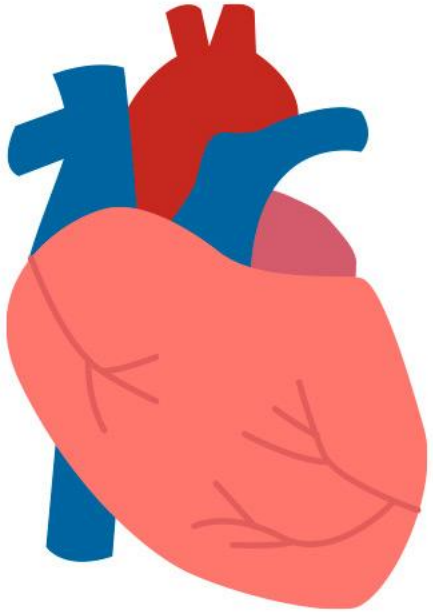
Manejo hemodinámico y de la hipotensión en el prematuro



Carla Miró Vicedo

Residente de pediatría de 4º año

Presentada en el servicio de Pediatría en el H. 12 Octubre

ABREVIATURAS:

EG: edad gestacional, HIV, hemorragia intraventricular; NEC, enterocolitis necrotizante; DBP, displasia broncopulmonar; FC, frecuencia cardiaca: TA, tensión arterial; SRIS, Síndrome de respuesta inflamatoria sistémica; GC, gasto cardiaco; VCS, vena cava superior; CAU: catéter arterial umbilical; RVP, resistencias vasculares pulmonares; RVS: resistencias vasculares sistémicas; VI, ventrículo izquierdo; DAP, ductus arterioso sistémico; EPM, edad postmenstrual

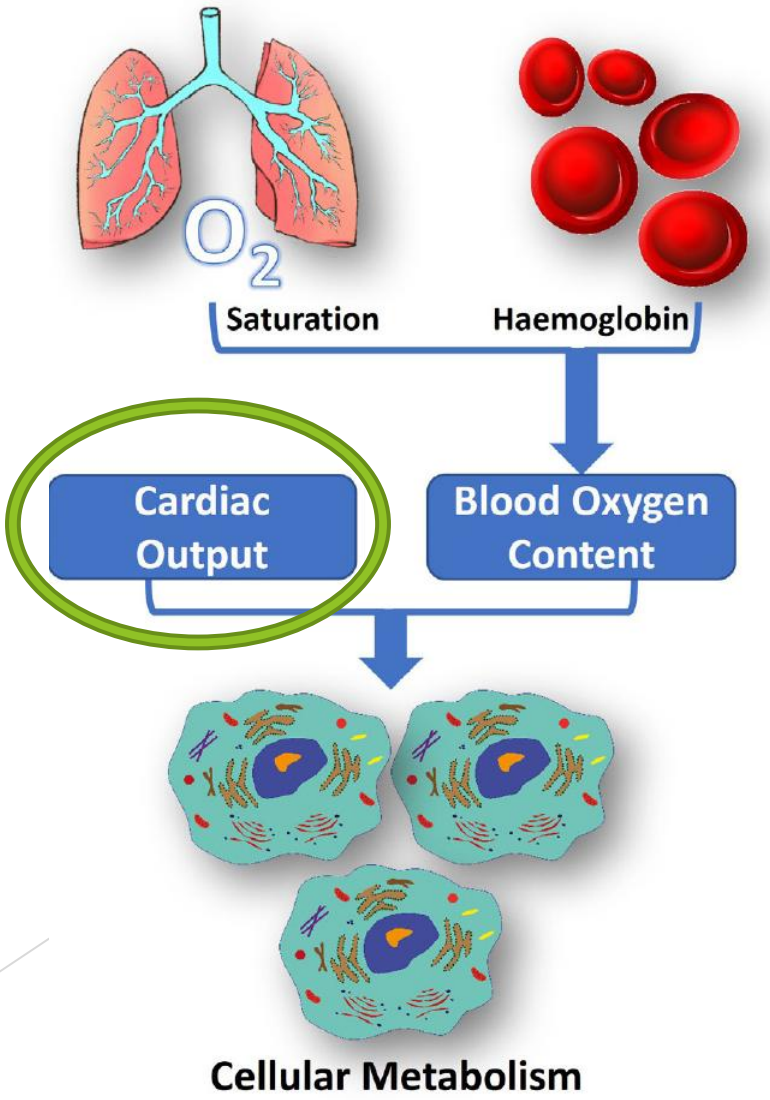
Insuficiencia circulatoria

- El aporte de O2 a los tejidos no satisface su demanda
- El pretérmino → especialmente vulnerable a presentarla
- Potencial repercusión sobre la perfusión cerebral y sus implicaciones pronósticas

Mantener el metabolismo celular

CONTENIDO DE O2
Hemoglobina y oxigenación

GASTO CARDIACO:
Precarga, postcarga, frecuencia cardiaca y contractilidad



Contractilidad cardiaca

- <u>Dependiente de la precarga:</u>

CURVA DE FRANK-STARLING

Aumento de longitud de los sarcómeros y tensión resultante → aumenta la fuerza de contracción

