Role of neonatologist-performed echocardiography in the assessment and management of patent ductus arteriosus physiology in the newborn

W.P. de Boode[a,*], M. Kluckow[b], P.J. McNamara[c], S. Gupta[d]

[a] Department of Neonatology, Radboud University Medical Center, Radboud Institute for Health Sciences, Amalia Children's Hospital, Nijmegen, The Netherlands
[b] Department of Neonatology, Royal North Shore Hospital, University of Sydney, Sydney, Australia
[c] Department of Paediatrics and Physiology, University of Toronto, Toronto, Canada
[d] Department of Neonatology, University Hospital of North Tees, Durham University, Stockton-on-Tees, UK

ARTICLE INFO

Keywords:
Neonatologist-performed echocardiography
Patent ductus arteriosus
Preterm infants
Haemodynamic significance

ABSTRACT

Neonatologist-performed echocardiography (NPE) is an indispensable tool in the haemodynamic management of critically ill newborn infants. NPE is used to facilitate timely diagnosis of a patent ductus arteriosus (PDA) in preterm infants and to assess its haemodynamic significance. Before treatment is considered, it is obligatory to confirm structural cardiac normality. Importantly, NPE offers the ability to guide therapeutic interventions, allowing an individualised haemodynamic management approach to the PDA. After discussing PDA pathophysiology, an overview is provided on the role of NPE in the assessment and management of PDA in preterm infants.

1. Introduction

The management of a patent ductus arteriosus (PDA) in preterm infants < 28 weeks gestation is currently one of the most debated topics, even though PDA has been recognised as a potential pathological entity for more than half a century. The approach towards a preterm infant with a PDA has transitioned from 'aggressive' active closure, either pharmacologically with cyclooxygenase inhibition (indomethacin, ibuprofen) or surgically with ductal ligation, to a more expectant policy. The rationale for this change was the observation that on one hand active closure of the PDA did not result in a decrease in mortality and morbidity and on the other hand spontaneous ductal closure occurs in a substantial portion of patients, particularly in more mature infants. Many trials lack precise and consistent definition of the haemodynamic significance of PDA, making assessment of their relevance difficult [1]. Moreover, the lack of proof of causality/treatment response between PDA and associated morbidity, such as pulmonary haemorrhage, bronchopulmonary dysplasia, intraventricular haemorrhage, necrotising enterocolitis, renal failure, and retinopathy of prematurity, has resulted in a worldwide increased interest in a wait-and-see/conservative management policy with the aim to prevent the – presumed redundant – adverse effects of pharmacologic or surgical closure. Nevertheless, evidence is still lacking for and against each of these two approaches. Current pending randomised controlled trials, comparing an expectant approach versus an active closure approach of the patent ductus arteriosus, in preterm infants may provide us with more knowledge about optimal management.

However, the question remains whether only one of the two management options (treat or not treat) will be optimal for all patients, or whether there might be a subgroup that will benefit from a modified approach regarding their PDA. In other words, there is likely to be a spectrum with, on one side, patients in whom spontaneous closure of the ductus arteriosus might be expected and 'watchful waiting' is justified, and on the other side neonates in whom a persistent PDA results in a significant left-to-right shunt flow with compromised haemodynamics (Fig. 1) that requires active ductal closure to limit harm.

Neonatologist-performed echocardiography (NPE) is used to diagnose a PDA and confirm normal structural cardiac anatomy, but is also indispensable in the selection of patients who would potentially benefit from treatment by estimation of the haemodynamic consequences of the PDA (haemodynamic significance), prediction of spontaneous closure, and prediction of risk of morbidity (PDA severity scores). Moreover, NPE enables monitoring the effect of treatment with the possibility of individualising therapeutic strategy, and evaluation of possible long-term effects.

In this review, we discuss the role of NPE in the assessment and management of a PDA in preterm infants.

* Corresponding author. Radboud University Medical Center, Radboud Institute for Health Sciences, Amalia Children's Hospital, Department of Neonatology (804), P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.
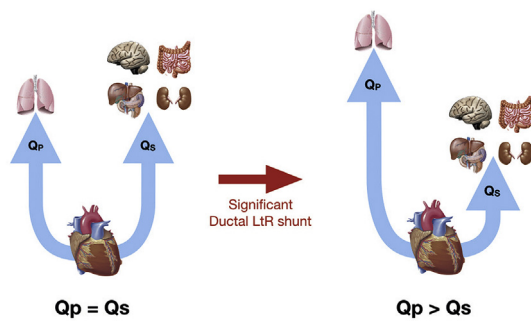   *E-mail address:* willem.deboode@radboudumc.nl (W.P. de Boode).

Fig. 1. Influence of transductal left-to-right (LtR) shunting on the balance between pulmonary (Qp) and systemic (Qs) perfusion.

2. Role of neonatologist-performed echocardiography in the assessment of a patent ductus arteriosus

Ultrasound is the gold standard method used to diagnose a PDA and analyse the impact on the systemic and pulmonary circulations. It has been proven that echocardiographic assessment is superior to clinical examination in the diagnosis of a PDA, since the predictive value of clinical symptoms such as murmur, diastolic hypotension, bounding pulses, and wide pulse pressure is rather disappointing, and echocardiographic indicators of a haemodynamically significant PDA precede these symptoms by ∼2 days [2–5].

