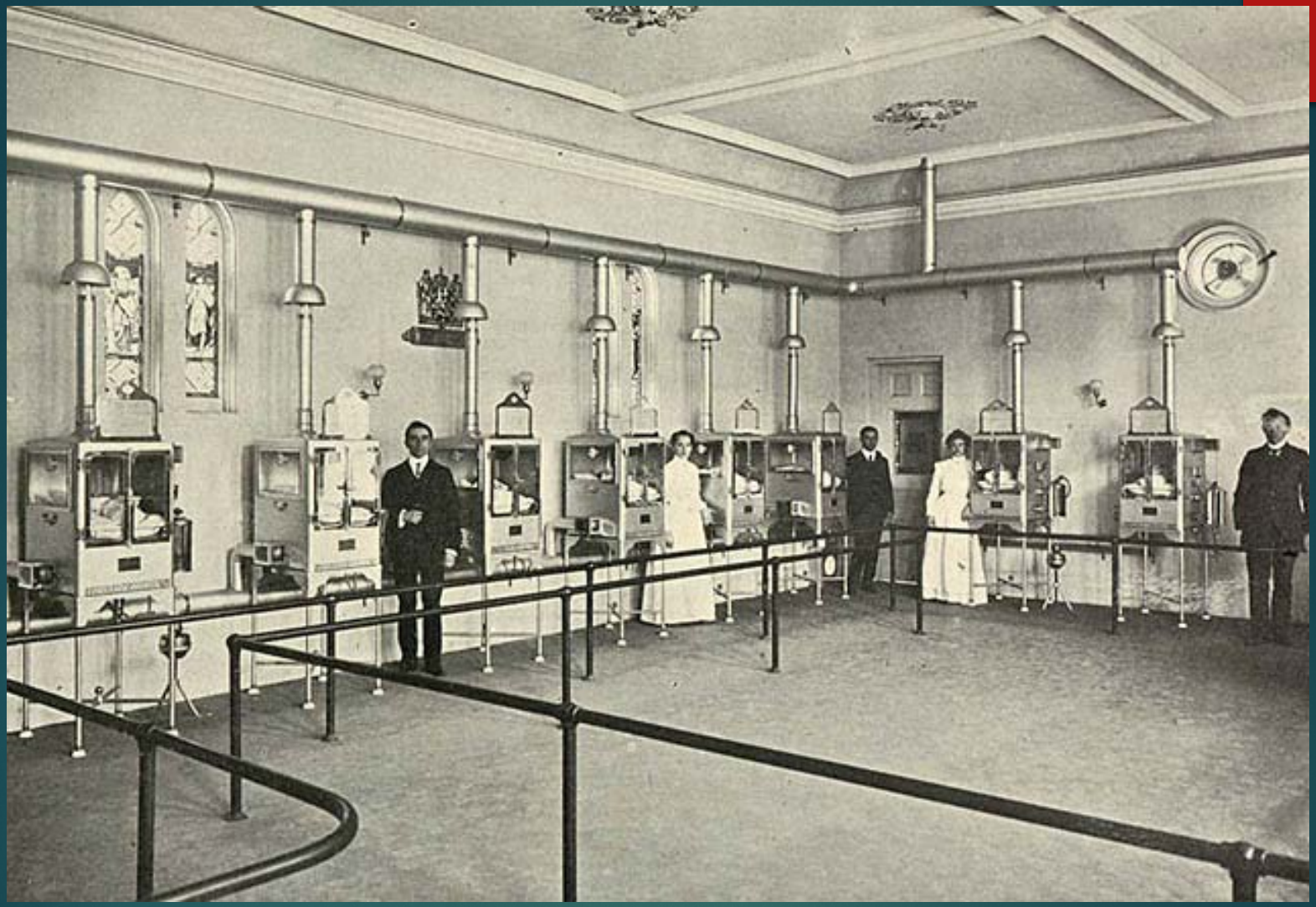
HPM



DIAGNÓSTICO: ECOCARDIOGRÁFICO

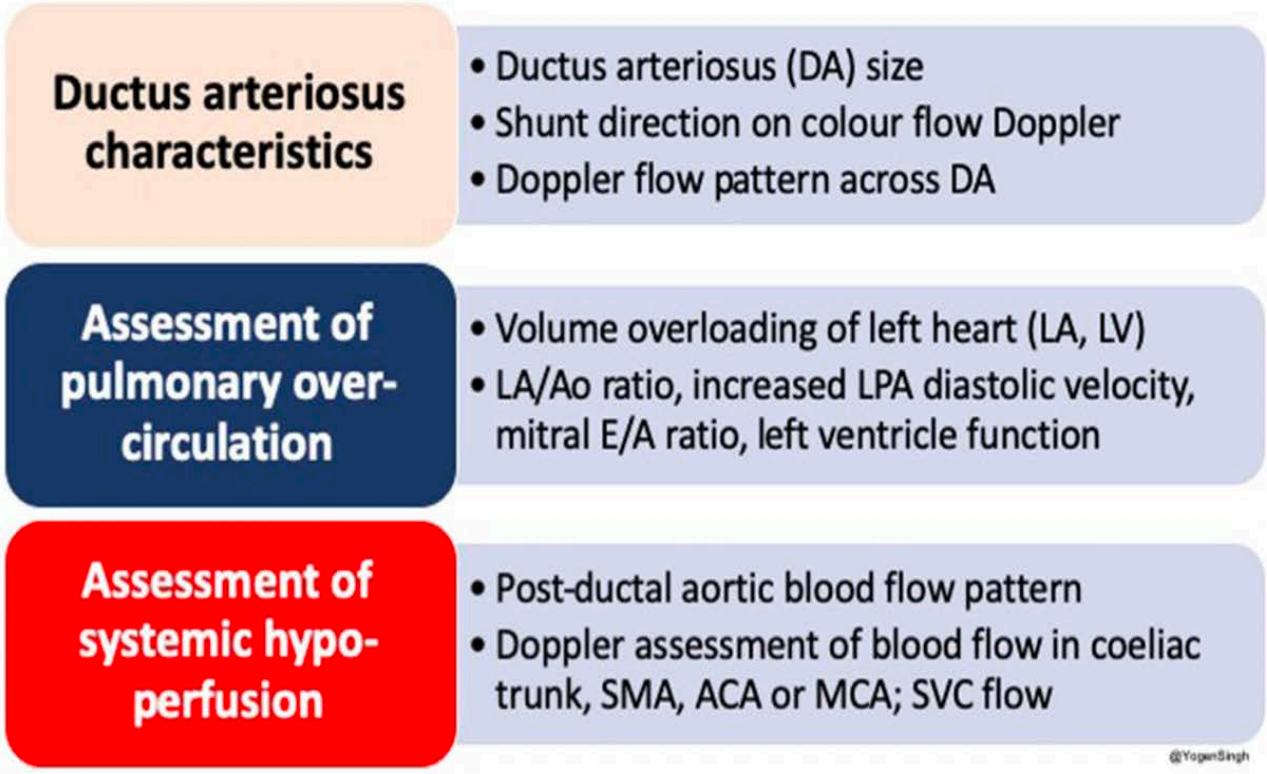


FIGURE 2 | Summary of an approach to echocardiographic assessment of PDA and hemodynamic evaluation; LA, left atrium; LV, left ventricle; DA, ductus arteriosus; Ao, aorta; SMA, superior mesenteric artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; SVC, superior vena cava.

Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)
Singh Y, et al. Front. Pediatr. 8:573627.

DIAGNÓSTICO: ECOCARDIO

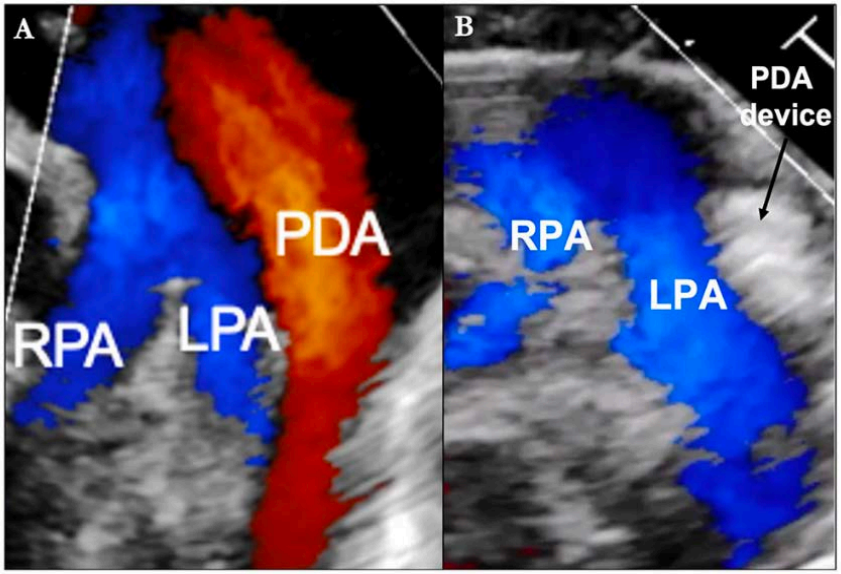
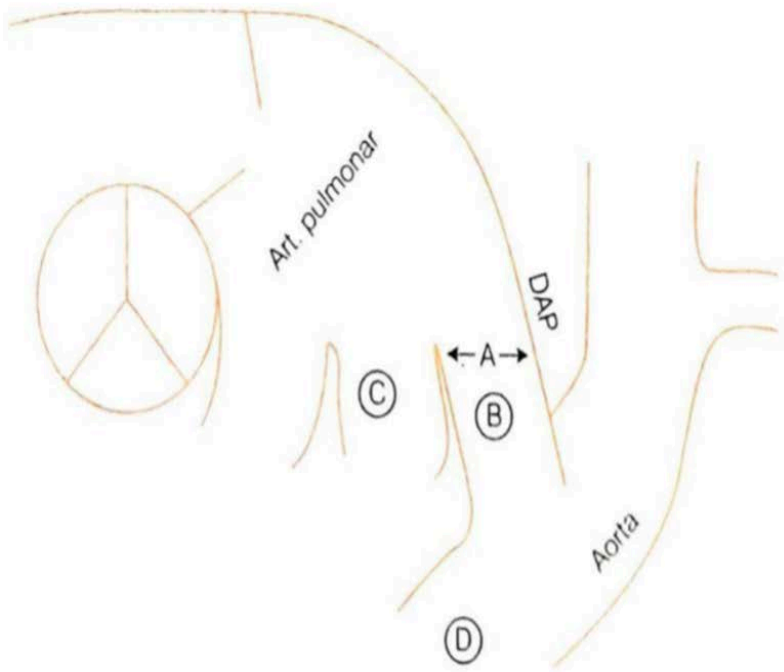


FIGURE 1 | (A) Transthoracic Echocardiogram (parasternal short axis image with color Doppler) demonstrating the relative size of the patent ductus arteriosus (PDA) in comparison to the left pulmonary artery (LPA) and right pulmonary artery (RPA). **(B)** Post-transcatheter PDA closure.

Parkerson S, et al. (2021) Front. Pediatr. 8:590578.

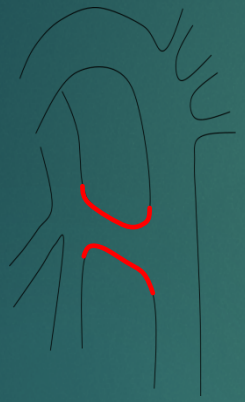
Figura 46-3. Sitios de evaluación ecocardiográfica de las d mensiones de *ductus* arterioso persistente (DAP) como de s significancia hemodinámica. A: sitio de medición del diámetro d DAP en cabo pulmonar, en que suele verse un punto hiperecogénic en su límite medial. B: sitio de interrogación con Doppler continu de sentido y velocidad del flujo por el DAP. C: sitio de interrogació con Doppler pulsado en arteria pulmonar izquierda para cuantifica el hiperflujo pulmonar. D: sitio de interrogación con Doppler pulsad en aorta descendente para cuantificar el robo sistémico.