- <u>Dependiente de la postcarga:</u>

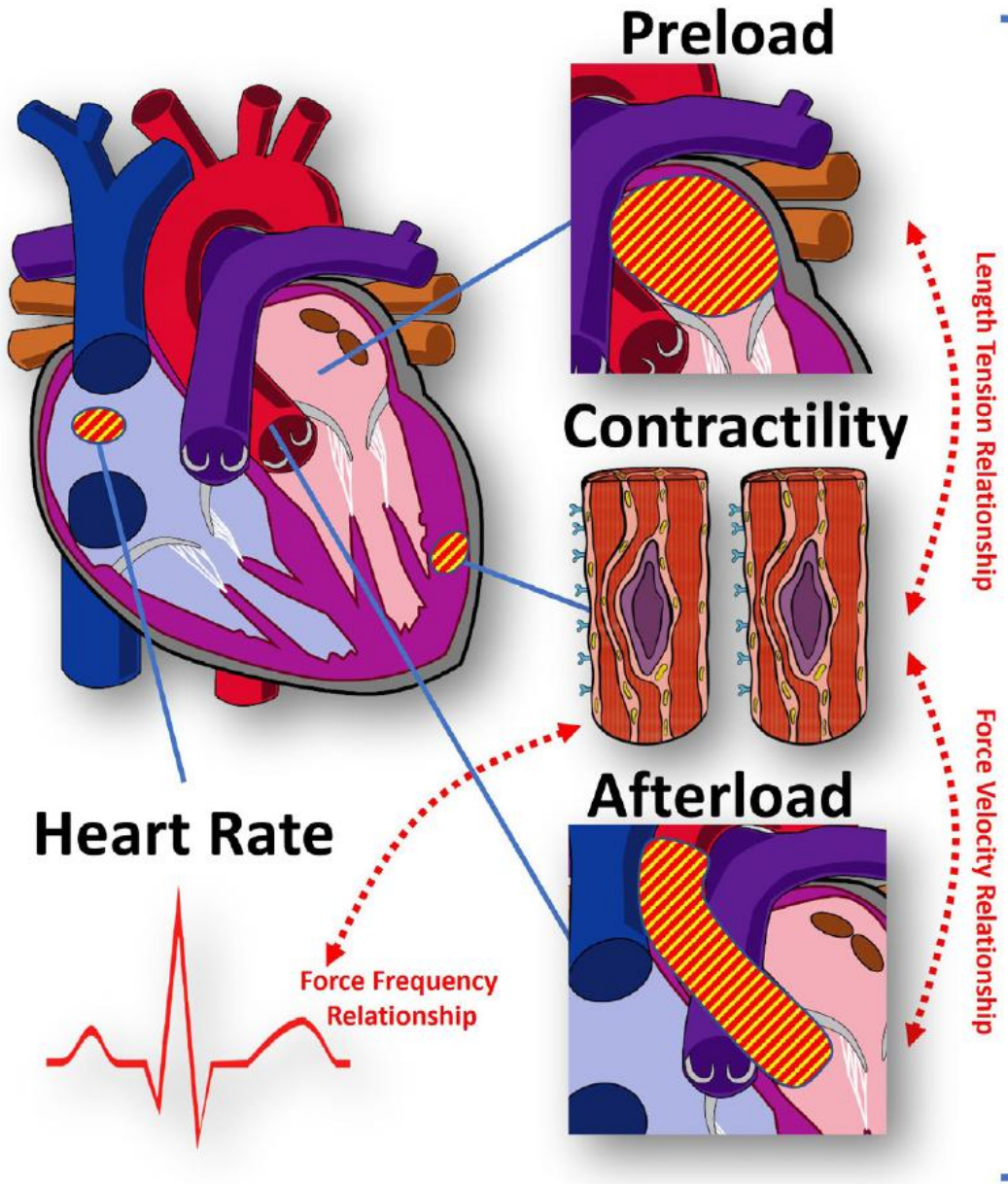
RELACIÓN FUERZA-VELOCIDAD

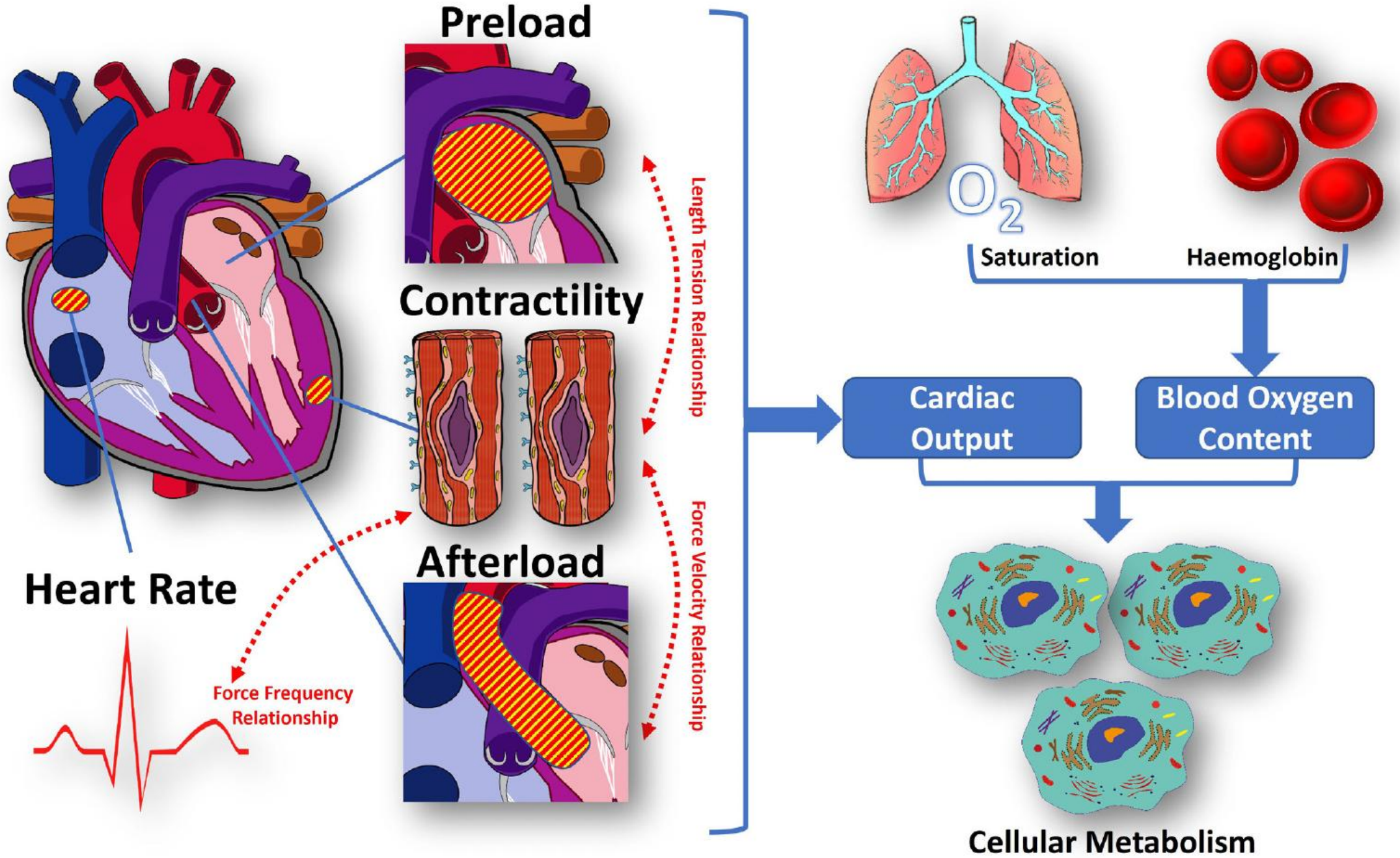
Al aumentar la postcarga se aumenta la contractilidad, hasta un punto que comienza a decaer (desacoplamiento)

- <u>Dependiente de la FC:</u>

RELACIÓN FUERZA-FRECUENCIA

Al aumentar la FC (cronotropismo) aumenta la fuerza de contracción




Preload
Contractility
Afterload
Heart Rate
Force Frequency Relationship
Length Tension Relationship
Force Velocity Relationship
O_2
Saturation
Haemoglobin
Cardiac Output
Blood Oxygen Content
Cellular Metabolism

Gasto cardiaco (GC) y flujo sanguíneo sistémico

- $GC = \frac{volumen\ sistólico\ (VS)\ x\ FC}{peso}$ =ml/kg/min

VS= Integral velocidad-tiempo (VTI) x Área seccional del vaso
Área seccional del vaso= π x radio²

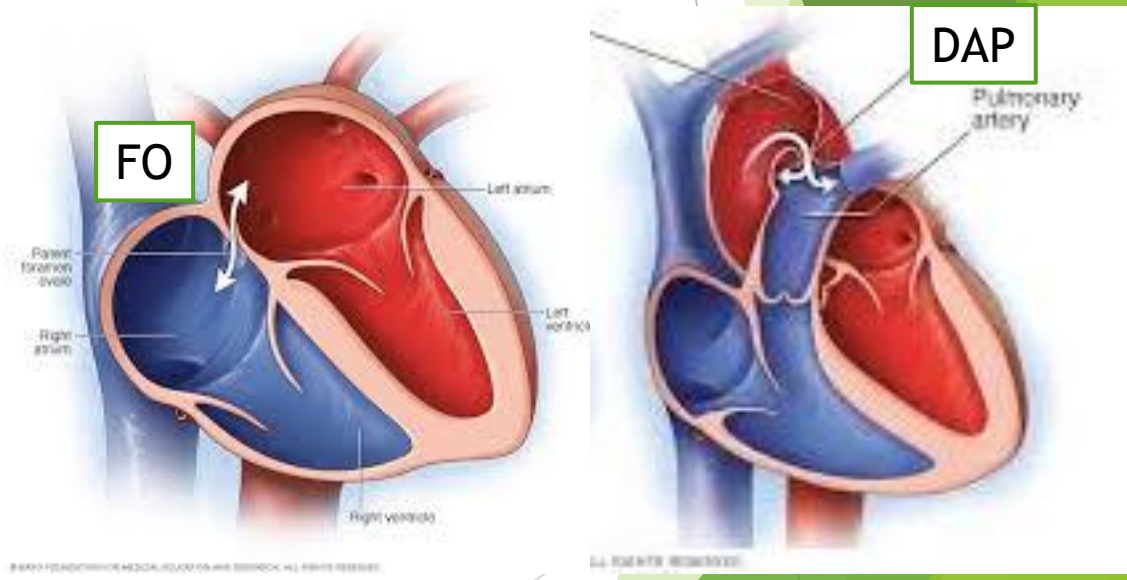
GC normal en prematuros sin flujo a través de los cortocircuitos: 150-300 mL/kg/min

Flujo sistémico alterado por cortocircuitos fetales

- GC derecho: retorno venoso del flujo sistémico (+/-) flujo FO
- GC izquierdo: retorno venoso del flujo pulmonar (+/-) flujo DAP

Table 1. Reference values blood flow measurements in mean (SD) mL/kg/min [12,28,36,38–50]

	Postnatal age			
	3–9 h	24 h	Day 2	Days 7–14
RVO				
Preterm		260 (90)	270 (90)	430 (100)
Term		255 (60)		
LVO				
Preterm		240 (60)	260 (60)	400 (75)
Term		220 (60)		



P. de Boode W, van der Lee R, et al. The role of Neonatologist Performed Echocardiography in the assessment and management of neonatal shock. Pediatric Research;2018:84:57-67

Gasto cardiaco (GC) y flujo sanguíneo sistémico

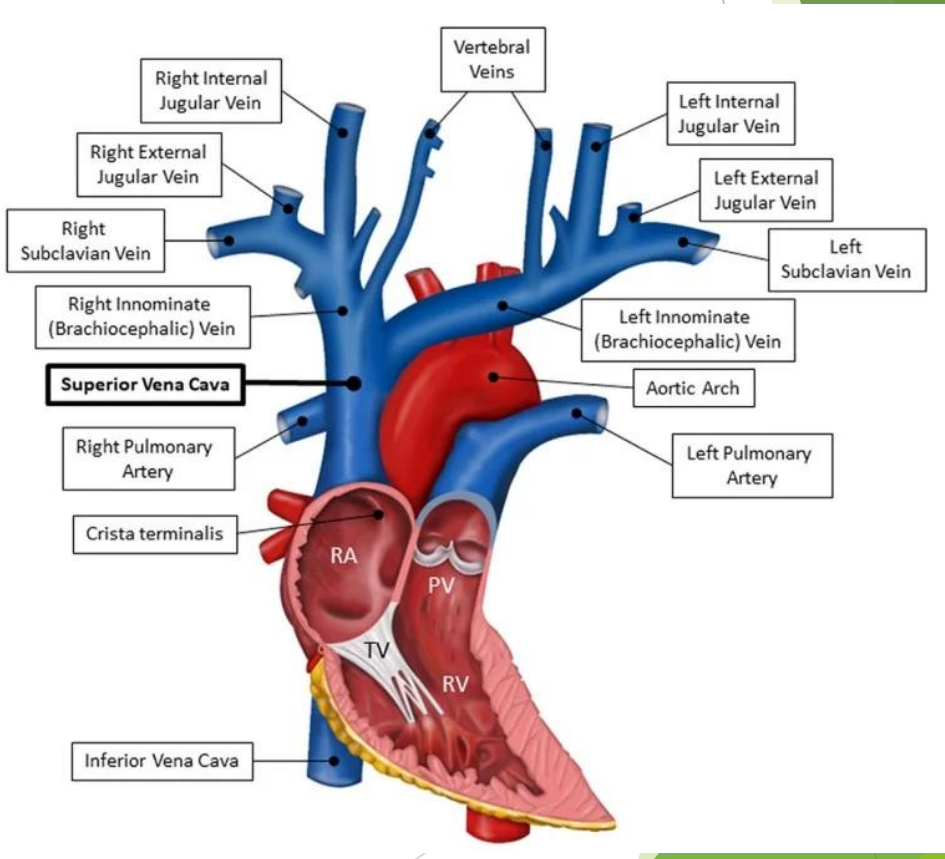
- Flujo en VCS → retorno venoso cerebral (70-80%) + hemicuerpo superior (medición más objetiva del flujo sistémico, sin alterarse por cortocircuitos)

Table 1. Reference values blood flow measurements in mean (SD) mL/kg/min [12,28,36,38–50]

	Postnatal age			
	3–9 h	24 h	Day 2	Days 7–14
SVC flow				
Preterm	60 (25)	80 (20)	90 (25)	90 (30)
Term	75 (25)	95 (30)	100 (30)	

RVO right ventricular output, *LVO* left ventricular output, *SVC* superior vena cava

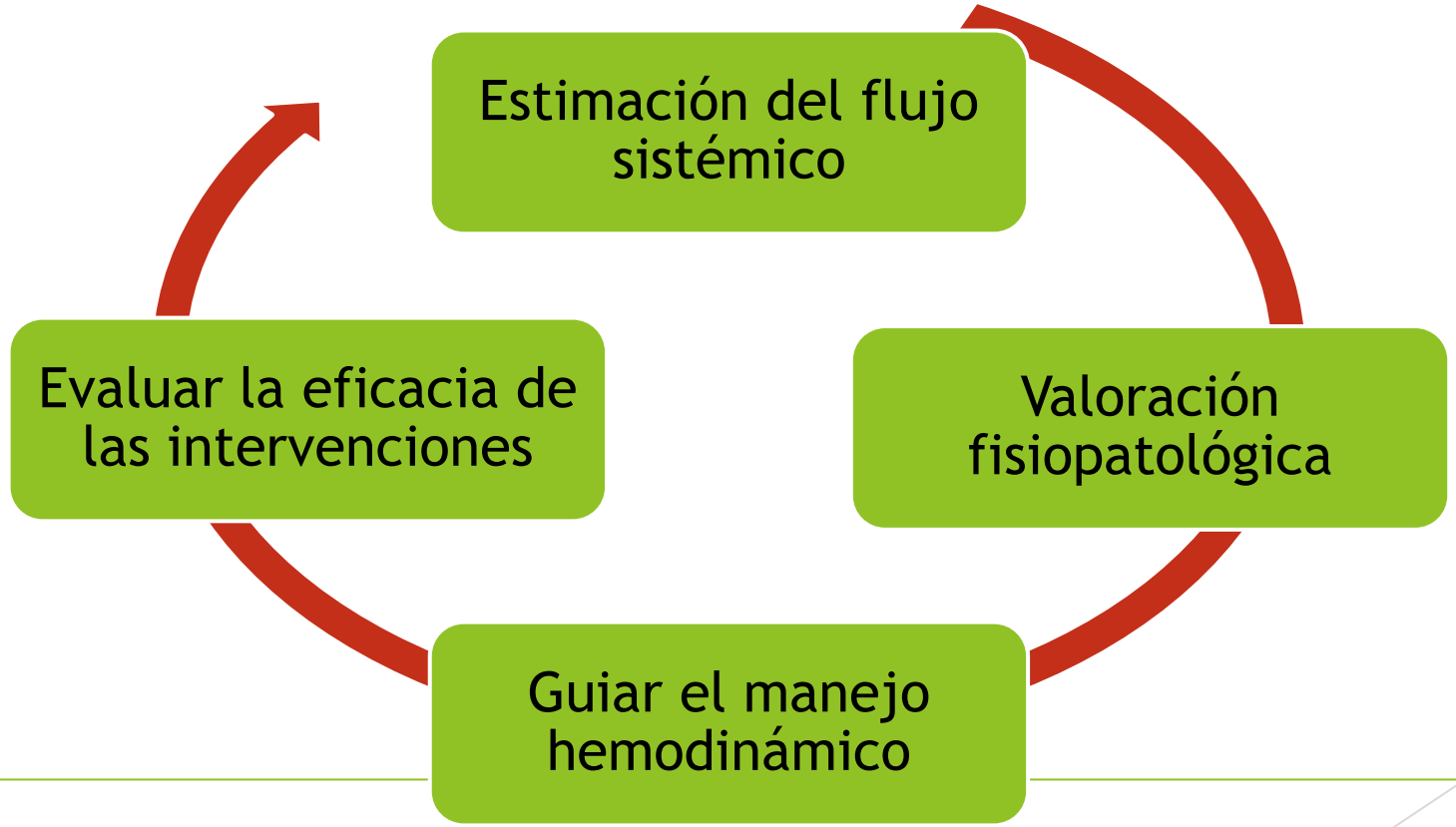
P. de Boode W, van der Lee R, et al. The role of Neonatologist Performed Echocardiography in the assessment and management of neonatal shock. Pediatric Research;2018:84:57-67



- Implicaciones pronósticas en prematuros:
  - Bajo flujo VCS (<30 a las 5h o <40-45ml/kg/min posteriormente) → HIV y peor neurodesarrollo

Gasto cardiaco (GC) y flujo sanguíneo sistémico

- Ecocardiografía a pie de cuna



Papel de la ecocardiografía

Flow & Output	Cavity Dimensions	Displacement	Velocity	Deformation
Those include left and right ventricular output in addition to SVC flow. They are influenced by intra- and extra cardiac shunts. Their reproducibility in preterm infants warrant further study.	Measurements include LV shortening fraction, LV ejection fraction and RV fractional area change. Those are dependent on loading conditions and demand clear image acquisition for accuracy.	Measure distance travelled by a point on the muscle wall during systole. Such as the movement of the TV annulus towards the apex. Displacement is also influenced by loading conditions.	Tissue Doppler velocity are Relatively easy to obtain, measure systolic & diastolic function. They only measure regional function (not global) and are also Load dependent. Can be misleading due to tethering.	Measurement of the change in shape of regional or global muscle. Systolic & diastolic function. Reliable in neonates. Some aspect of deformation are less load dependent and reflect intrinsic contractility.