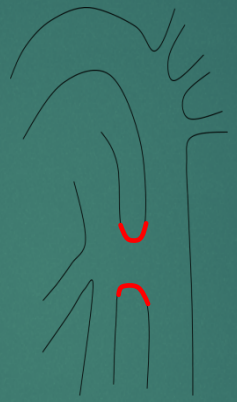
Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)

Arquitectura del ductus

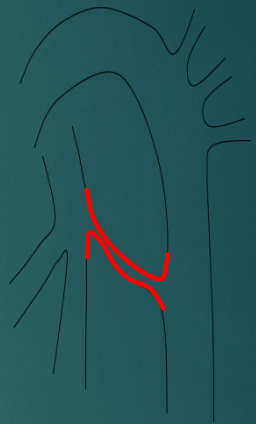
recto



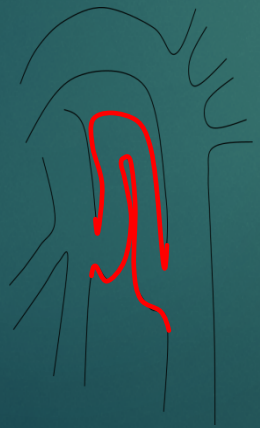
corto



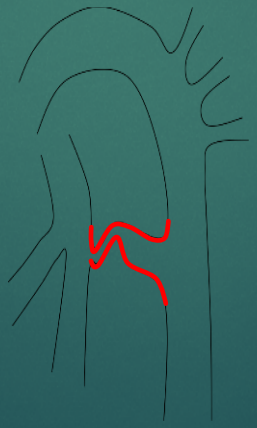
estrecho



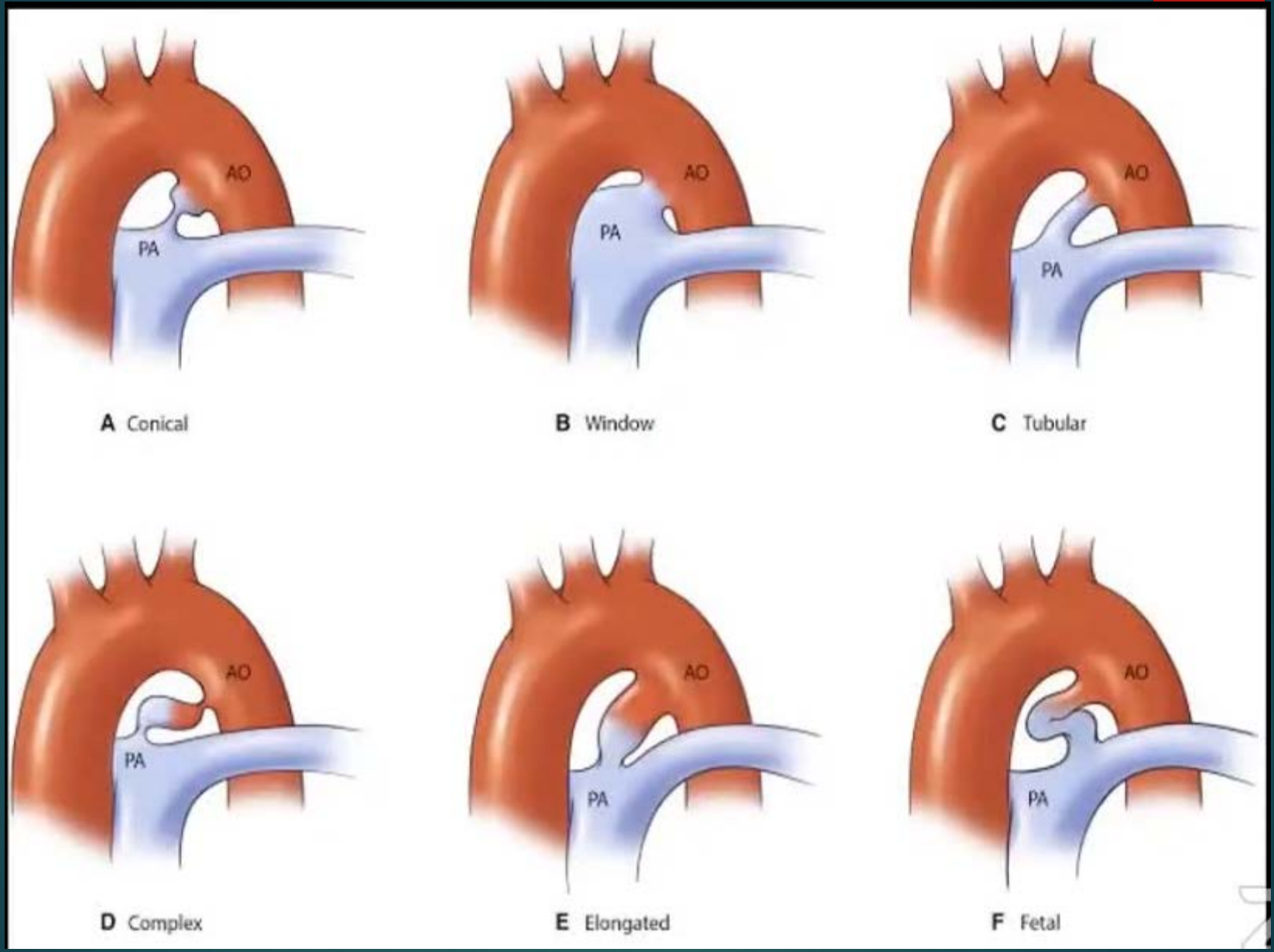
Serpentina



regadera



Embudo


AO
PA
A Conical
AO
PA
B Window
AO
PA
C Tubular
AO
PA
D Complex
AO
PA
E Elongated
AO
PA
F Fetal

Echocardiography Parameters of PDA Hemodynamic Significance in Extremely Preterm Infants (<29 Weeks'Gestation) After the First Postnatal Day

	HEMODYNAMIC SIGNIFICANCE		
Parameter[a]	**Mild**	**Moderate**	**Severe**
PDA Diameter			
2D diameter (mm)	<1.5	1.5–3	>3
PDA to LPA ratio	<0.5	0.5–1	>1
PDA Doppler			
Vmax (m/s)	>2.5	1.5–2.5	<1.5
Systolic to diastolic velocity ratio	<2	2–4	>4
LV chamber dilatation (Z score)	<+2.0	+2.0 to +3.0	>+3.0
Pulmonary Overcirculation			
LA to Ao ratio	<1.5	1.5–2.0	>2.0
Mitral valve E to A ratio	<1	<1	>1
IVRT (milliseconds)	>40	30–40	<30
LPA Vmax diastole (m/s)	<0.3	0.3–0.5	>0.5
LVO (mL/kg/min)	<200	200–300	>300
PV D wave (m/s)	<0.35	0.35–0.45	>0.45
Systemic Hypoperfusion			
Abdominal Ao diastolic flow	Forward	Reversed	Reversed
Celiac artery diastolic flow	Forward	Absent	Reversed
MCA diastolic flow	Forward	Forward	Absent/Reversed

2D, Two-dimensional; *Ao*, aorta; *IVRT*, isovolumic relaxation time; *LA*, left atrium; *LPA*, left pulmonary artery; *LV*, left ventricle; *LVO*, left ventricular output; *MCA*, middle cerebral artery; *PDA*, patent ductus arteriosus; *PV*, pulmonary vein; *Vmax*, maximum velocity.

[a] Applies beyond the first 48 hours.

Tabla 1. Clasificación ecocardiográfica del cortocircuito ductal (adaptado del GT-EcografíaSENeo)

	SHUNT LEVE	SHUNT MODERADO	SHUNT GRAVE
Tamaño ductal*	<1.4 mm/kg <1.5 mm Ductus/API <0.5	1.4-2 mm/kg 1.5-3 mm Ductus/API 0.5-1	≥2 mmkg ≥3 mm Ductus/API >1
Relación AI/Ao	<1.4	1.4-1.8	≥1.8
Vmáx shunt (m/seg)	>2 m/s + Patrón continuo	<1.5 m/s o Patrón pulsátil	≤1.5 m/S + Patrón pulsátil
API Vtd (m/seg) API Vmedia (m/seg)	<0.3 <0.42	0.3-0.5 ≥0.42	≥0.5
Ratio E/A	<1	=1	≥1
TRIV (mseg)	>45	35-45	<35
Flujo Ao descendente	Flujo diastólico	Reverso parcial	†Reverso holodiástole
Flujo ACA/ACM	Flujo diastólico anterógrado	Diastole llega a 0	†Reverso
GVI (ml(kg/min)	<200	200-250	>250
Flujo VCS/GVI	<2.4	2.5-4	>4

El problema es:

Table II. Interobserver variability for echocardiography variables

Variables	Correlation coefficient (95% CI)
DD	0.85 (0.68-0.94)*
LPA diameter	0.62 (0.34-0.80)*
E/A ratio	0.90 (0.77-0.95)*
IVRT	0.84 (0.63-0.93)*
Aortic diameter	0.90 (0.80-0.95)*
Aortic VTI	0.79 (0.63-0.90)*
LVO	0.97 (0.94-0.99)*
LVEDD	0.93 (0.86-0.97)*
LA:Ao	0.65 (0.44-0.82)*
Descending aorta diastolic flow	0.75 (0.43-1.00)†
Celiac diastolic flow	0.88 (0.65-1.00)†

Aortic VTI, velocity time integral; *IVRT*, isovolumic relaxation time; *LVEDD*, left ventricular end-diastolic diameter; *LVO*, left ventricular output.

*Lin concordance correlation coefficient.

†κ coefficient.

The definition of a haemodynamic significant duct in randomized controlled trials: a systematic literature review

Inge Zonnenberg (koert.dewaal@hnehealth.nsw.gov.au)[1], Koert de Waal[2]

1.Department of Neonatology, VU Medical Centre, Amsterdam, The Netherlands
2.Department of Neonatology, John Hunter Hospital, Newcastle NSW and University of Newcastle, NSW, Australia

Table 1 The establishment of the diagnosis of a PDA and the criteria used for the definition of an HSDA in 67 randomised trials evaluating ductal treatment

How was the PDA diagnosis established	Studies (%)	Criteria used for the definition of an HSDA	Studies (%)
Not mentioned	17 (25)	Not mentioned	3 (4)
Clinical only	7 (10)	Clinical only	7 (10)
Clinical, then ultrasound	41 (62)	Clinical and ultrasound	44 (66)
Ultrasound only	2 (3)	Ultrasound only	13 (20)

HSDA = haemodynamically significant duct; PDA = patent ductus arteriosus.

Conclusion: We found a wide variety in the definition of an HSDA. This finding implies that comparison of studies is difficult. International consensus should be reached on the definition of an HSDA, which will make future studies more comparable.

Apoyo de la AI en la interpretación del Ecocardio

npj | Digital Medicine

www.nature.com/npjdigitalmed

ARTICLE OPEN

Deep learning interpretation of echocardiograms

Amirata Ghorbani[1,6], David Ouyang[2,6*], Abubakar Abid[1], Bryan He[3], Jonathan H. Chen[2], Robert A. Harrington[2], David H. Liang[2], Euan A. Ashley[2] and James Y. Zou[1,3,4,5*]

Echocardiography uses ultrasound technology to capture high temporal and spatial resolution images of the heart and surrounding structures, and is the most common imaging modality in cardiovascular medicine. Using convolutional neural networks on a large new dataset, we show that deep learning applied to echocardiography can identify local cardiac structures, estimate cardiac function, and predict systemic phenotypes that modify cardiovascular risk but not readily identifiable to human interpretation. Our deep learning model, EchoNet, accurately identified the presence of pacemaker leads (AUC = 0.89), enlarged left atrium (AUC = 0.86), left ventricular hypertrophy (AUC = 0.75), left ventricular end systolic and diastolic volumes ($R^2 = 0.74$ and $R^2 = 0.70$), and ejection fraction ($R^2 = 0.50$), as well as predicted systemic phenotypes of age ($R^2 = 0.46$), sex (AUC = 0.88), weight ($R^2 = 0.56$), and height ($R^2 = 0.33$). Interpretation analysis validates that EchoNet shows appropriate attention to key cardiac structures when performing human-explainable tasks and highlights hypothesis-generating regions of interest when predicting systemic phenotypes difficult for human interpretation. Machine learning on echocardiography images can streamline repetitive tasks in the clinical workflow, provide preliminary interpretation in areas with insufficient qualified cardiologists, and predict phenotypes challenging for human evaluation.

npj Digital Medicine (2020)3:10 ; https://doi.org/10.1038/s41746-019-0216-8

CORRESPONDENCE

Check for updates

PD(AI): the role of artificial intelligence in the management of patent ductus arteriosus

Journal of Perinatology (2023) 43:257–258; https://doi.org/10.1038/s41372-023-01606-7

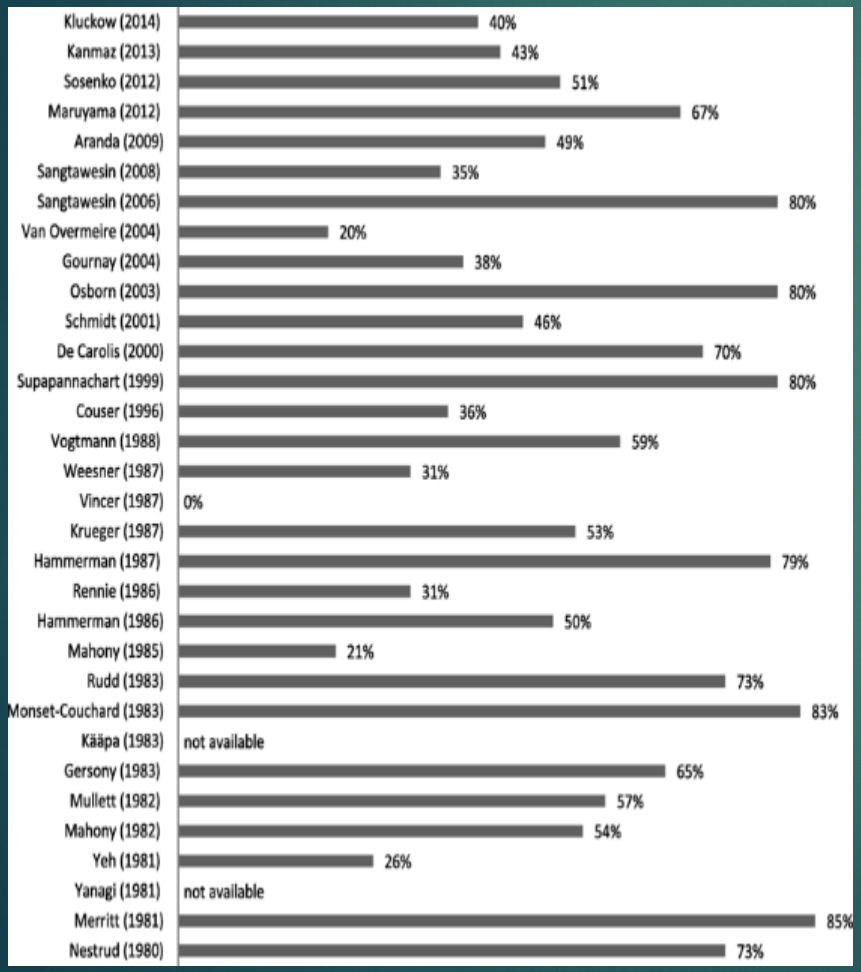
that in cohort of over 8000 neonates that AI could be used to predict the presence of a hsPDA based on numerous clinical factors such as gestational age, birth anthropometrics, and

Artificial Intelligence in Health Professions Education: Proceedings of a Workshop (2023)

DETAILS

96 pages | 6 x 9 | PAPERBACK
ISBN 978-0-309-70732-9 | DOI 10.17226/27174

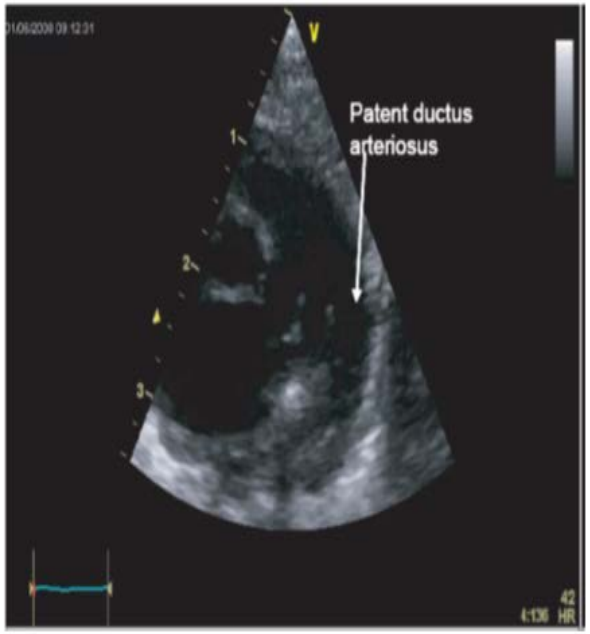
Un verdadero grupo control?