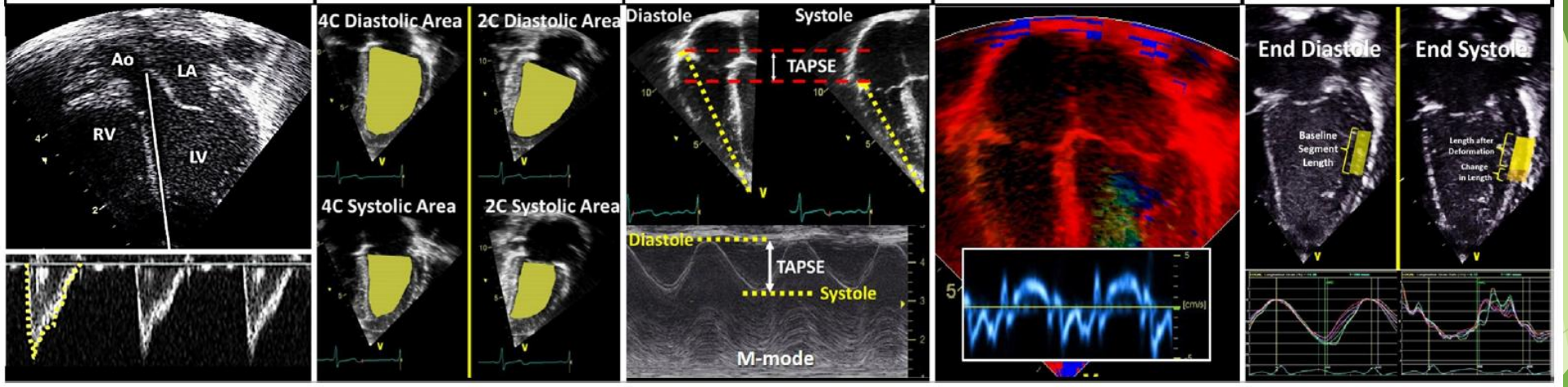


Figure 3 Echocardiography assessment of myocardial function. LV, left ventricular; RV, right ventricular; SVC, superior venacava; TV, tricuspid valve.

- Dependen de la precarga
(no miden directamente contractilidad intrínseca)
- Se necesita el contexto clínico para valorar adecuadamente resultados alterados

- Menos influenciadas por precarga
- Si alterada puede relacionarse directamente con la contractilidad

Valoración de la insuficiencia circulatoria

- Marcadores útiles en prematuros:
  - Frecuencia cardiaca
  - Relleno capilar y gradiente térmico
  - Débito urinario
  - Lactacidemia
  - TA media

Limitaciones de forma aislada

Más utilizado para el diagnóstico de hipotensión

  - Ecocardiografía a pie de cuna
  - aEEG
  - Oximetría tisular

Gasto cardiaco (GC) y flujo sanguíneo sistémico

- Oximetría cerebral

- Ensayo SafeBoosC-II: ↓ 58% hiperoxia e hipoxia en el grupo con oximetría cerebral

¿Beneficio a nivel clínico?

- Ensayo SafeBoosC-III:

No ↓ incidencia de muerte o daño cerebral grave a las 36s EPM

Table 2. Outcomes at 36 Weeks' Postmenstrual Age.*

Outcome	Cerebral Oximetry (N=772)	Usual Care (N=807)	Relative Risk (95% CI)†
Primary			
Death or severe brain injury — no. (%)‡	272 (35.2)	274 (34.0)	1.03 (0.90–1.18)
Components of the primary outcome			
Death — no. (%)	164 (21.2)	160 (19.8)	1.07 (0.89–1.28)
Severe brain injury — no./total no. (%)‡	185/763 (24.2)	188/797 (23.6)	1.02 (0.85–1.21)
Exploratory			
Death or bronchopulmonary dysplasia — no./total no. (%)§	484/736 (65.8)	524/772 (67.9)	0.96 (0.89–1.02)
Death or retinopathy of prematurity — no. (%)¶	235 (30.4)	228 (28.3)	1.08 (0.94–1.24)
Death or late-onset sepsis — no. (%)‖	565 (73.2)	598 (74.1)	0.98 (0.93–1.03)
Death or necrotizing enterocolitis — no. (%)**	232 (30.1)	209 (25.9)	1.16 (1.00–1.35)

TA en prematuros

Hipotensión arterial → Complicaciones a corto plazo (NEC y HIV) → Peores resultados a largo plazo

La Red Neonatal Alemana: TA media más baja en 1ddv en prematuros <32SG (n=5000)
TA media < a la EG → predictor de HIV, DBP y muerte

1. ¿La TA baja es causa o consecuencia? → falta evidencia
2. ¿Aumentar TA mejora los resultados a corto o largo plazo? → falta evidencia

Administrar a todos los prematuros tratamiento para aumentar la TA de forma reglada
→ mayor riesgo de muerte y alteración del neurodesarrollo a los 2 años

TA en prematuros

Establecer el umbral de circulación estable → desafío

Table 2 – Blood pressure thresholds at third percentile according to gestational age (GA).[16]

GA (weeks)	SYSTOLIC (mmHg)	MEAN (mmHg)	DIASTOLIC (mmHg)
24	32	26	15
25	34	26	16
26	36	27	17
27	38	27	17
28	40	28	18
29	42	28	19
30	43	29	20
31	45	30	20
32	46	30	21
33	47	30	22
34	48	31	23
35	49	32	24
36	50	32	25

Hemodynamic instability in the critically ill neonate: An approach to cardiovascular support based on disease pathophysiology

Regan E. Giesinger, BScH, MD, FRCPC[a,b], and Patrick J. McNamara, MB, BCH, BAO, MSc, MRCP, MRCPH[a,b,c,]*

Table IV. Blood pressure ranges in different gestational age groups

Gestational age (wk)	n	Systolic (mm Hg)	Diastolic (mm Hg)
<24	11	48-63	24-39
24-28	55	48-58	25-36
29-32	110	47-59	24-34
>32	68	48-60	24-34

Blood pressure ranges in premature infants. I. The first hours of life

Thomas Hegyi, MD, Mary Terese Carbone, MD, Mujahid Anwar, MD, Barbara Ostfeld, PhD, Mark Hiatt, MD, Anne Koons, MD, Jennifer Pinto-Martin, PhD, and Nigel Paneth, MD, MPH

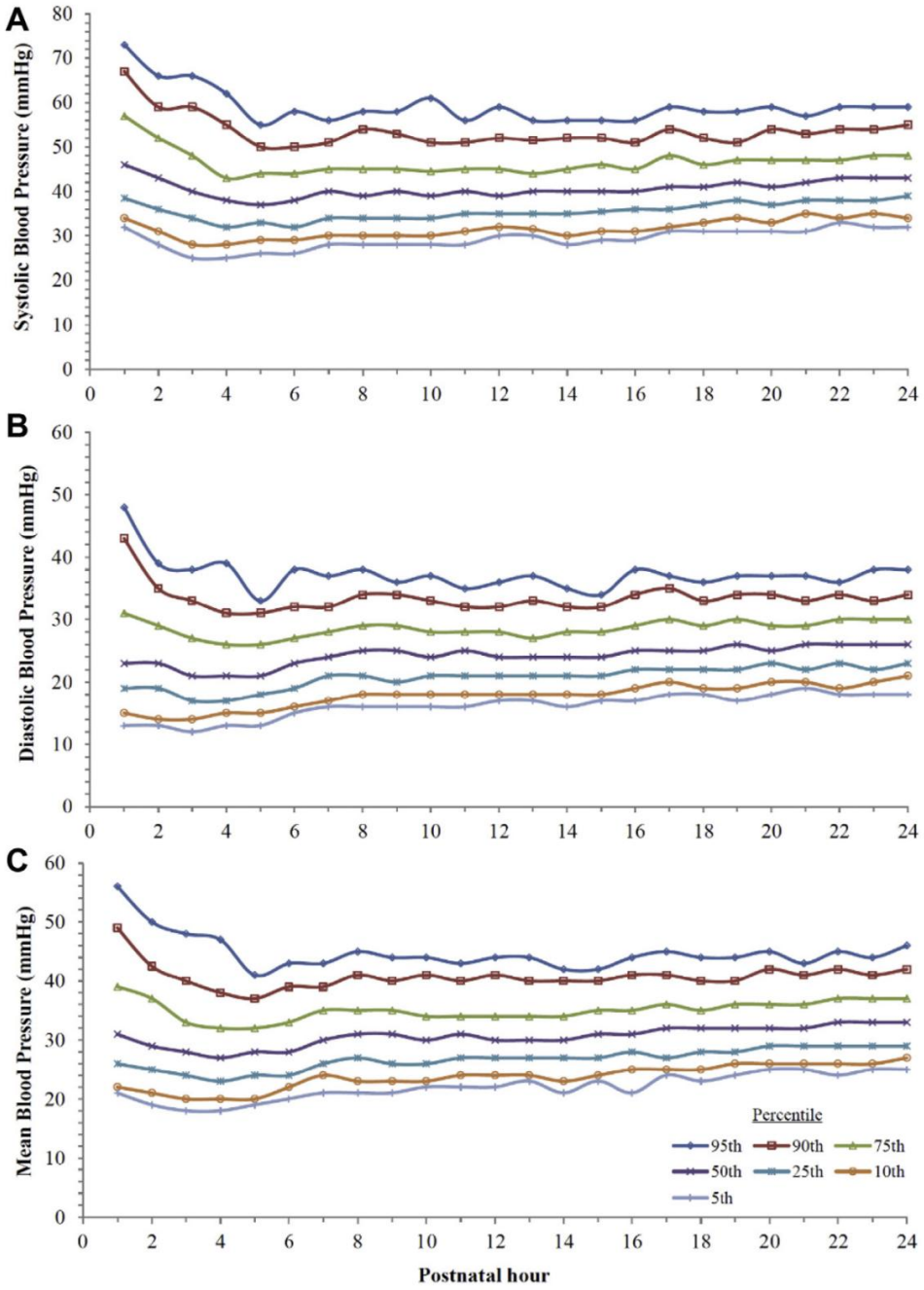


Fig. 2. Systolic (*A*), diastolic (*B*), and mean (*C*) arterial blood pressure curves over the first 24 hours for extremely preterm infants born at $23^{0/7}$ to $26^{6/7}$ weeks gestation (n = 367).

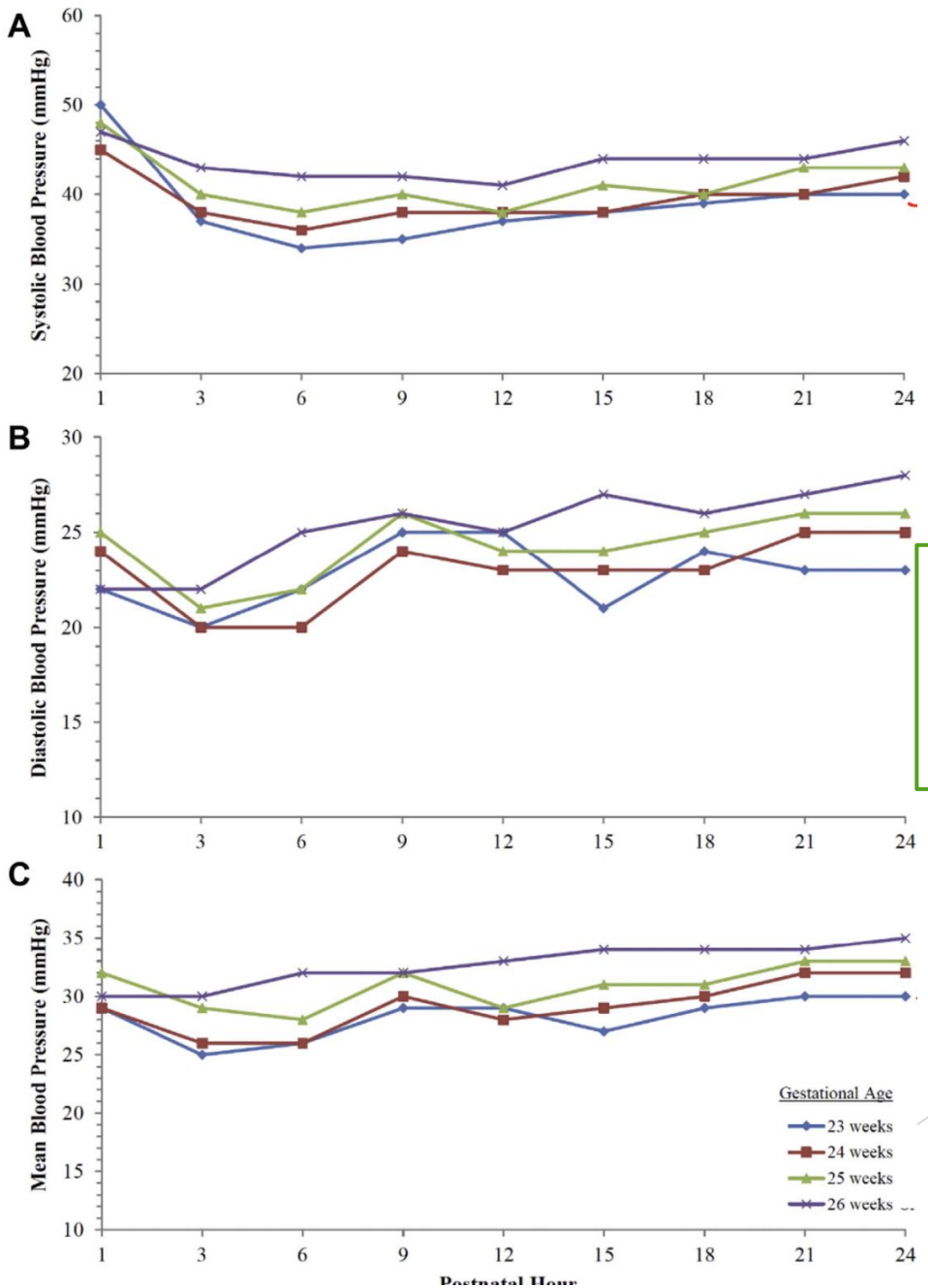


Fig. 3. GA-specific changes in the systolic (*A*), diastolic (*B*), and mean (*C*) arterial blood pressure 50th percentile curves over the first 24 hours for infants born at $23^{0/7}$ to $26^{6/7}$ weeks GA (n = 367).

Batton B. Neonatal Blood Pressure Standards: What Is "Normal"?. Clin Perinatol 2020;47:469-485

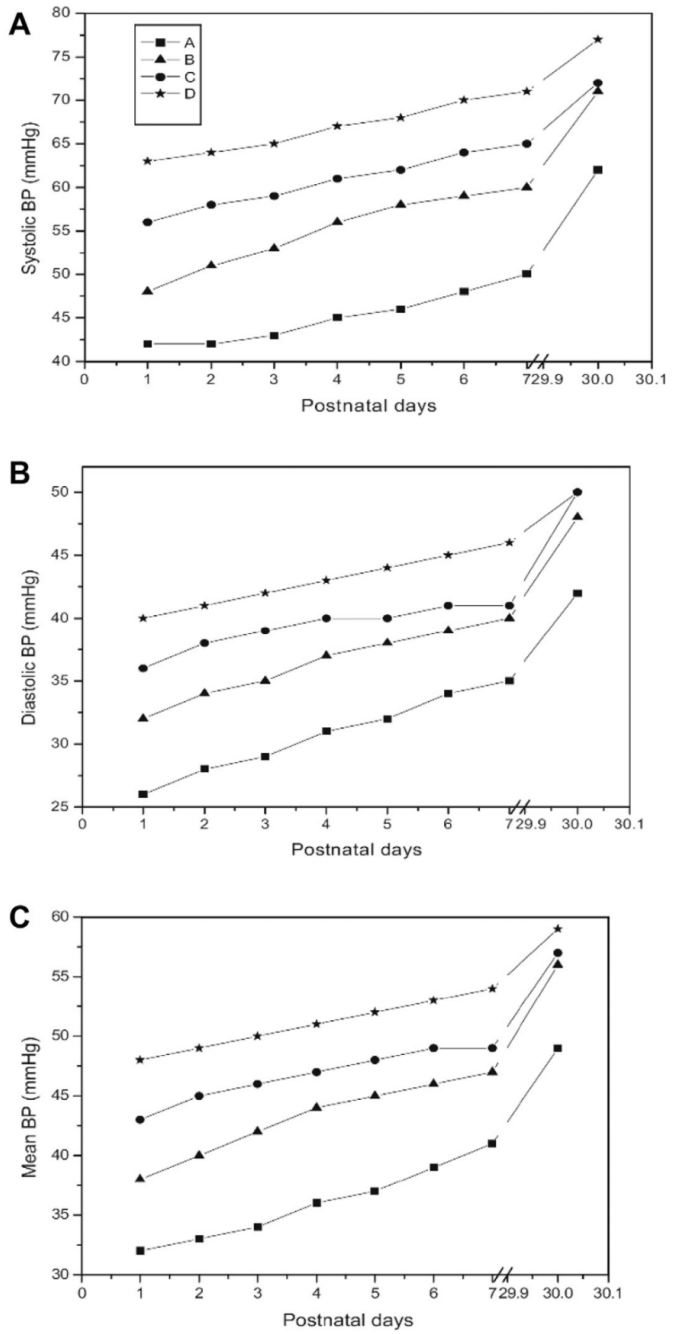


Fig. 5. Increase in systolic (*A*), diastolic (*B*), and mean (*C*) arterial blood pressure during the first month of life in groups of infants classified by estimated gestational age: ≤28 weeks (*squares*), 29 to 32 weeks (*triangles*), 33 to 36 weeks (*circles*), and ≥37 weeks (*stars*).