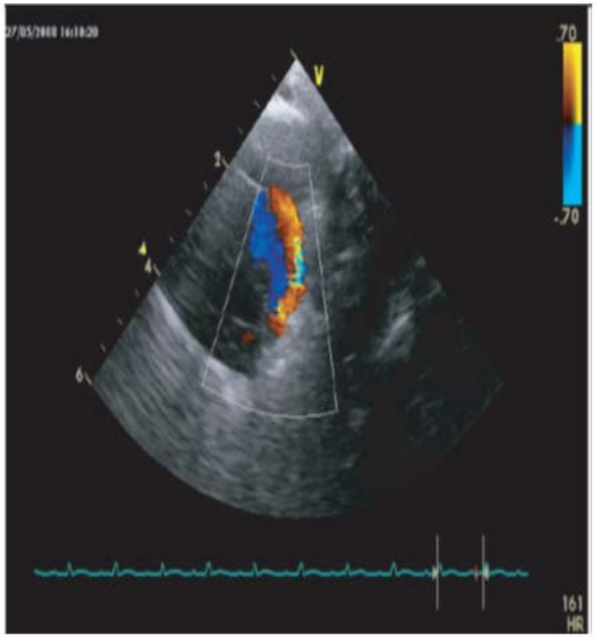


Mas de 50% de los pacientes del grupo control recibieron tratamiento

PDA tolerate trial – 63%
“ menos hipotension refractaria la primera semana de vida”

Hundscheid 2018 BMC Pediatrics, Clyman 2018 J Peds

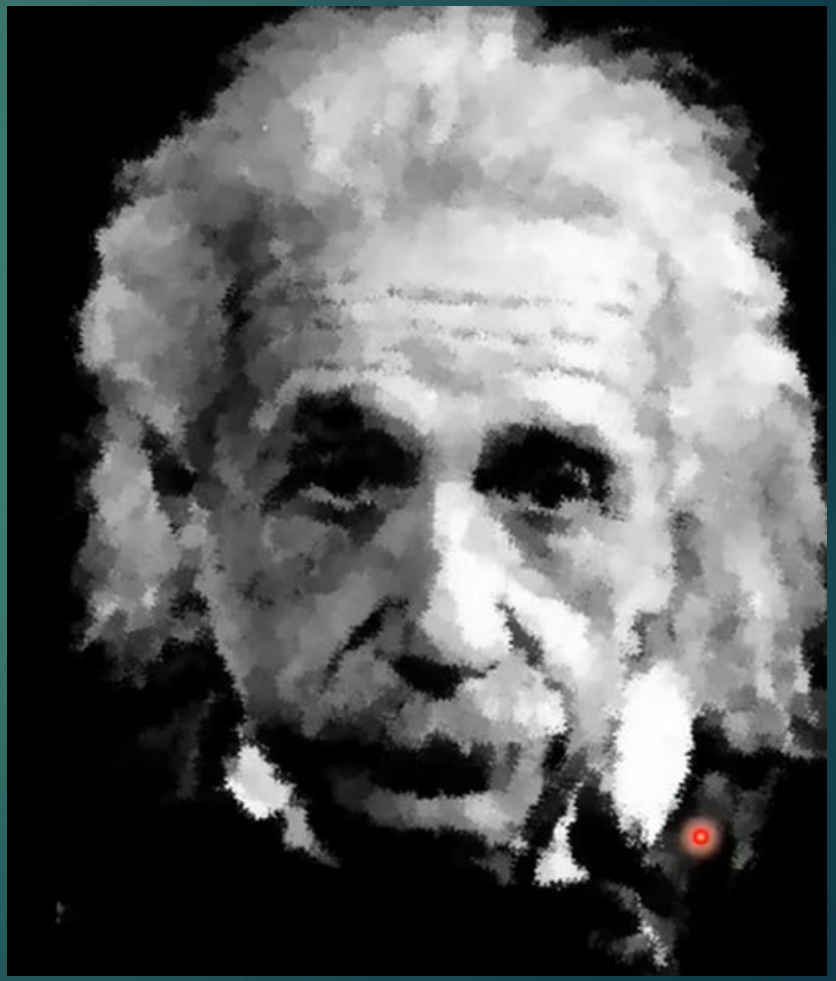




2. La evaluación ecográfica es limitada

- Error de medición [Operador]
- Error de medición [Equipamiento]
- Error de medición [ubicación]

- Si tuviera una hora para resolver un problema y mi vida dependiera de la solución, dedicaría los primeros 55 minutos a determinar la pregunta adecuada a formular, porque una vez que sepa la pregunta adecuada, podría resolver el problema en cinco minutos.
- Albert Einstein



Argumentos para cuestionar diagnóstico:

1. Todas las series de uso terapéutico o profiláctico fueron sesgadas

2. La evaluación clínica del DAP es limitada

3. Ecocardiografia Contemporánea es limitada

Sin embargo: La evaluación ecocardiográfica integral realizada por especialistas en hemodinámica proporciona una mayor precisión fisiológica

DETERMINANTES DEL RIESGO EN DAP

Lower Risk	Determinants of Risk (hsPDA)	Higher Risk
No	**Tachycardia**	Yes
No	**Tachypnea**	Yes
No need for respiratory support or oxygen, stable Spo_2 and Pao_2	**Respiratory support**	Need for invasive or non-invasive respiratory support Worsening respiratory situation (eg, increasing flow and Fio_2 on HFNC; increasing PEEP, PIP and Fio_2 on CPAP; NIV; MV) and frequent desaturations
Abdomen soft, not distended	**Abdominal signs and symptoms**	Abdominal distension, residual feeding volume (other pre-NEC signs)
Not present	**Signs of organ dysfunction**	Renal failure, NEC, impaired NIRS variables
• LA only mildly dilated: LA/Ao ≤ 1,2 (PLAX) • Normal LV size • Normal systolic LV function (LVEF ≥ 55%) • Ductal Diameter ≤ 1 mm (at narrowest ID) • PDA Vmax ≥ 3 m/s (CW Doppler) • Ductal systolic and diastolic left-to-right flow ≥ 2 m/s (continuous) usually indicates narrowing (closing) PDA • Normal mean and diastolic PA flow • ACA RI ≤ 0,75 • No (or only early) diastolic retrograde DAO flow	**Echocardiography, Doppler sonography (cerebral, abdominal)**	• Severe LA dilation: LA/Ao ≥ 1,4 (PLAX) • Severe LV dilation (4C view, PSAX) • Systolic LV dysfunction (LVEF < 50%) • Ductal diameter ≥ 2 to 3 mm (at narrowest ID) or ductal diameter greater than or equal to MPA diameter • PDA Vmax ≤ 2 m/s (CW, unrestrictive) • Ductal left-to-right diastolic flow ≥ 0,5 m/s • Highly elevated mean + diastolic PA flow • Severe PA dilation (eg, LPA > AAO) • ACA RI ≥ 0,9 • Holodiastolic retrograde DAO flow (steal)

PEDIATRICS Volume 146, number 5, November 2020:e20201209. State Of the Art Review Article. Patent Ductus Arteriosus of the Pret
Infant

DETERMINANTES DE LA SIGNIFICANCIA DEL DAP

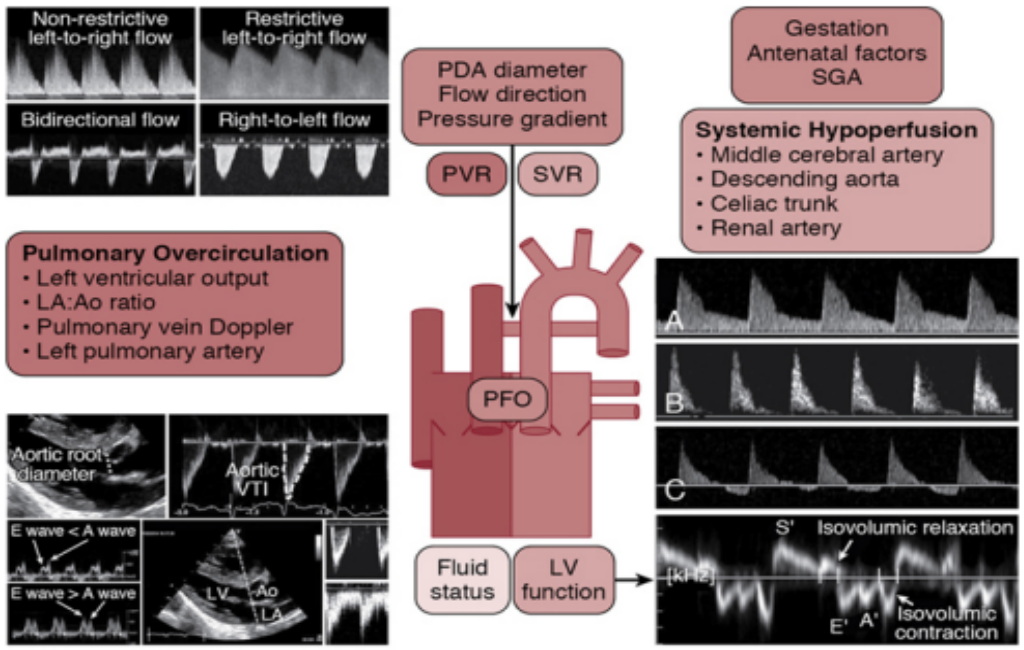


FIG. 16.8 Determinants of hemodynamic significance of a patent ductus arteriosus (PDA). Volume of the shunt, left ventricular function, and clinical parameters are all important in determining treatment. *Ao*, Aorta; *LA*, left atrium; *LV*, left ventricle; *PFO*, patent foramen ovale; *PVR*, pulmonary vascular resistance; *SGA*, small for gestational age; *SVR*, systemic vascular resistance; *VTI*, velocity time integral.

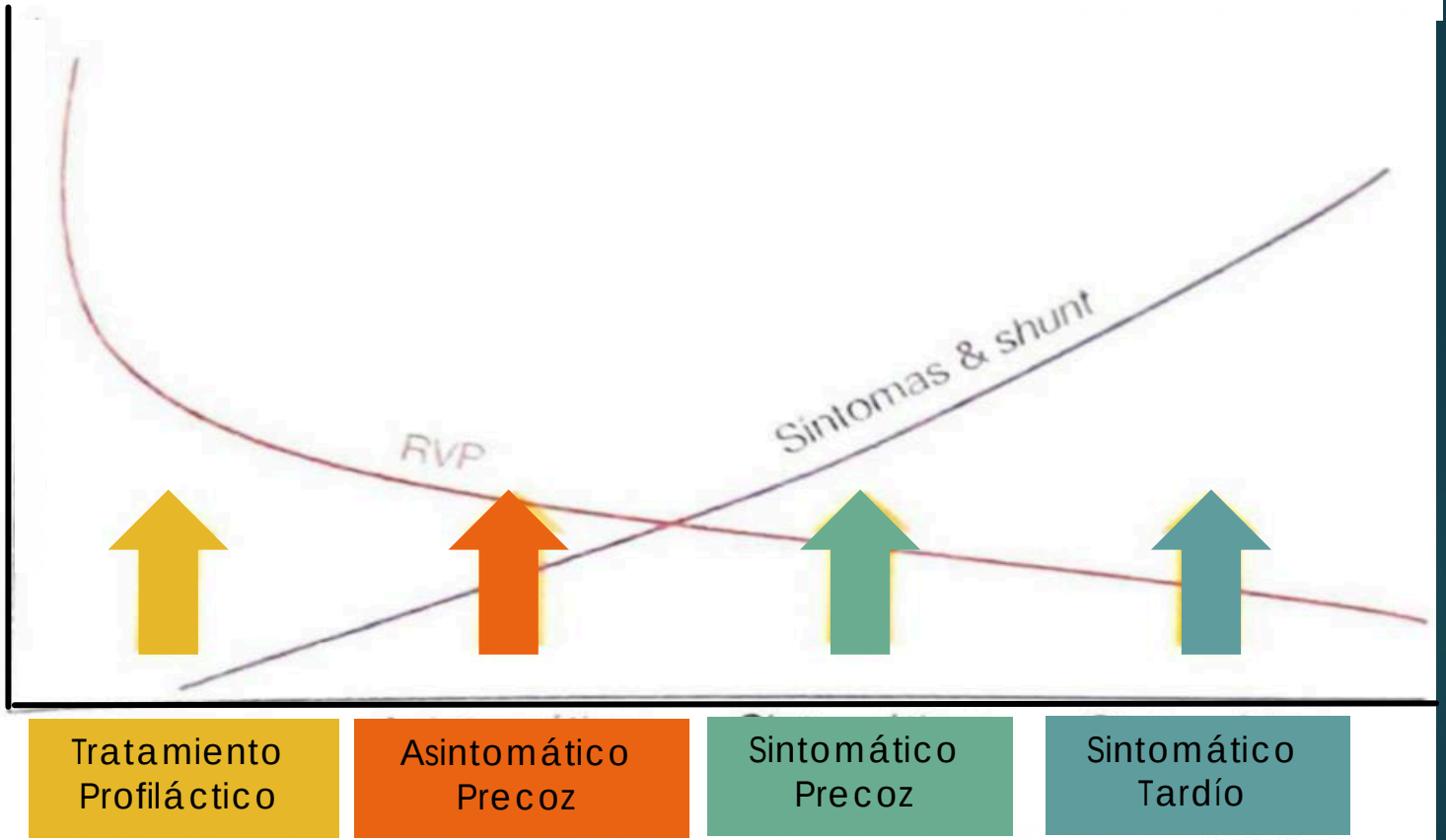
TRATAMIENTO: GENERAL

Ambiente térmico neutro	• Minimizar demanda de oxígeno.
Adecuada oxigenación y apoyo ventilatorio	• PEEP mod-alto para ↓ EPA y consecuencia del shunt por el DAP.
Evitar aporte excesivo líquidos	• Balance para aporte adecuado y evitar restricción liquidos con falla renal 2°.
Hcto >35%	• Mejorar entrega de oxigeno si la perfusión esta limitada.
Evitar uso de furosemida	• Estimula secreción PGE2, con desarrollo DAP.

Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)
Waal K., Prasad R., Kluckow M. Seminars in Fetal and Neonatal Medicine 26 (20

TRATAMIENTO:MODALIDADES

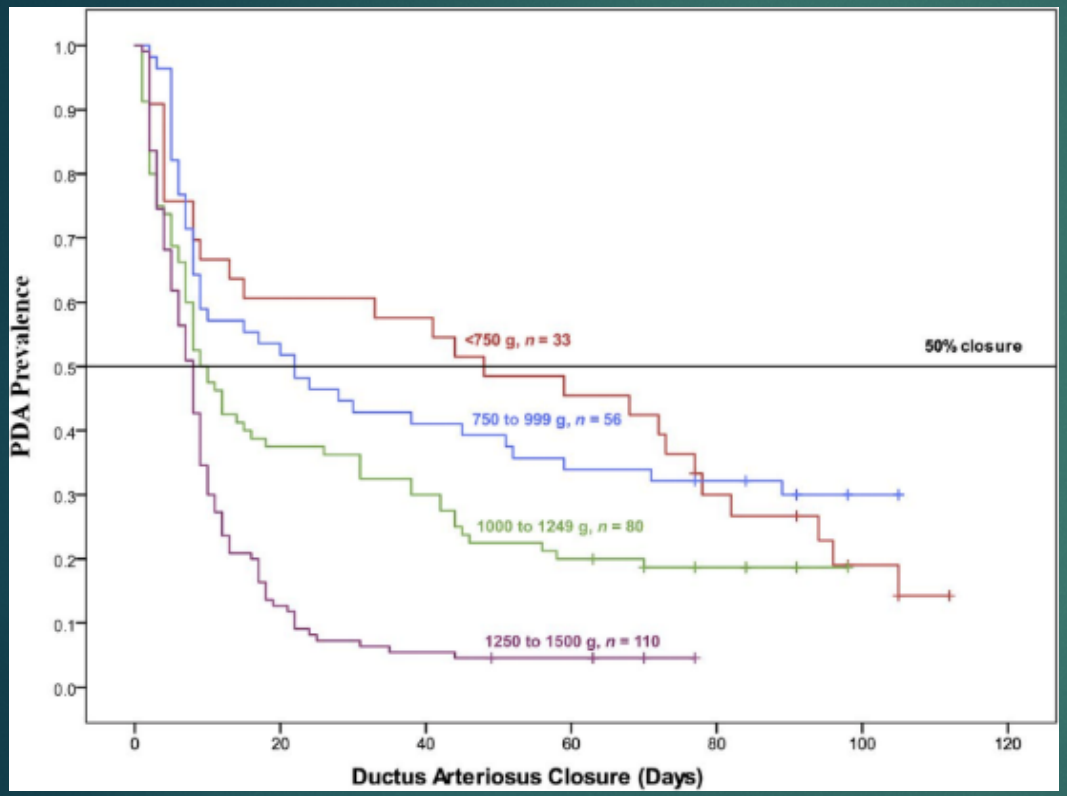
Fig. 46-4. Períodos de tratamiento DAP



Singh Y, et al. Front Pediatr. 8:573627.

Tapia, J.L., Gonzalez A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología*. Ed 4ª. (p 397-406)

EL CIERRE ESPONTANEO OCURRE CON ALTA FRECUENCIA



Miletin 2015 J Pedi

- ¿Es un riesgo aceptable la exposición de 50% de los prematuros < 750 gramos?
- ¿Como ocurre el cierre espontáneo?
  - Remodelación natural del DAP
  - modelación del flujo secundaria a remodelacion vascular pulmonar

www.nature.com/jp

Journal of Perinatology

ARTICLE

Check for updates

Natural evolution of the patent ductus arteriosus in the extremely premature newborn and respiratory outcomes

Gabriela de Carvalho Nunes [1], Punnanee Wutthigate[1], Jessica Simoneau[1], Marc Beltempo [1], Guilherme Mendes Sant'Anna [1] and Gabriel Altit [1] ✉

OBJECTIVE: Evaluate spontaneous closure of the patent ductus arteriosus (PDA) in extremely preterm infants and their respiratory outcomes, especially at <26 weeks gestational age (GA).
STUDY DESIGN: Retrospective study in <29 weeks, admitted within 24 h after birth (Feb 2015 and Dec 2019). Infants without any intervention to promote ductal closure, ≥1 echocardiography, and alive at discharge were included.
RESULTS: Two hundred and fourteen infants (average GA 26.3 ± 1.5 weeks) were included; 84 (39%) <26 weeks. PDA closed spontaneously in 194 (91%); 76/84 (90%) for infants <26 weeks. PDA closure was ascertained on an echocardiography performed at a median age of 36.4 [34.4–40.1] weeks. Rate of moderate-to-severe bronchopulmonary dysplasia decreased throughout the study period (OR for year of birth: 0.70 [95% CI: 0.57–0.87], $p = 0.001$).
CONCLUSION: Majority of extremely preterm infants, including <26 weeks, had spontaneous closure of the ductus before term corrected age. There was a concomitant improvement of respiratory outcomes.

Journal of Perinatology (2022) 42:642–648; https://doi.org/10.1038/s41372-021-01277-2

Table 2. Spontaneous closure of the Ductus arteriosus (DA) in survivors to hospital discharge.

	≥26 weeks *n* = 130	<26 weeks *n* = 84
During NICU stay		
Spontaneous closure	86 (66)	64 (76)
Age at spontaneous closure, days	57 [41–70]	81 [60–88]
CGA at spontaneous closure, weeks	35.7 [33.0–36.7]	36.1 [34.1–37.2]
After NICU discharge		
Spontaneous closure	32 (25)	12 (14)
Age (post-discharge) at spontaneous closure, days	204 [145–309]	129 [99–362]
CGA (post-discharge) at spontaneous closure, weeks	57.3 [48.0–71.9]	43.1 [39.1–77.4]
After NICU discharge		
DA still patent	12 (9)	8 (10)
Age at follow-up with open DA, days	230 [23–548]	427 [221–555]
CGA at follow-up with open DA, weeks	60.1 [31.8–105.4]	85.3 [56.1–103.7]
Spontaneous closure (total)	118 (91)	76 (90)

Results as expressed as mean (standard deviation), median [Interquartile range] or number (percentage).
DA ductus arteriosus, *ECHO* echocardiography, *NICU* neonatal intensive care unit, *CGA* corrected gestational age.

La probabilidad de cierre ductal espontáneo (CDE) es también esencial. Dicha probabilidad es alta en caso de EG> 28 semanas, peso >1000 g, DA pequeños (<1.4 mm/Kg en 2D, 2 mm/Kg en color) y flujo continuo a alta velocidad (>2.5 m/seg). Un NT-proBNP "bajo" (<5000 ng/mL) o en descenso sugiere CDE, respuesta al tratamiento y escasa repercusión hemodinámica.

DAP Y DBP

APS European Society for Paediatric Research SPR Society for Pediatric Research

www.nature.com/pr

CLINICAL RESEARCH ARTICLE

Check for updates

Patent ductus arteriosus and the risk of bronchopulmonary dysplasia-associated pulmonary hypertension

Hythem Nawaytou[1], Nancy K. Hills[2,3] and Ronald I. Clyman[1,4]✉

BACKGROUND: The aim of the study was to determine whether prolonged exposure to a moderate/large patent ductus arteriosus left-to-right shunt (PDA) increases the risk of late (beyond 36 weeks) pulmonary hypertension (BPD-PH) and pulmonary vascular disease (BPD-PVD) during the neonatal hospitalization in preterm infants (<28 weeks' gestation) with bronchopulmonary dysplasia (BPD).

METHODS: All infants requiring respiratory support ≥36 weeks had systematic echocardiographic evaluations for BPD-PH at planned intervals. Infants were classified as having either flow-associated BPD-PH (BPD-flow-PH) or BPD-PVD.

RESULTS: 256 infants survived ≥36 weeks: 105 had NO BPD (were off respiratory support by 36 weeks); 151 had BPD. 22/151 had BPD-PH (12/22 had BPD-flow-PH from a PDA that persisted beyond 36 weeks; 10/22 had BPD-PVD). Moderate/large PDA shunts that persisted beyond 36 weeks were significantly associated with an increased incidence of BPD-PH due to BPD-flow-PH. We found no association between the duration of PDA exposure and the incidence of BPD-PVD.

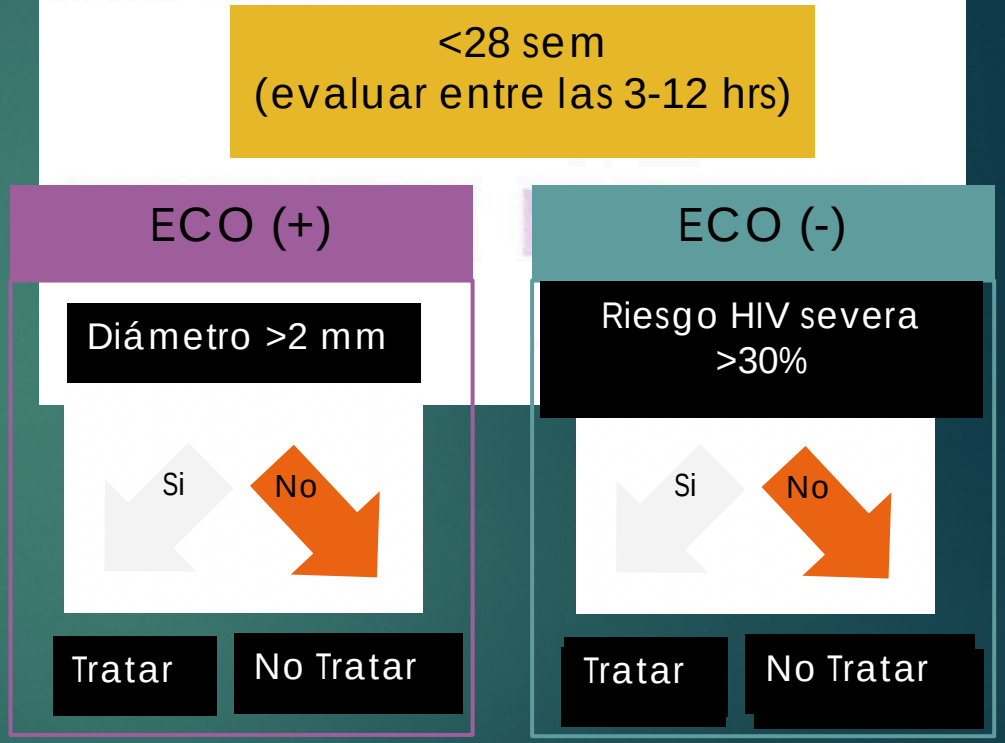
CONCLUSIONS: Moderate/large PDA shunts increase the risk of flow-associated BPD-PH when present beyond 36 weeks. Although term infants with PDA-congenital heart disease can develop pulmonary vascular remodeling and PVD after months of PDA exposure, we found no echocardiographic evidence in preterm infants that prolonged PDA exposure increases the incidence of BPD-PVD during the neonatal hospitalization.

Pediatric Research (2023) 94:547–554; https://doi.org/10.1038/s41390-023-02522-4

¿Cómo tratar?