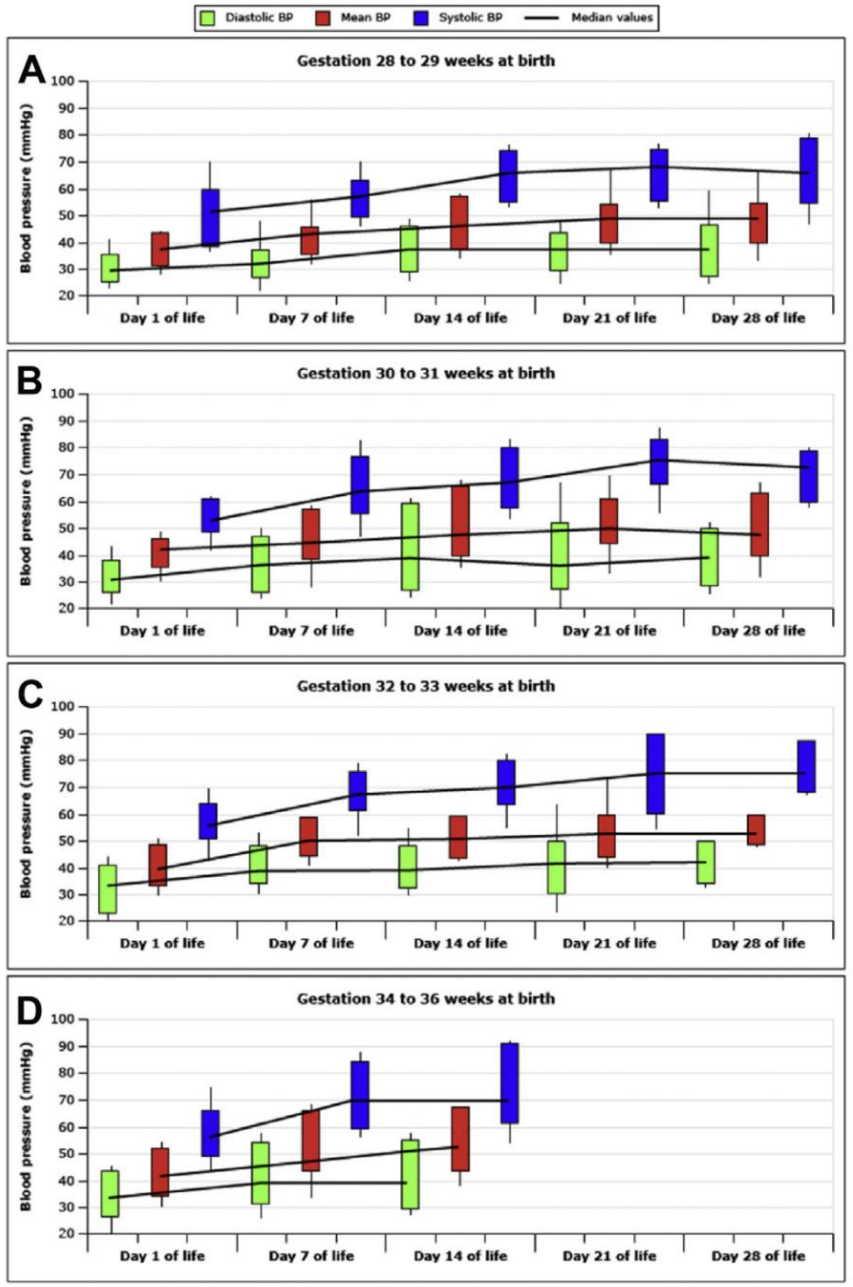


Fig. 6. GA-specific normative BP trends for preterm infants over the first 28 postnatal days. (*A*) BP for infants born at 28 to 29 weeks GA. (*B*) BP for infants born at 30 to 31 weeks GA. (*C*) BP for infants born at 32 to 33 weeks GA. (*D*) BP for infants born at 34 to 36 weeks GA. *Boxes* delineate 10th and 90th percentiles, and *vertical black marks* delineate range.

Batton B. Neonatal Blood Pressure Standards: What Is "Normal"?. Clin Perinatol 2020;47:469-485

TA en prematuros

Establecer el umbral de circulación estable → desafío

1. Definir valores normales
2. Cambios fisiológicos rápidos en el periodo postnatal inmediato
3. Diversas técnicas para medir la TA
4. Múltiples factores que pueden afectar los valores
    a. Antenatales
    b. Postnatales

Factores que afectan a la TA

Table 1
Antenatal factors affecting neonatal blood pressure measurements

Category	Reference #
Medications	
General anesthesia	48
Corticosteroids	35,41,42,46
Magnesium sulfate	36,47
Maternal conditions	
Smoking	33,34,39
Advanced maternal age	37,43
Chorioamnionitis	38,42,44
Hypertension	31,32,37,49
Perinatal factors	
Mode of delivery	33,40,45
Delayed umbilical cord clamping	46,53,54
Fetal conditions	
Intrauterine growth restriction	50–52
Breech presentation	43
Twin-twin transfusion syndrome	55,56

Table 2
Postnatal factors other than gestational age, birth weight, and postnatal age that can affect neonatal blood pressure measurements

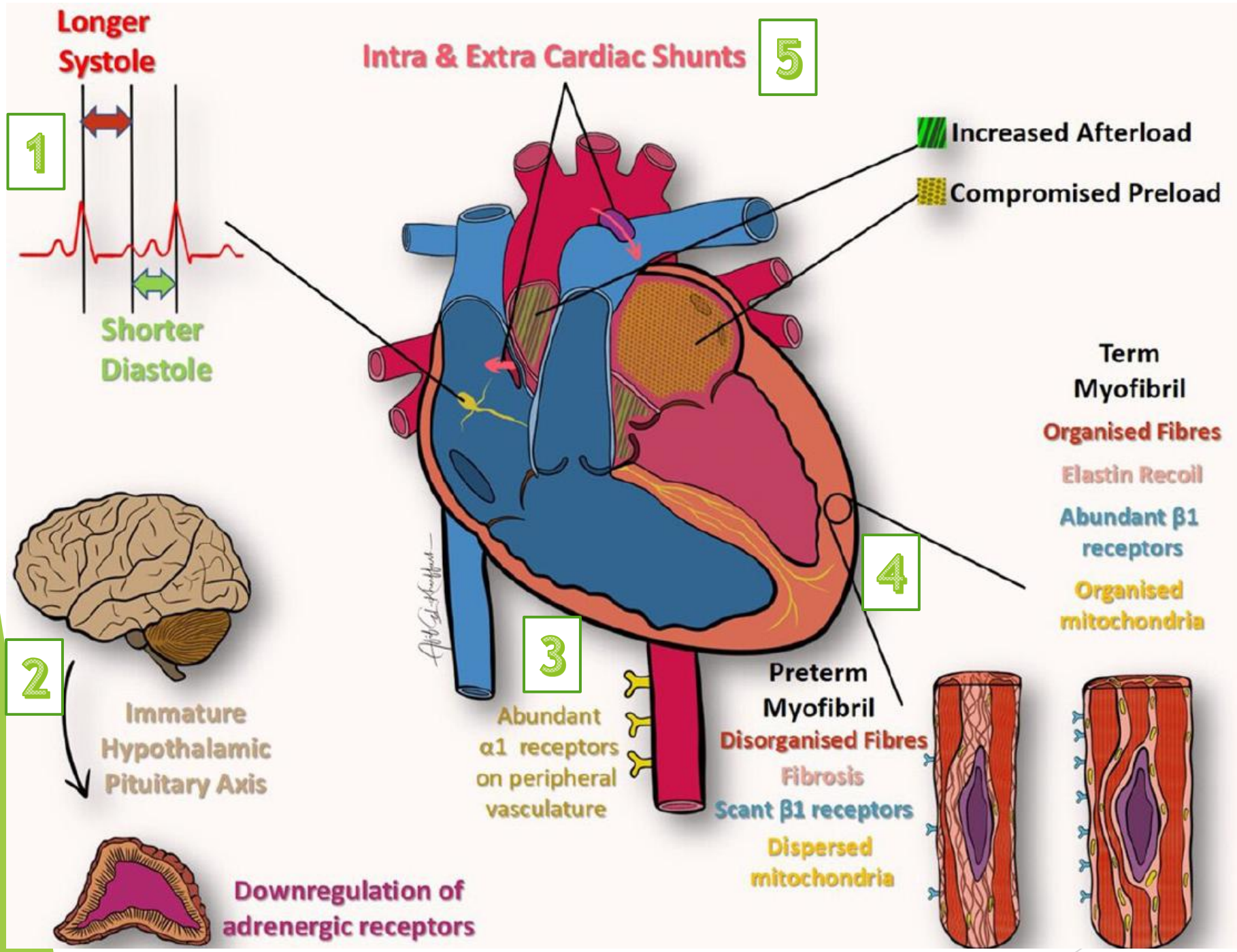
Category	Reference #
Patient variables	
Race/ethnicity	43,58,60,64
Gender	58,59,63
Multiple gestation	9,67
Small for gestational age	70,73
Circadian rhythm/sleep	59,72
Medical conditions	
Patent ductus arteriosus	82
Anesthesia	83
Sepsis	85
Hypovolemia	85
Perinatal distress/acidosis/low Apgar score	58
Cardiac disease, congenital heart disease	65,85
Bronchopulmonary dysplasia	61,62
Care interventions	
Pacifier use	66,75
Hands-on care	68
Infant position (prone vs supine)	57,76
Enteral feeding	58,66,71
Caffeine	84
Blood transfusions	17,80,85
Therapies for low blood pressure	
Isotonic fluid boluses	17,80
Dopamine	17,77,78,80,81
Dobutamine	77,80,81
Epinephrine	80,85
Corticosteroids	78–80