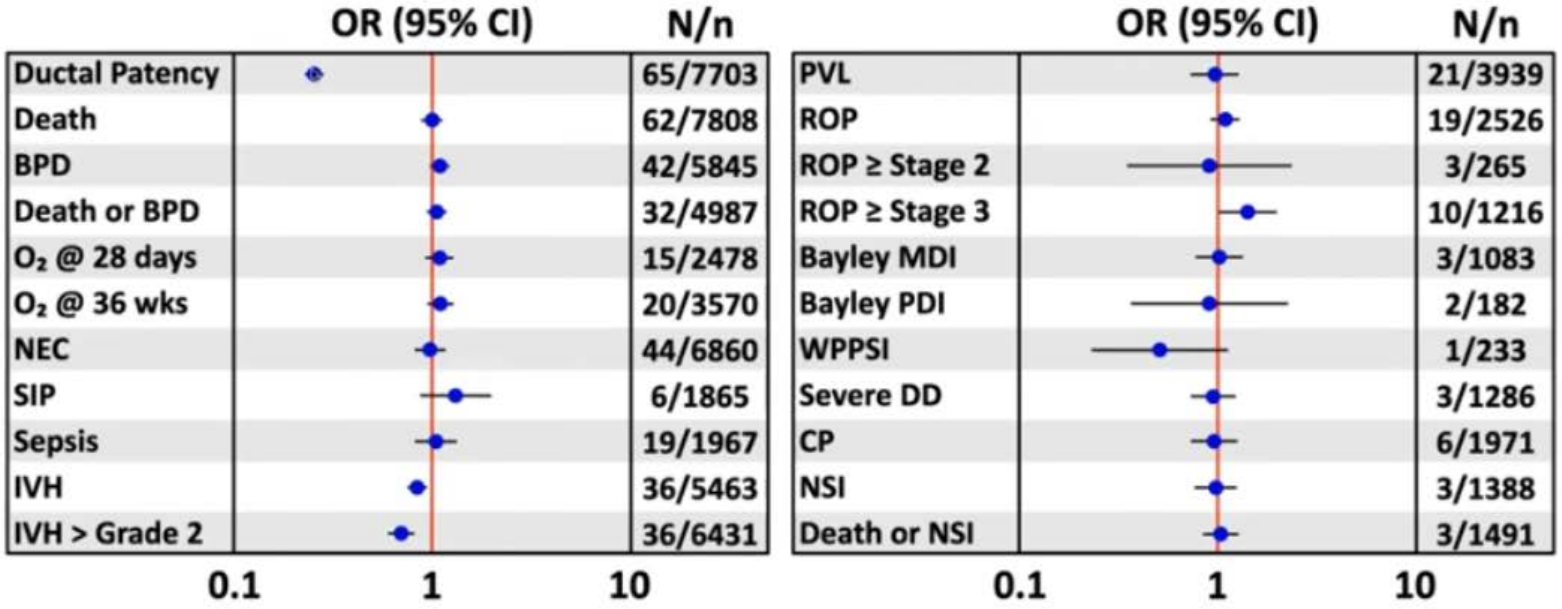
TRATAMIENTO: PROFILÁCTICO

Figura 46-5. Esquema de tratamiento profiláctico en el prematuro < 28 semanas.



., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)

PDA Treatment/Prophylaxis: 67 RCT Reports Including 8057 Subjects



Results are not different for trials selected by agent, indication, route (PO or IV), age at treatment, use of rescue, year of trial, or subject gestational age.

N = reports, n = subjects
Updated April 25, 2022

Hirano 2007, Lin 2012, Sankar 2020, El-Khuffash 2021, Rozé 2021, Potsiurko 2022, Hundscheid 2022, Gupta 2022

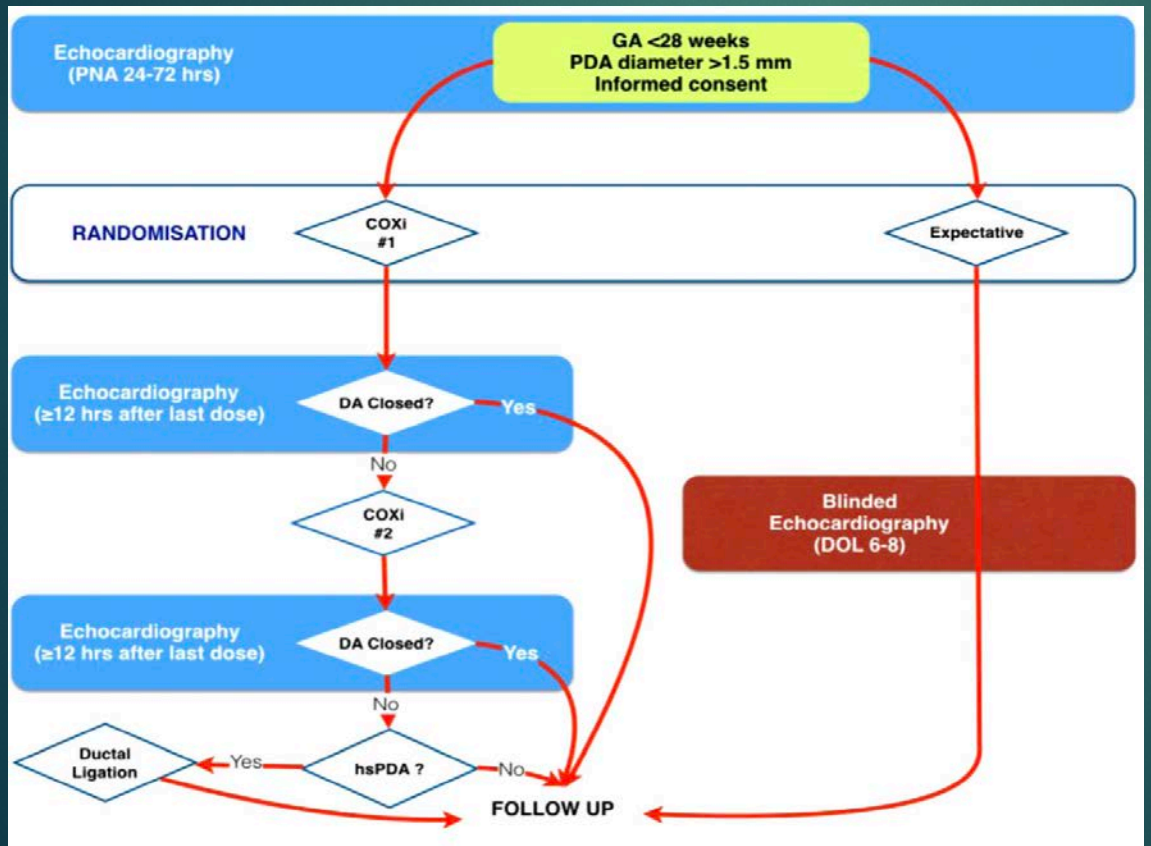
Hundscheid et al. BMC Pediatrics (2018) 18:262
https://doi.org/10.1186/s12887-018-1215-7

BMC Pediatrics

STUDY PROTOCOL Open Access

Early treatment versus expectative management of patent ductus arteriosus in preterm infants: a multicentre, randomised, non-inferiority trial in Europe (BeNeDuctus trial)

Tim Hundscheid[1*], Wes Onland[2], Bart van Overmeire[3], Peter Dijk[4], Anton H. L. C. van Kaam[5], Koen P. Dijkman[6], Elisabeth M. W. Kooi[4], Eduardo Villamor[7], André A. Kroon[8], Remco Visser[9], Daniel C. Vijlbrief[10], Susanne M. de Tollenaer[11], Filip Cools[12], David van Laere[13], Anne-Britt Johansson[14], Catheline Hocq[15], Alexandra Zecic[16], Eddy Adang[17], Rogier Donders[17], Willem de Vries[10], Arno F. J. van Heijst[1] and Willem P. de Boode[1]



Métodos:

- E° multicéntrico, aleatorizado UCIN.
- RNPT < 28 sem con DAP con diámetro transductal > 1,5 mm.
- Tratamiento precoz (24 y 72 h) con COX1 ibuprofeno v/s manejo expectante.

Resultados esperados:

- **Resultado 1°:** mortalidad y/o NEC estadio Bell ≥ IIa, y/o DBP.
- **Resultado 2°:** secuelas a corto plazo insuf. cardiovascular, desarrollo neurológico a los 2 años.

Tratamiento Expectante o Ibuprofeno precoz ?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Expectant Management or Early Ibuprofen for Patent Ductus Arteriosus

T. Hundscheid, W. Onland, E.M.W. Kooi, D.C. Vijlbrief, W.B. de Vries, K.P. Dijkman, A.H. van Kaam, E. Villamor, A.A. Kroon, R. Visser, S.M. Mulder-de Tollenaer, B. De Bisschop, P.H. Dijk, D. Avino, C. Hocq, A. Zecic, M. Meeus, T. de Baat, F. Derriks, T.B. Henriksen, K.J. Kyng, R. Donders, D.H.G.M. Nuytemans, B. Van Overmeire, A.L. Mulder, and W.P. de Boode, for the BeNeDuctus Trial Investigators*

- The study was underpowered recruiting half of the original target group.
- We don't know if the control arm were exposed to chronic PDA shunting.
- Selecting patients for treatment based on PDA diameter alone (especially after day 2) is no better than flipping a coin - many babies with a PDA diameter >1.5mm do not need treatment
- There is no data on whether ibuprofen treatment resulted in shunt elimination.
- There was a relatively high rate of Paracetamol use in both arms.
- The rate of the primary outcomes in both groups are relatively low suggesting that many infants entered into this trial were relatively low risk and did not warrant treatment.

PDA-TOLERATE Trial: An Exploratory Randomized Controlled Trial of Treatment of Moderate-to-Large Patent Ductus Arteriosus at 1 Week of Age

Ronald I. Clyman, MD[1,2], Melissa Liebowitz, MD[1], Joseph Kaempf, MD[3], Omer Erdeve, MD[4], Ali Bulbul, MD[5],

Diseño: 202 RN <28 sem con PDA moderado-grande, 6 y 14 DDV.

- Ensayo controlado randomizado, 2014- 2017

Resultados

- Sin diferencias resultado 1° (ligadura Qx o DAP al alta).
- Sin diferencias resultado 2°: DBP, muerte, y necesidad VM.
- ERT < necesidad soporte inotrópico, > retraso alimentación completa, > tasas sepsis tardía y muerte RNPT ≥26 sem.

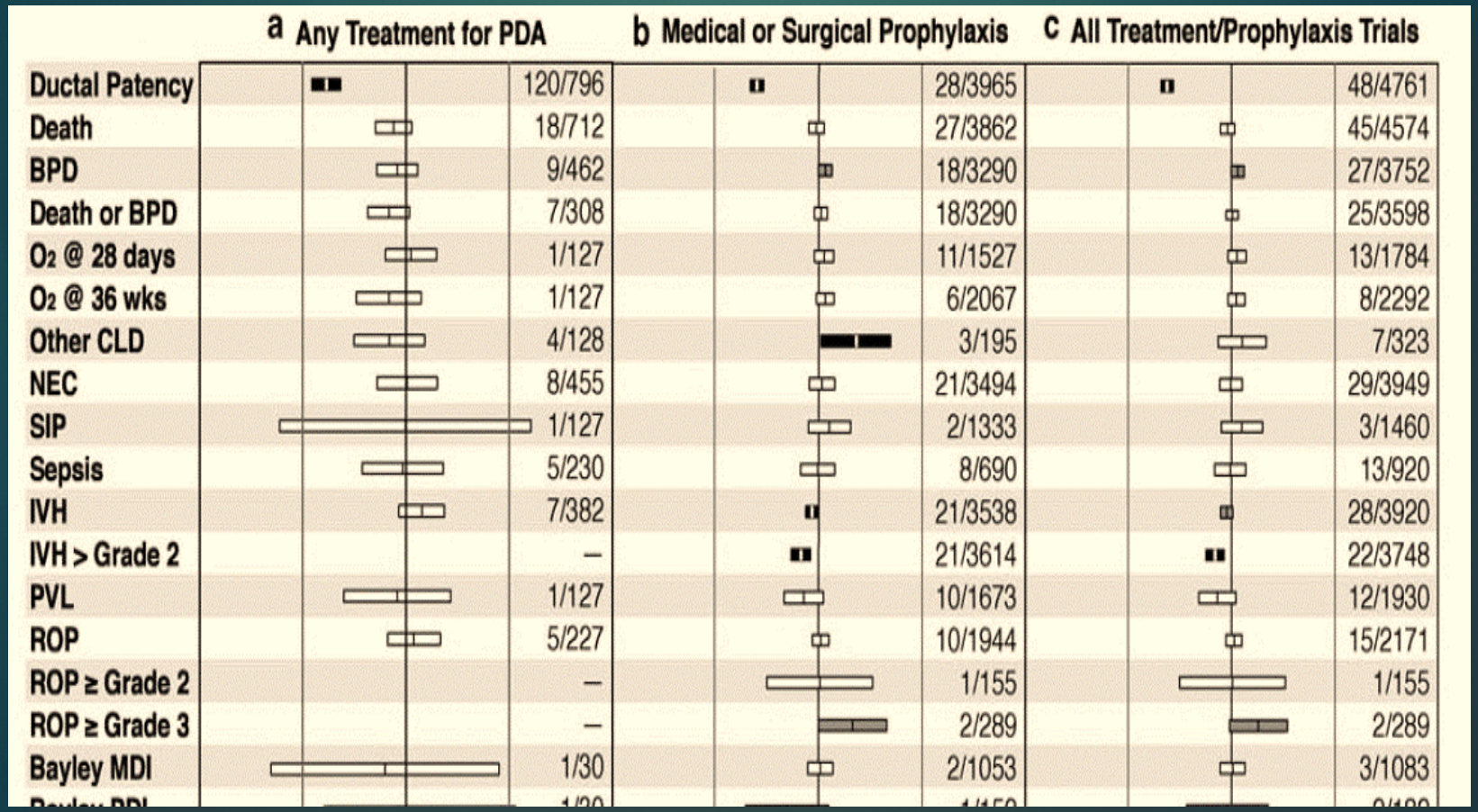
Table VI. Neonatal outcomes in infants <26 weeks and ≥26 weeks gestation

Outcomes	<26 wk (n = 106)			≥26 wk (n = 96)		
	CT group (n = 51)	ERT group (n = 55)	Risk ratio (95% CI)	CT group (n = 47)	ERT group (n = 49)	Risk ratio (95% CI)
Primary outcome						
Ligation or outpatient PDA follow-up, %	44	31	0.72 (0.43-1.20)	34	32	0.93 (0.52-1.70)
PDA ligation, %	18	15	0.86 (0.36-2.00)	6.4	8.9	1.40 (0.33-5.90)
Outpatient PDA follow-up, %	26	16	0.63 (0.28-1.40)	28	23	0.82 (0.40-1.70)
Secondary outcomes						
NEC, %*	24	18	0.76 (0.36-1.60)	13	13	0.94 (0.33-2.70)
BPD, %	70	62	0.89 (0.66-1.20)	37	36	0.97 (0.56-1.70)
BPD or death, %	75	69	0.93 (0.73-1.20)	38	45	1.20 (0.72-1.90)
Death, %	18	22	1.20 (0.57-2.70)	2.1	16†	7.70 (1.04-59.0)
PDA (moderate/large) 10 d after randomization, %*	80	47‡	0.59 (0.43-0.80)	79	33‡	0.42 (0.27-0.66)
Rescue criteria met, %	80	40‡	0.50 (0.34-0.71)	43	20†	0.47(0.24-0.92)
Received rescue treatment, %	63	23‡	0.36 (0.21-0.62)	34	13†	0.39 (0.17-0.91)
Received furosemide ≥14 d, %*	49	40	0.82 (0.53-1.30)	43	29	0.67 (0.39-1.20)
Days until enteral intake 120 ml/kg/d, median (IQR)*	20 (10-31)	18.5 (11-31)	0.92 (0.85-1.00)¶	6 (3-14)	14† (4.5-19)	2.30 (2.10-2.60)¶
Daily weight gain, g/kg/d, mean ± SD*	21.2 ± 4.6	21.4 ± 4.1	−0.26 (−2.10 to 1.60)¶	24.2 ± 4.2	23.7 ± 5.2	0.59 (−1.40 to 2.60)¶
Days until last gavage feeding, median (IQR)*	88 (74-118)	90 (74-116)	0.96 (0.92-1.00)¶	65 (49-84)	68 (57-84)	1.20 (1.20-1.30)¶
Other exploratory analyses						
Pulmonary hemorrhage, %*	2.0	1.8	0.93 (0.06-14.4)	2.1	2.0	0.96 (0.06-14.9)
sIVH, %	15.7	23.6	0.93 (0.32-2.70)	6.4	12.2	1.4 (0.25-8.20)
PVL (cystic), %	20	13	0.64 (0.26-1.50)	2.1	12	5.8 (0.72-46.0)
ROP (treated), %	30	24	0.81 (0.41-1.60)	2.2	12§	5.5 (0.67-45.0)
Pneumonia, %*	13	7	0.53 (0.16-1.70)	4	8	1.9 (0.37-10.0)
Bacteremia, %*	29	35	1.17 (0.67-2.10)	13	24	1.9 (0.78-4.70)
Bacteremia, CONS, %*	2	7	0.23 (0.03-2.01)	6	0	**
Bacteremia Non-CONS, %*	27	27	0.99 (0.53-1.90)	6	24†	3.8 (1.20-12.7)
Received dopamine ≥3 d, %*	44	22†	0.49 (0.26-0.90)	6.4	4.3	0.67 (0.12-3.80)
Received corticosteroids ≥7 d, %*	53	42	0.79 (0.53-1.20)	21	12	0.58 (0.23-1.50)
Days until discharge, median (IQR)*	103 (91-129)	106 (89-127)	0.98 (0.95-1.00)¶	76 (62-94)	78 (63-97)	1.2 (1.10-1.20)¶

Univariate analyses examining the effects of treatment assignment on neonatal outcomes are presented

Clyman R., et al. J Pediatr. 2019 Feb;205:41-48.e6.

1. Todas las series están sesgadas



Utilidad del tratamiento

Journal of Paediatrics. 2020 Dec 9;S0022-3476(20)31488-8

Effect of Early Targeted Treatment of Ductus Arteriosus with Ibuprofen Survival Without Cerebral Palsy at 2 Years in Infants with Extreme Prematurity: A Randomized Clinical Trial

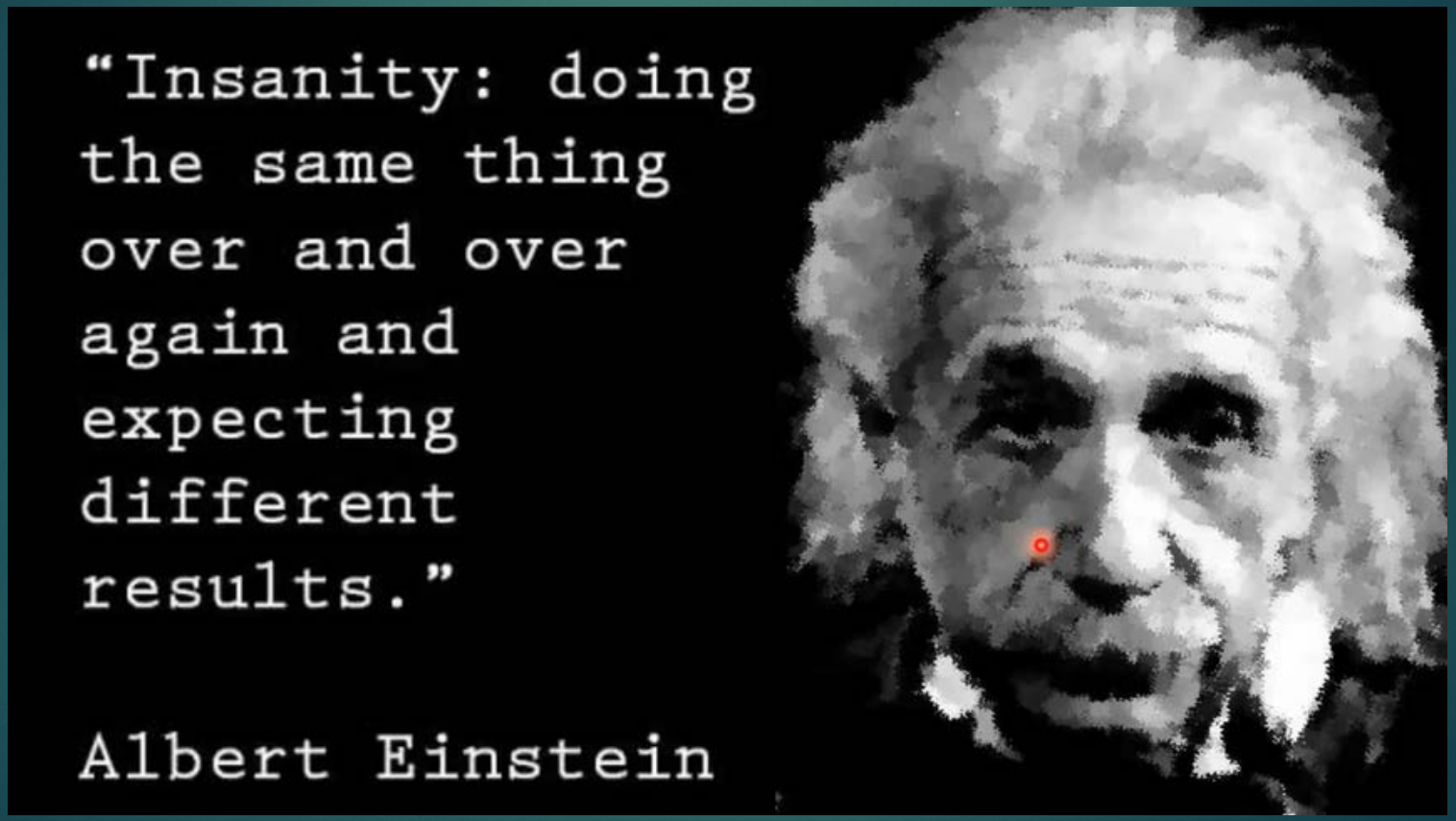
Question: We hypothesized that the early elimination of a PDA shunt with ibuprofen might improve long-term neurodevelopmental outcomes.

Study design: Infants <28 weeks a large PDA at 6-12 hours after birth to ibuprofen or placebo by 12 hours of age. Open-label ibuprofen was allowed for pre-specified criteria

Primary outcome: Survival without cerebral palsy at 24 months of corrected age.

Results: 228 were randomized. Survival without cerebral palsy occurred in 77 of 108 (71.3%) after ibuprofen, 73 of 102 (71.6%) after placebo (adjusted relative risk 0.98, 95% CI 0.83-1.16, P = .83), and 77 of 101 (76.2%) in reference group.

Conclusions: Early echocardiography-targeted ibuprofen treatment of a large PDA did not change the rate of survival without cerebral palsy.


“Insanity: doing the same thing over and over again and expecting different results.”
Albert Einstein

TRATAMIENTO: MÉDICO

	Dosis	Vía	Contraindicaciones
Indometacina	**<48 hrs:** 0,2 mg/kg inicial. Luego 2 dosis de 0,1 mg/kg cada 12 hrs **2-7 días:** 0,2 mg/kg inicial. Luego 2 dosis de 0,2 mg/kg cada 12 hrs **>7 días:** 0,2 mg/kg inicial. Luego 2 dosis de 0,25 mg/kg cada 12 hrs	Endovenosa	Contraindicaciones: BUN>50MG% Crea >1,8 mg/% Plaquetas <50.000 Diátesis hemorrágica NEC *Infusiones deben ser lentas: 2-3 hrs.
Ibuprofeno	10 mg/kg inicial, luego 2 dosis de 5 mg/kg cada 24 hrs	Endovenosa Oral	Precaución si plaquetas <50.000 → > riesgo diátesis hemorrágica
Paracetamol	15 mg/kg/dosis cada 6 hrs por 3-5 días	Endovenosa Oral	No usar en falla hepática. *Control pruebas hepáticas 24-48 hrs.

Tapia, J.L., González A. (2018). Cap 46 DAP. Luco M, et al. *Neonatología.* Ed 4°. (p 397-406)

RESEARCH

2017

JPPT | Clinical Investigation

Acetaminophen for Patent Ductus Arteriosus in Extremely Low-Birth-Weight Neonates

Caitlyn M. Luecke, PharmD; Caren J. Liviskie, PharmD; Brandy N. Zeller, PharmD; Zachary A. Vesoulis, MD; and Christopher McPherson, PharmD

MÉTODOS: dosis PCT 15 mg/kg c/ 6 hrs (88 % IV).

- Marcadores fn hepática y renal, soporte respiratorio y morbilidades para describir seguridad del PCT.

RESULTADOS: N° 41 RN → mediana PN 760 g y mediana EG 25 sem.

- 27 RN (66 %) no requirieron más tratamiento → Sin RAM en terapia con PCT.

Table 2. Patient Characteristics of Responders and Non-Responders to Acetaminophen

Table 3. Safety Parameters

Parameter	Baseline	Treatment	p value
Alanine transaminase, units/L, median (IQR)	6 (0–8)	8 (5–13)	0.019
Aspartate transaminase, units/L, median (IQR)	24 (19–30)	25 (19–35)	0.362
Alkaline phosphatase, units/L, median (IQR)	405 (263–604)	381 (328–636)	0.286
Bilirubin, mg/dL, median (IQR)	3.0 (1.6–4.4)	2.8 (1.8–3.8)	0.314
Serum creatinine, mg/dL, median (IQR)	0.6 (0.4–1.0)	0.5 (0.4–0.8)	0.040
Positive end expiratory pressure, mm Hg, median (IQR)	6 (5–7)	6 (5–7)	1
Fraction of inspired oxygen, median (IQR)	0.37 (0.27–0.49)	0.35 (0.26–0.42)	0.131
Any intraventricular hemorrhage, n (%)	19 (46)	19 (46)	1
Grade III/IV intraventricular hemorrhage, n (%)	9 (22)	9 (22)	1
Necrotizing enterocolitis, n (%)	0 (0)	4 (10)	0.13
Spontaneous intestinal perforation, n (%)	7 (17)	8 (20)	1

Luecke CM., et al. J Pediatr Pharmacol Ther 2017;22(6):461–466

JAMA | Original Investigation

2018

Association of Placebo, Indomethacin, Ibuprofen, and Acetaminophen With Closure of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Infants
A Systematic Review and Meta-analysis

Souvik Mitra, MD; Ivan D. Florez, MD, MSc; Maria E. Tamayo, MD, MSc; Lawrence Mbuagbaw, MD, PhD; Thuva Vanniyasingam, MSc; Areti Angeliki Veroniki, PhD; Adriana M. Zea, RD; Yuan Zhang, PhD; Behnam Sadeghirad, PharmD, MPH; Lehana Thabane, PhD

OBJETIVOS

- Calcular probabilidad cierre DAP con compromiso HDN con intervenciones farmacoterapéuticas y sus RAMS.

FUENTES DE DATOS: MEDLINE, Embase y Cochrane → 2015- 2017.

- ECA RNPT <37 sem tratados con indometacina, ibuprofeno o acetaminofén IV/VO.

RESULTADOS:

- Resultado 1°: cierre del PDA hemodinámicamente significativo
- Resultado 2°: cierre quirúrgico, mortalidad, NEC, y HIV.

RESULTADOS: 68 Estudios Controlados Aleatorizados → 4802 RN

- Tasa general cierre DAP: 67,4 %.
- Una dosis alta ibuprofeno VO → probabilidad significativamente > cierre DAP v/s dosis estándar IV.
- Sin diferencias significativas en mortalidad, NEC, HIV v/s placebo.

Souvik Mitra, et al. *JAMA*. 2018;319(12):1221-1238.