Batton B. Neonatal Blood Pressure Standards: What Is "Normal"?. Clin Perinatol 2020;47:469-485

TA en prematuros

Establecer el umbral de circulación estable → desafío

1. Definir valores normales
2. Cambios fisiológicos rápidos en el periodo postnatal inmediato
3. Diversas técnicas para medir la TA
4. Múltiples factores que pueden afectar los valores
    a. Antenatales
    b. Postnatales
5. Particularidades del prematuro



Clinical Phenotype

4 Poor tolerance of increased afterload → low cardiac output

1 Reduced diastolic filling → pulmonary venous congestion

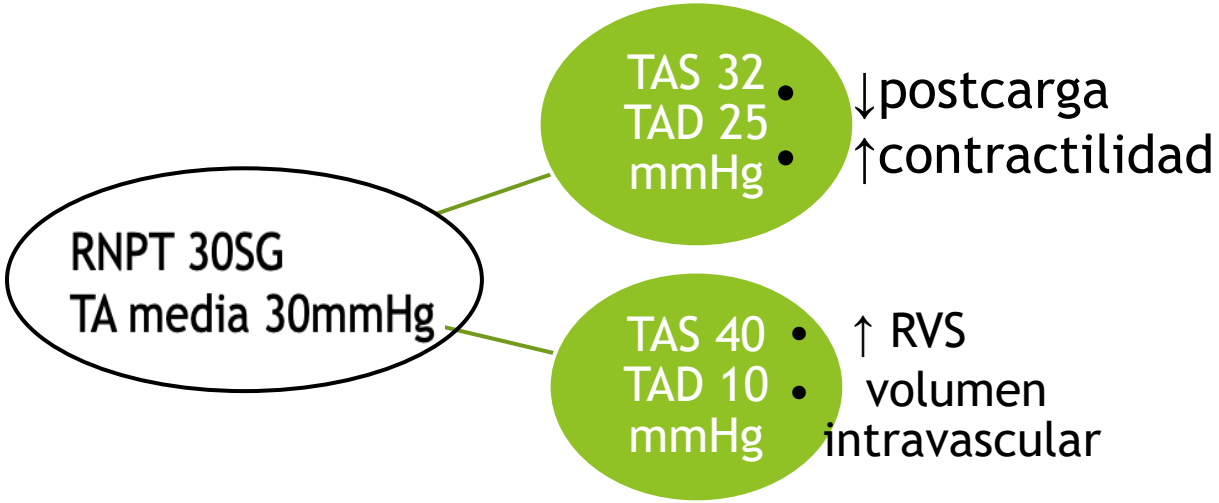
3 Vasoactive drugs have a predominant vasopressor effect

4 Inotropes are not effective in improving contractility

2 No cardiac reserve at times of stress (Sepsis & NEC)

3 High resting vascular tone

Utilidad de la TA sistólica y diastólica



Valorar la TA media aislada puede inducir error

- TA sistólica

Determinada: precarga y contractilidad

Marcador: fuerza de contracción miocárdica y GC

- TA diastólica

Determinada: pérdida de líquidos, shunts, vasodilatación

Marcador: RVS

- La hipotensión sistólica y diastólica → estadio avanzado

Insuficiencia circulatoria

Evaluar el escenario clínico + fisiopatología

Precarga comprometida	Volumen (aumentar precarga) o restaurar el flujo sanguíneo pulmonar
Postcarga aumentada	Vasodilatador e inotrópico
Postcarga disminuida	Vasopresor
Contractilidad débil	Inotrópico

1. Asociación frecuente de varios fenómenos fisiopatológicos
2. El escenario evoluciona

Sustancias vasoactivas

1. Vasopresores primarios (noradrenalina, dopamina y vasopresina):
   Vasoconstricción y ↑ TA diastólica y media

2. Inotrópicos primarios (adrenalina, milrinona y dobutamina):
   ↑ contractilidad cardíaca y potencialmente del GC

3. Lusotrópicos (milrinona):
   Promueven la relajación del miocardio

4. Cronotrópicos (adrenalina y dobutamina):
   ↑ FC

5. Vasodilatadores (milrinona)

Vasoactive Drugs Mode of Action

	SV	SVR	PVR
Adrenaline	↑↑↑	↑↑↑	↑↑
Noradrenaline	↑/≈	↑↑↑	↓/≈
Vasopressin	≈	↑↑↑	↓/≈
Dobutamine	↑↑	↓/≈	≈
Milrinone	↑↑	↓↓	↓↓
Dopamine	↑	↑↑	↑↑↑

SV = stroke volume; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance
↑ = increase; ↓ = decrease; ≈ = no effect

Table 1 Vasoactive agents used in the neonatal intensive care unit

Agent	Mechanism of action	Clinical considerations
Predominant vasopressors		
Dopamine	It has mixed β-1 and α-adrenergic effects, in addition to its dopaminergic effects. Up to 25% of dopamine is converted to norepinephrine. It can have an unpredictable effect in premature infants. Due to the relative abundance of α-1 receptors in preterm infants, vasoconstrictive effects can occur at low levels, leading to increased SVR and PVR and potentially reducing CO and end-organ perfusion.[45]	Dopamine exhibits many extracardiac effects including impaired cerebral autoregulation[46] and pituitary suppression resulting in reduced levels of thyroid stimulation hormone and thyroxine in addition to prolactin.[47] Higher doses of dopamine may be associated with arrhythmias.[48] The use of dopamine should be reconsidered. Recent data suggest that dopamine is associated with increased mortality, neurological injury and morbidity including NEC.[49 50] This finding of increased mortality and morbidity is also observed in older children.[51]
Norepinephrine	A potent vasopressor as it has predominant α-1 effects and weaker β-1 effects. Norepinephrine will raise BP without and effective increase in CO. Norepinephrine may decrease PVR through α-2 stimulation and nitric oxide release. In term infants with acute pulmonary hypertension, norepinephrine can increase PVR but to a lesser ratio than SVR, with an associated improvement in pulmonary blood flow.[52]	It may be a useful agent to use in severe cases of vasodilatory shock associated with NEC and/or sepsis. Norepinephrine demonstrates favourable survival and postuse morbidity compared with dopamine in preterm infants with sepsis, and therefore, it may be the preferred first-line agent clinical scenarios of septic shock.[49]
Vasopressin	It exerts its effects through V1 receptors, resulting in an increase in SVR through phospholipid-mediated calcium release and a theoretical fall in PVR secondary to nitric oxide release.[53] Its antidiuretic properties are mediated through V2 receptors, found in the collecting ducts of the kidneys.	It has a potential role in the treatment of severe diastolic hypotension in infants with septic shock who do not respond to more traditional vasopressors and/or corticosteroids. Given its potential PVR-lowering properties, it may have a role in the treatment of pulmonary hypertension. The lack of chronotropic effects makes it an ideal choice in situations where maintaining vascular tone without an increase in heart rate is required. Clinical examples include severe septal hypertrophy secondary to gestational diabetes and hypertrophic obstructive cardiomyopathy.[27] It must be used with caution, as evidence of safety is currently lacking and there are reports that it may lead to oliguric renal failure or liver necrosis secondary to compromised splanchnic perfusion in some patients.[54]