Received: 21 April 2021 | Revised: 1 June 2021 | Accepted: 2 June 2021

DOI: 10.1111/apa.15970

2021

ACTA PÆDIATRICA
NURTURING THE CHILD
WILEY

EBNEO COMMENTARY

Is intravenous paracetamol as effective as ibuprofen in closing haemodynamically significant patent ductus arteriosus after the first treatment course in preterm babies?

Asad Abbas | Matthew Cawsey

Birmingham Women's Hospital, Birmingham, UK

Método: E° controlado aleatorio prospectivo → RN 25+0 y 31+6 sem.

- Objetivo comparar un ciclo de 3 días de paracetamol IV v/s ibuprofeno IV para cerrar hsPDAP.

E° PDA-TOLERATE

- En comparación con la tasa de cierre espontáneo DAP, la razón de probabilidad de cierre ductal inducido por paracetamol fue menor v/s ibuprofeno.
- PCT TTO DAP: < incidencia de trombocitopenia y < RAMS renales y gastrointestinales.

2 RS que compararon PCT v/s ibuprofeno

- Diferencia significativa a favor del paracetamol en niveles creatinina, producción orina, recuento plaquetas, bilirrubina e incidencia hemorragia gastrointestinal.

Abbas A., Matthew Cawsey M. *Acta Paediatrica*. 2021;00:1–2.

RCT of Selective Early Treatment of PDA with Ibuprofen for Prevention of Death or BPD (OSCAR Trial)

- Multicenter, placebo-controlled, masked trial in the UK
- Infants between 23 to 28+6 weeks
- Diagnosed with large PDA on echocardiogram within 72 hr after birth
    - DA diameter > 1.5 mm
    - Pulsatile or growing pulse wave doppler flow
- Randomized to treatment with iv Ibuprofen or placebo
- Primary Outcome was rate of death or moderate/severe BPD

Gupta S. et al. Arch Dis Child 2022; 107:A148.

RCT of Selective Early Treatment of PDA with Ibuprofen fo Prevention of Death or BPD (OSCAR Trial)

	Ibuprofen N=324	Placebo N= 322	Adjusted Effect Estimate (95% CI)
Death or Mod/Severe BPD	69.2%	63.5%	1.09 (0.98-1.20)
Death by 36 wk	13.6%	10.3%	1.32 (0.92-1.90)
Mod or Severe BPD	64.2%	59.3%	1.09 (0.96-1.23)
Severe IVH	13.9%	10.6%	1.30 (0.93-1.82)
NEC (Bell 2-3)	12.7%	12.7%	1.01 (0.67-1.51)
Closed PDA at 3 wk	55.5%	37.0%	1.50 (1.30-1.74)
Surgical ligation	2.8%	9.6%	0.29 (0.18-0.47)

Gupta S. et al. Arch Dis Child 2022; 107:A148.

Paracetamol oral vs iv

Pediatric Cardiology (2023) 44:748–756
https://doi.org/10.1007/s00246-022-03053-1

REVIEW

A Network Meta-Analysis of Intravenous Versus Oral Acetaminophen for Patent Ductus Arteriosus

Abiola Olowoyeye[1,2] · Onyinye Nnamdi-Nwosu[3] · Maika Manalastas[1,2] · Charles Okwundu[4]

Received: 2 September 2022 / Accepted: 14 November 2022 / Published online: 24 November 2022

Abstract
The use of acetaminophen to close a PDA in preterm infants is increasing; however, the most effective route of administration is not yet known. This network meta-analysis compares the efficacy of IV versus PO routes of acetaminophen administration on clinical outcomes related to the presence of a PDA in preterm neonates. Medline, Embase, Cochrane Central Register of Controlled Trials, Embase, Web of Science, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform were searched from inception to October 2020. A total 21 randomized controlled trials in neonates less than 37 weeks at birth, comparing oral or intravenously administered acetaminophen to close a PDA based on study criteria were included. Two authors extracted data independently and in duplicate. All outcomes were binary, and a frequentist network meta-analysis was performed. After one or two courses, both PO and IV acetaminophen were efficacious in closing a PDA with oral ranking higher than IV (low confidence). Neither medication was better than no treatment for secondary outcomes of NEC or BPD (moderate and low confidence respectively). We did not test the rectal route of acetaminophen administration and cannot make generalized statements. This study suggests oral acetaminophen increases the odds of being able to close a PDA in preterm neonates when compared to IV acetaminophen.

Latest Reports of Randomized Trials

El-Khuffash 2021 The PDA RCT	Rozé 2021 TRIOCAPI	Potsiurko 2022	Hundscheid 2022 BeNeDuctus	Gupta 2022 Baby-OSCAR
n = 60 Ibuprofen v. Placebo	n = 228 Ibuprofen v. Placebo	n = 208 Ibuprofen or Acetaminophen v. Placebo	n = 273 Ibuprofen v. No Intervention	n = 653 Ibuprofen v. Placebo
PDA closure rate was 57% with intervention and 17% in controls. No difference in CLD/death rates (OR 0.8; 95% CI 0.3-2.1).	Early echo-targeted treatment did not change survival without cerebral palsy (aRR 0.98; 95% CI 0.83-1.16).	Expectant management is non-inferior to early treatment for reducing death/BPD (OR 1.27; 95% CI 0.73-2.19).	Expectant management is non-inferior to early treatment for death/NEC/ mod-severe BPD (aRD -17.2%; 95% CI < -7.4%).	No reduction in death or moderate to severe BPD with early selective treatment (aRR 1.09; 95% CI 0.98 to 1.20).

Repercusión hemodinámica y probabilidad de cierre espontáneo

Al no existir una definición universalmente aceptada de DA hemodinámicamente significativo (DAhs), dicha valoración se basa en datos clínicos, ecocardiográficos y biomarcadores, combinados de distintas maneras en los llamados "scores de estadiaje ductal", que intentan estimar dicha repercusión de la forma más objetiva posible. En todo caso, **la ecocardiografía es la base de la valoración** y permite clasificar el cortocircuito (tabla 1).

El NT-proBNP es el biomarcador más utilizado. Se trata de una determinación ya introducida en la mayoría de centros, idónea en RN por precisar muestras muy pequeñas, que ha demostrado clara asociación con la repercusión hemodinámica y respuesta al tratamiento, pero con puntos de corte variables entre 10000-20000 ng/mL, según los distintos trabajos.

JAMA Pediatrics | Original Investigation

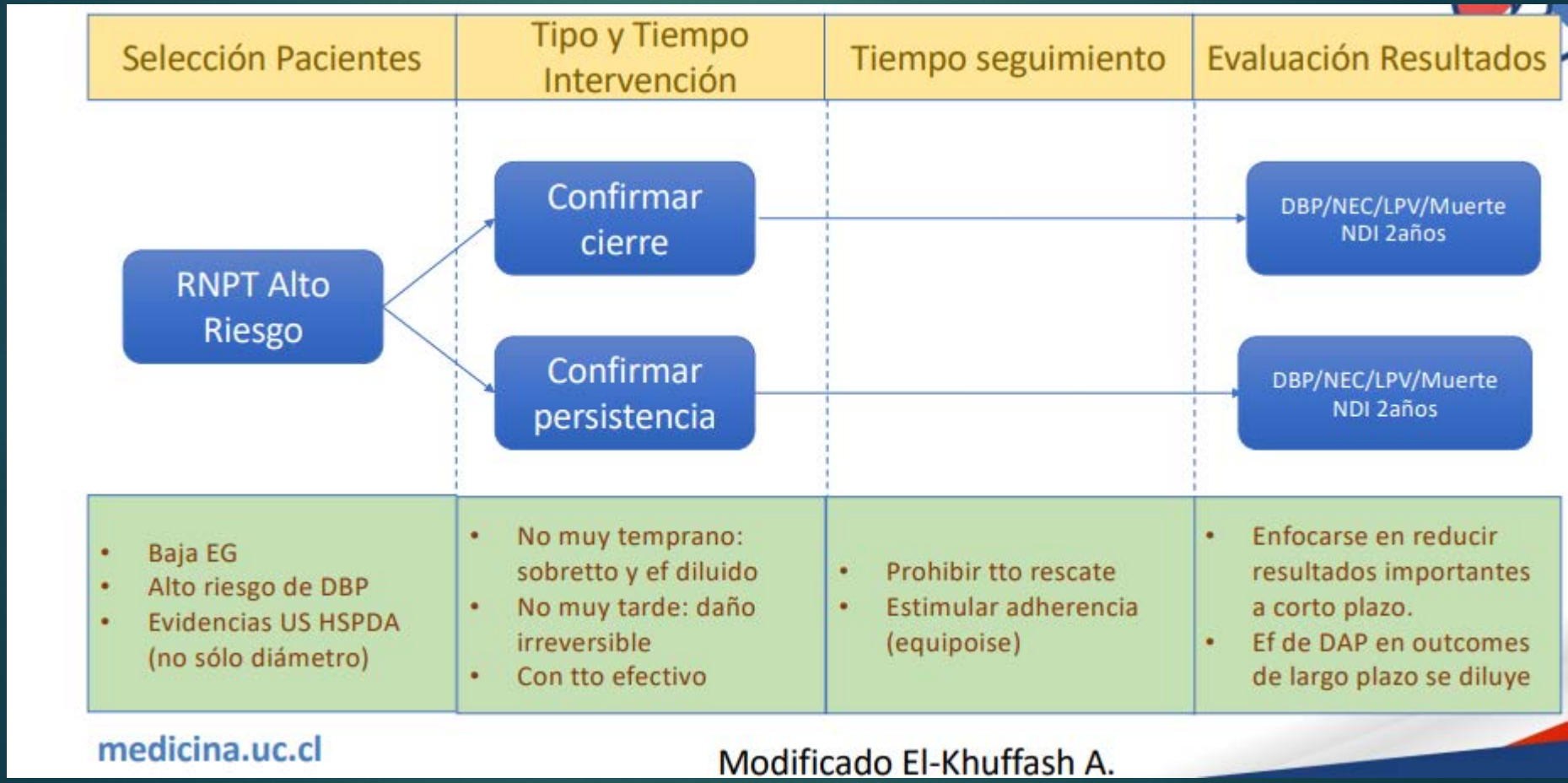
Effect of Nonintervention vs Oral Ibuprofen in Patent Ductus Arteriosus in Preterm Infants
A Randomized Clinical Trial

Se In Sung, MD, PhD; Myung Hee Lee, PhD; So Yoon Ahn, MD, PhD; Yun Sil Chang, MD, PhD; Won Soon Park, MD, PhD

CONCLUSIONS AND RELEVANCE Nonintervention showed noninferiority compared with ibuprofen treatment in closing of hemodynamically significant PDA and reduction of BPD or death. The noninferiority of nonintervention over ibuprofen might be attributable to the low efficacy of oral ibuprofen for closing PDA, especially in infants born at 23 to 26 weeks' gestation.

JAMA Pediatr. doi:10.1001/jamapediatrics.2020.1447
Published online June 15, 2020.

Estudio que se necesita



RCT of Active Treatment vs Expectant Management of Symptomatic PDA (NRN Trial)

- Multicenter, unmasked trial in centers of the Neonatal Research Network
- Infants between 22 to 28+6 weeks
- Postnatal age 48 hr to 21 days
- Diagnosed with symptomatic PDA defined as:
    - Mild, moderate or severe clinical criteria with small or moderate size PDA on echocardiogram
    - Mild or moderate clinical criteria with large PDA on echocardiogram
- Randomized to treatment with Ibuprofen or Indomethacin
- Primary Outcome is rate of death or BPD (physiologic)
- Includes follow up at 2 years
- Enrolled 252/836 infants as of Nov 07, 2022

Laughon M. et al. NRN; https://clinicaltrials.gov/ct2/show/NCT03456336

RECRUITING

Management of the PDA Trial (PDA)

ClinicalTrials.gov ID NCT03456336

Sponsor NICHD Neonatal Research Network

Information provided by NICHD Neonatal Research Network (Responsible Party)

Last Update Posted 2023-03-22

Study record dates

TRATAMIENTO: QX

- **Ligadura quirúrgica endoscópica**
  - Menos complicaciones: embolización, trombosis arterial, trauma valv. Tricupidea,
- **Ligadura quirúrgica abierta por toracotomía:** método tradicionalmente utilizado para cierre ductal definitivo → *complicaciones*:
  - Parálisis de las cuerdas vocales
  - Quilotórax
  - Síndrome post ligadura
  - FR independiente de deterioro motor, retraso en el desarrollo y discapacidad funcional de moderada a grave.

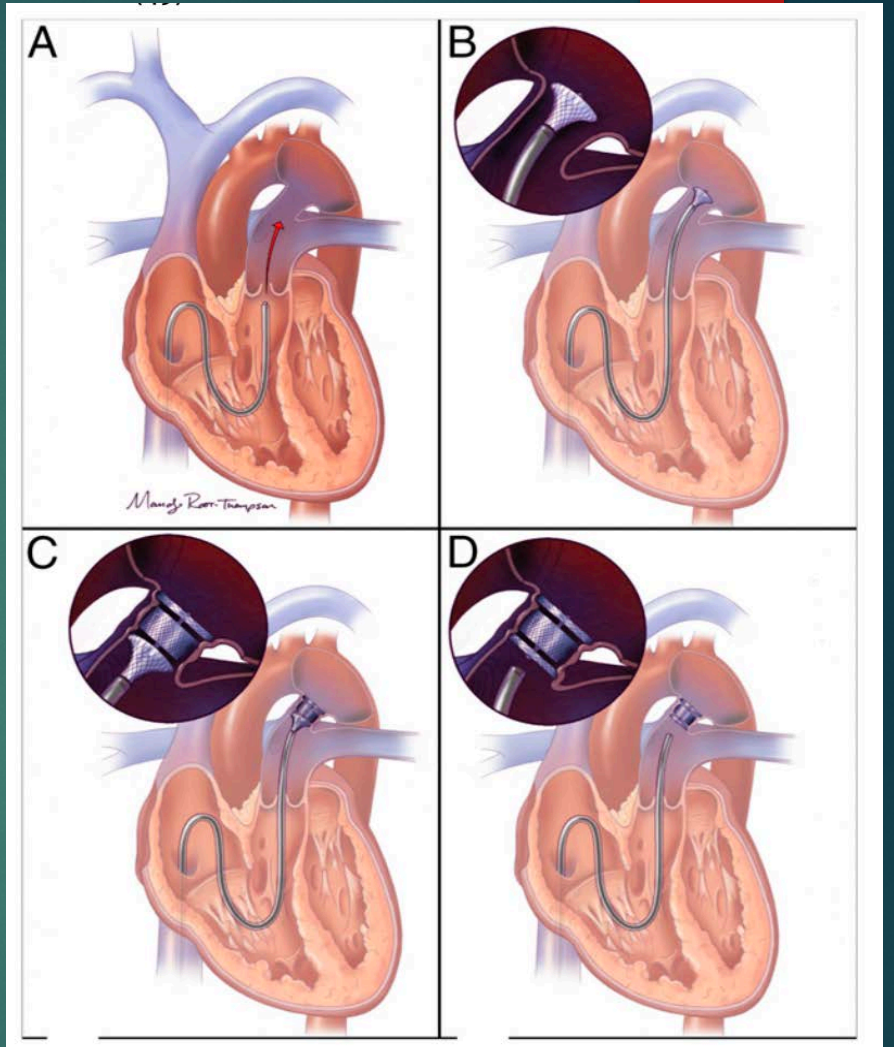


Figure 2. Procedural steps for percutaneous delivery of occlusive devices for patent ductus arteriosus closure. (33)(42) Originally published in Backes, Giesinger, Rivera et al. Percutaneous Closure of the Patent Ductus Arteriosus in Very Low Weight Infants. *Journal of Pediatrics*. 2019;213:219. Mandy Root-Thompson, Medical Illustrator.

Scerbo D., et al. Neoreviews. 2020 Jul;21(7):e469-e478.

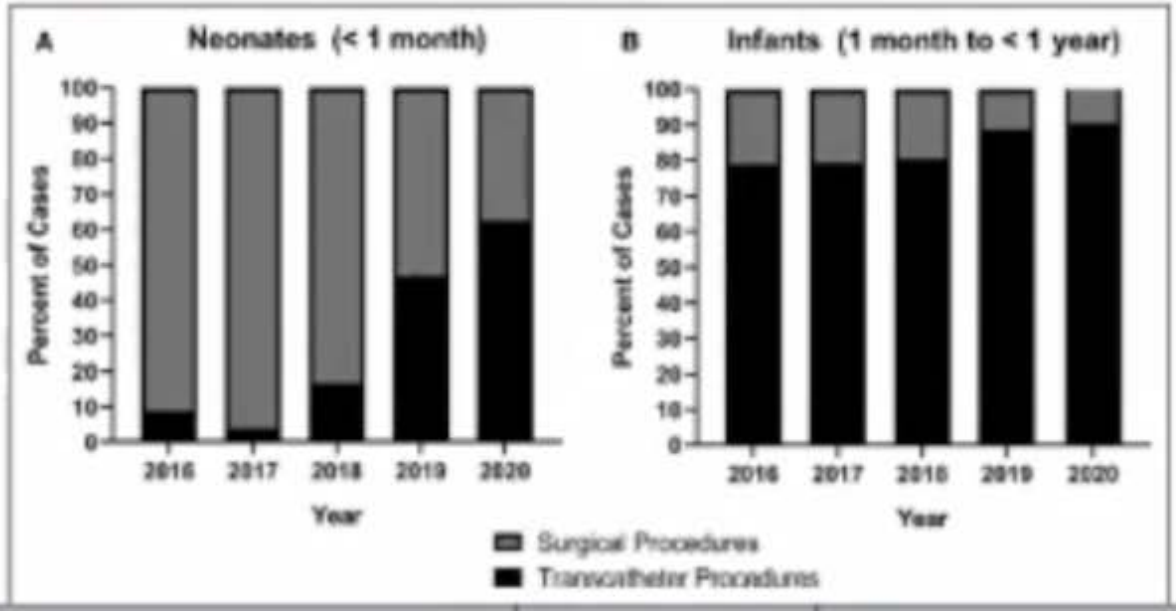
Surgical ligation of a Patent Ductus Arteriosus: Report of a first successful case. JAMA 112: 729, 1938

Lorraine Sweeney

Robert E. Gross M.D.

Surgical ligation of a Patent Ductus Arteriosus: Report of a first successful case. JAMA 112: 729, 1938

Surgical Treatment of PDA. Ligation vs Transcatheter Closure



Outcome variable	Transcatheter closure (n=102)	Surgical ligation (n=105)	*P* value
In-hospital mortality	0 (0)	3 (2.9)	0.247
ICU admission	24 (23.5)	8 (7.6)	0.002*
NICU admission	60 (58.8)	94 (89.5)	<0.001*
ICU/NICU admission began on or after procedure day[1]	20/74 (27)	26/96 (29.2)	0.759
Duration of postoperative ICU/NICU admission, d	3 (2–7)	7 (2–100)	0.002*
Mechanical ventilation	63 (61.8)	92 (87.6)	<0.001*
Mechanical ventilation started on or after procedure day[1]	40/61 (65.6)	34/89 (38.2)	0.001*
Duration of postoperative mechanical ventilation, d	2 (2–4)	3.5 (2–30)	0.007*
Hospital length of stay, d	4 (1–9)	12 (3–115)	<0.001*
Postoperative length of stay, d	3 (1–7)	8 (2–89)	<0.001*

Kuntz M et al. J Am Heart Assoc 2022; 11: e022776

La aproximación actual para el tto del DAP ha fracasado en identificar la via correcta de investigación

Hasta ahora los estudios han realizado una pregunta errónea y encontrado una respuesta incorrecta

Se requiere un cambio radical en el enfoque de los próximos estudios, dados:

La complejidad y naturaleza única del sistema CV

La naturaleza heterogénea de las causas

El mejor entendimiento de la fisiología

Las mejorías en el diagnóstico y monitoreo

SE CONSIDERA AN-ETICO SEGUIR RANDOMIZANDO NIÑOS SOLO EN BASE AL TAMAÑO DEL DAP

LA EVIDENCIA

Numerosos estudios randomizados para tratamiento de cierre ductal han mostrado ausencia de beneficios

Si ha habido niños que se han beneficiado del cierre ductal, probablemente constituyan solo una pequeña minoría de los que fueron tratados

Si continuamos tratando niños por DAP, debemos:

-identificar que niños se benefician (quién,cuando y porqué)

-especificar cual sería el beneficio y comprobarlo en series randomizadas

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journal homepage: www.elsevier.com/locate/siny

Patent ductus arteriosus management and the drift towards therapeutic nihilism – What is the evidence?

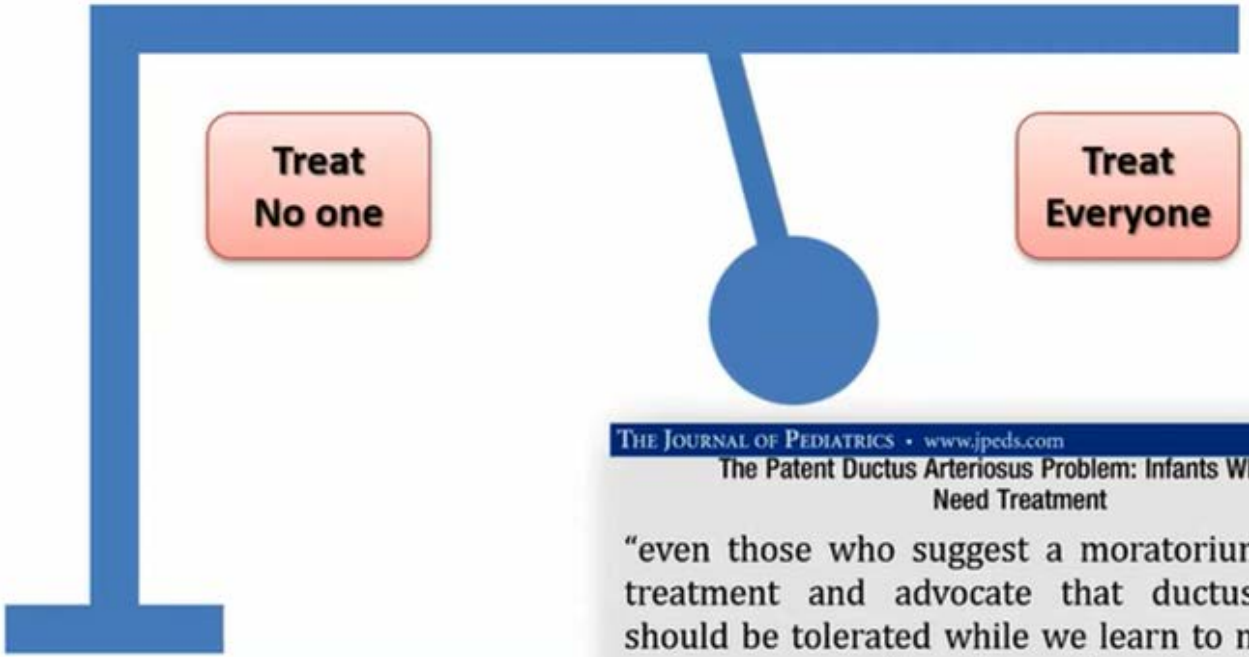
Koert de Waal [a,*], Rahul Prasad [b], Martin Kluckow [c]

[a] John Hunter Children's Hospital Department of Neonatology and University of Newcastle, Newcastle, NSW, Australia
[b] Randwick Children's Hospital Department of Neonatology, Sydney, NSW, Australia
[c] Royal North Shore Hospital Department of Neonatology and University of Sydney, Sydney, NSW, Australia

ABSTRACT

The published literature on patent ductus arteriosus (PDA) management is challenging to interpret due to poorly designed trials with high rates of open label treatments, homogenisation of patients with varying physiological subtypes, poor treatment efficacy, and spontaneous closure in more mature infants. The perceived lack of clinical benefit has led to a drift away from medical and surgical treatment of all infants with a PDA. This therapeutic nihilism as a default response to PDA management fails to recognise the physiological relevance of a left-to-right shunt with early haemodynamic instability after birth and subsequent pulmonary volume overload with prolonged exposure. Clinicians need to know if therapeutic nihilism is safe. This review will provide an overview of the available data on the efficacy of known PDA treatments, conservative management and supportive care measures that are currently applied.

TRATAMIENTO DEL DAP: El péndulo siempre en movimiento



THE JOURNAL OF PEDIATRICS • www.jpeds.com EDITORIALS

The Patent Ductus Arteriosus Problem: Infants Who Still Need Treatment

"even those who suggest a moratorium on PDA treatment and advocate that ductus patency should be tolerated while we learn to manage its consequences rather than attempting to achieve its closure ***acknowledge that some infants may benefit from DA closure***"

Jeff Reese, MD Matthew M. Laughon, MD, MPH

A pesar de que se incluyeron más de 6.000 niños prematuros en ensayos aleatorios y muchos más descritos en estudios de cohortes, todavía no sabemos cuál es la mejor manera de tratar un DAP. Un ductus plantea un potencial riesgo hemodinámico para los prematuros y se debe encontrar una mejor manera de seleccionar a los niños con mayor riesgo y tener la oportunidad de tratar de una manera fácil, segura y más eficaz para ayudar a resolver uno de las mayores encrucijadas de la neonatología.

PUNTOS CLAVES

- Aunque la presencia de un conducto arterioso permeable (DAP) puede confirmarse fácilmente con una ecocardiografía, el diagnóstico de DAP hemodinámicamente significativo es más desafiante y no está estandarizado.
- • La Evaluación de la importancia clínica y hemodinámica de un ductus debe incluir una evaluación del tamaño del ductus, magnitud del volumen de la derivación, la capacidad del corazón para acomodar y compensar la derivación, y el impacto de su flujo en la circulación pulmonar y sistémica.
- • Características clínicas como la edad gestacional y cronológica, grado de soporte cardiopulmonar y presencia de otras variables que pueden mejorar o mitigar los posibles efectos perjudiciales de un DAP pueden ser útiles en la evaluación de la importancia hemodinámica y clínica de un ductus.
- • Sistemas de puntuación basados en características clínicas, mediciones de ecocardiografía y otras tecnologías como NIRS pueden ser útiles en la evaluación y seguimiento de un DAP en el futuro.

CONCLUSIONES

- El DAP corresponde a la persistencia del vaso sanguíneo que comunica el tronco de la arteria pulmonar con la aorta descendente, pudiendo tener consecuencias hemodinámicas negativas en el RN.
  - **DBP, NEC, HIV, ICC, AKI.**
- El principal factor de riesgo es la **menor edad gestacional.**
- El diagnóstico del DAP con compromiso hemodinámico se puede realizar a través de:
  - **Triada clínica:** Hipotensión + Soplo sistólico infraclav izq irradiado a dorso + pulsos saltones.
  - **Evaluación ecocardiográfica.**
  - En proceso de evaluación de **marcadores bioquímicos.**
- Existen **discrepancias en los beneficios del tratamiento** (conducta expectante cierre espontáneo), cuando realizarlo (preventivo o sintomático?) y mediante que forma (médico o quirúrgico?)Hemos fallado en identificar la forma correcta de enfocar el tratamiento

Mientras tanto: ¿A quién tratamos?

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