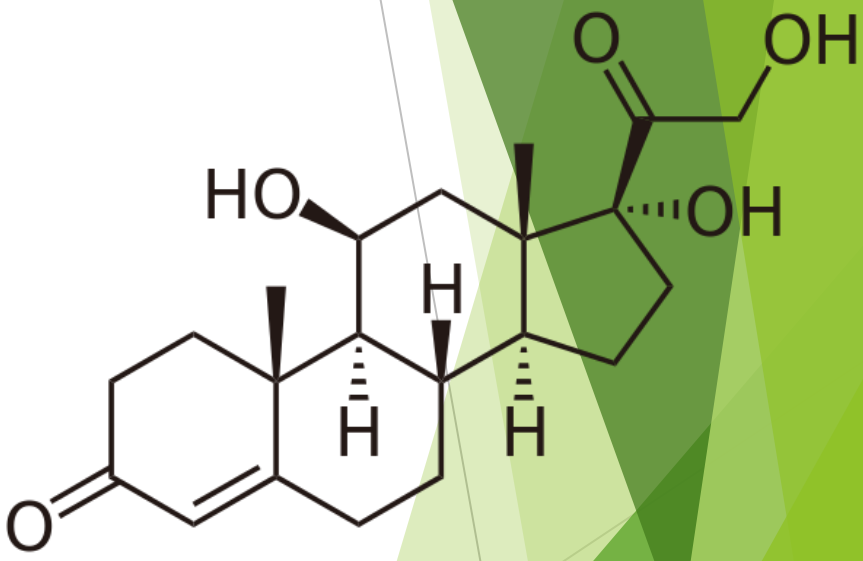
Table 1 Vasoactive agents used in the neonatal intensive care unit

Agent	Mechanism of action	Clinical considerations
Predominant inotropes		
Epinephrine	An endogenous catecholamine with β-1 effects at lower doses and α-adrenergic effects at higher doses, resulting in a combined inotropic and vasopressor effect Low-dose epinephrine may increase CO in neonates more effectively than dopamine. This is achieved through β-1 stimulation, which results in an increase in SV and heart rate.	Prolonged use may be associated with myocardial ischaemia and dysfunction as it increases myocardial oxygen demand. At higher doses, it is an effective vasopressor, raising both SVR and PVR through α-adrenergic stimulation. Epinephrine use in preterm infants is associated with a rise in lactate and blood glucose levels; this effect may be independent of dosing and duration and can be reversed with discontinuation of therapy.[55]
Dobutamine	A synthetic inotrope with predominant β-1-mediated increase in myocardial SV, heart rate and β-2 vascular vasodilatory action; it increases CO and reduces SVR. This could result in a marginal increase in BP.[56 57]	Due to the relative lack of expression of β-2 receptors in preterm vasculature, its vasodilatory effect is not generally seen in this population, although caution is still advised with higher doses. Dobutamine is considered in clinical situations of increased afterload and impaired myocardial contractility such as cold shock, asphyxia and pulmonary hypertension.
Inodilator		
Milrinone	Acts via phosphodiesterase III inhibition, thereby increasing the bioavailability of cyclic AMP; this leads to vasodilation in systemic and pulmonary vasculature in addition to inotropic and lusitropic myocardial effects.	In the literature, evidence of its use in neonates is limited to case series demonstrating an improvement in oxygenation when used in combination with inhaled nitric oxide in the setting of acute pulmonary hypertension.[58 59] Its lusitropic and potential inotropic properties make it an effective agent in the presence of right ventricular and left ventricular dysfunction in the setting of pulmonary hypertension. In addition, it has been used in preterm infants following patent ductus arteriosus ligation to prevent low CO states and subsequent respiratory deterioration.[60]

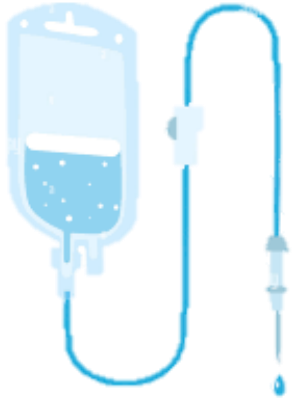
BP, blood pressure; CO, cardiac output; NEC, necrotising enterocolitis; PVR, pulmonary vascular resistance; SV, stroke volume; SVR, systemic vascular resistance.

Uso de corticoesteroides

- Respuesta inadecuada al estrés
- ¿Cuándo plantear su uso?:
  - Hipotensión refractaria a 2 fármacos inotrópicos
  - Alteración en la perfusión de la glándula
  - Datos sugestivos de ISR
- Efectos:
  - ↑ R adrenérgicos y su sensibilidad
  - ↑ calcio citosólico disponible en el músculo liso vascular
  - ↓ producción de vasodilatadores locales (ON y PG)
  - Liberación de catecolaminas vasoactivas



Expansión de volumen



CRISTALOIDES Y COLOIDES

- ¿Beneficio? → Uso indiscriminado → ↑ DAP, NEC, distrés respiratorio y muerte
- La albúmina → ↑ R retención de líquidos y altera el intercambio gaseoso
- **SI** se benefician:
  - En shock distributivo (sepsis y NEC)
  - AP de pérdida sanguínea → TF hematíes
  - Cuando se considera uso de un inodilatador (milrinona)

ALGORITMO

Marcadores clínicos
Hipotensión, láctico, oliguria/anuria, taquicardia, hipoxemia…

Sospecha de insuficiencia circulatoria

Antecedentes pre, peri y postnatales
Hemorragias, corioamnionitis, asfixia, hydrops fetalis, hipoplasia pulmonar, medicaciones maternas…

Ecocardio a pie de cuna
NIRS, EEGa

Valorar **TA** (media, sistólica y diastólica)*
Categorizar en función de la **fisiopatología**

↓ TA DIASTÓLICA	↓ TA SISTÓLICA	↓ AMBAS
Shock caliente (sepsis)	Shock frío (sepsis)	
NEC	Hipertensión pulmonar	
DAP	Circulación transicional	
Hipovolemia	Shock cardiogénico	

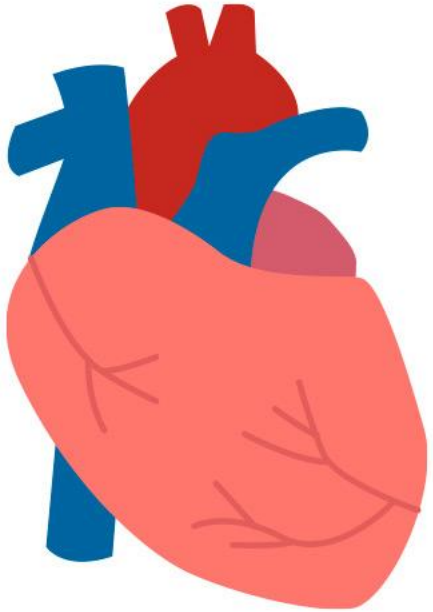
Actitud terapéutica

* Saber que objetivos buscamos de tensión en función de la EPM y las SG

Conclusiones

1. Valorar en conjunto toda la situación clínica, los biomarcadores (TA, FC, débito urinario, láctico, perfusión periférica) y los antecedentes personales (prenatales, perinatales y postnatales)
2. Ante una sospecha de insuficiencia circulatoria valora si tenemos disponibles otros marcadores (ecocardiografía: GC, flujo VCS, STRAIN…)
3. Valorar no solo la TA media, sino la sistólica y la diastólica y tener referencias de la tensión que se buscará como objetivo
4. Actitud terapéutica en función de la fisiopatología
5. Reevaluar el efecto (no solo sobre la TA)

Manejo hemodinámico y de la hipotensión en el prematuro



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