Neonatologist-performed echocardiography allows a longitudinal assessment that enables the early detection of a PDA and estimation of haemodynamic significance [6].

A mono-centre study about the clinical impact of the introduction of serial echocardiographic assessment of the PDA in preterm infants < 1500 g revealed an earlier diagnosis (median 3 (range: 3–4) versus 4 days (2−13)) and treatment (median 3 (3–7) versus 5 (3–25)) [5]. Another interesting observation was that echocardiographic screening resulted in fewer ventilation days in the PDA group and fewer severe intraventricular haemorrhages (grade III or higher) in both the PDA group and control group.

To evaluate the impact of a left-to-right transductal shunt on systemic and pulmonary perfusion and the haemodynamic significance, one would preferably want to quantify the transductal blood flow, also called shunt volume (in mL/kg/min). Regrettably, this is not feasible. This implies that the shunt volume can only be estimated by indirect echocardiographic parameters, namely characteristics of the PDA itself and indices reflecting pulmonary hyperperfusion or systemic hypoperfusion (Fig. 2). Table 1 provides an overview of all applicable echocardiographic indices of transductal shunt volume and their cut-off values that can be used to differentiate between a small, moderate, or large shunt, respectively [4,7,8].

It is essential to differentiate between a pathological and a supportive role of the ductus arteriosus during the transitional phase. As mentioned before, a duct-dependent structural heart disease should be excluded before the commencement of pharmaceutical closure. In the presence of a low cardiac output state secondary to a severely increased pulmonary vascular resistance, systemic blood flow will be heavily dependent on transductal right-to-left shunting (supportive PDA). Another example of a supportive PDA is in a patient with severe impairment of right ventricular performance, where a transductal left-to-right shunt is essential to maintain adequate pulmonary blood flow.

In summary, the primary goals of NPE in the assessment of a PDA are:

– Confirm normal cardiac anatomy and shunt directionality.
– Appraise shunt volume using characteristics of the PDA and indirect markers of pulmonary hyperperfusion and systemic hypoperfusion.
– Evaluate the role of the PDA in relation to heart function (pathological or supportive).

2.1. Characteristics of the patent ductus arteriosus

The following characteristics of the PDA can be directly assessed: absolute or relative ductal diameter and the transductal blood flow pattern.

2.1.1. Ductal diameter

The internal diameter of the ductus arteriosus is measured in the high left parasternal view at the point of maximal constriction, generally near its insertion into the pulmonary artery, in either the two-dimensional image or with colour Doppler imaging. One should be cautious with increasing the gain of the colour Doppler for this purpose, since this potentially leads to an overestimation of the diameter. It remains challenging to accurately assess ductal diameter, given the large variation in geometry and length of the ductus arteriosus, vasoresponsiveness and variability related to the operator and equipment. Fig. 3 shows different morphology types of the PDA. The absolute ductal diameter can also be indexed either to the body weight, expressed in mm/kg, or to the diameter of the left pulmonary artery (see Table 1).

2.1.2. Transductal blood flow pattern

The transductal blood flow pattern can be visualised using pulsed or continuous wave Doppler imaging, revealing the direction and velocity of the ductal shunt. The magnitude of transductal blood flow is determined by the transductal pressure gradient and the vascular resistance of the ductus arteriosus. The latter depends on the diameter and length (tortuosity) of the ductus arteriosus and on the rheological properties of blood. The direction of the shunt depends on the balance between the systemic and pulmonary blood pressure throughout the cardiac cycle. The postnatal haemodynamic transition is – under normal circumstances – characterised by a decrease in pulmonary arterial pressure and increase in systemic arterial pressure. This is reflected in the transductal shunt pattern transitioning from right-to-left to bidirectional and finally left-to-right. Closure of the ductus arteriosus (increase in vascular resistance) will also affect transductal blood flow. A non-restrictive ductus arteriosus will show a blood flow pattern with low peak systolic velocity, resulting in an increased systolic-to-diastolic transductal velocity gradient (V_{sys}/V_{dia}), whereas in a restricting ductus a high peak systolic blood velocity will be assessed with a decreased V_{sys}/V_{dia}. It must be noted that with prolonged high-volume transductal left-to-right shunting with partial restriction, a high peak systolic velocity can be observed, which in this case does not represent a closing ductus arteriosus.

Transductal blood flow patterns are subdivided into: (a) right-to-left (pure RtL or bidirectional with RtL component for ≥30% of the cardiac cycle); (b) growing (bidirectional with RtL component < 30% of the cardiac cycle); (c) pulsatile or non-restrictive (LtR with V_{sys}/V_{dia} ≥ 2.0); and (d) closing or restrictive (LtR with V_{sys}/V_{dia} < 2.0) (Fig. 4). A right-to-left transductal flow pattern should always be interpreted as pathologic, and ductal-dependent structural heart disease or persistent pulmonary hypertension must be considered.
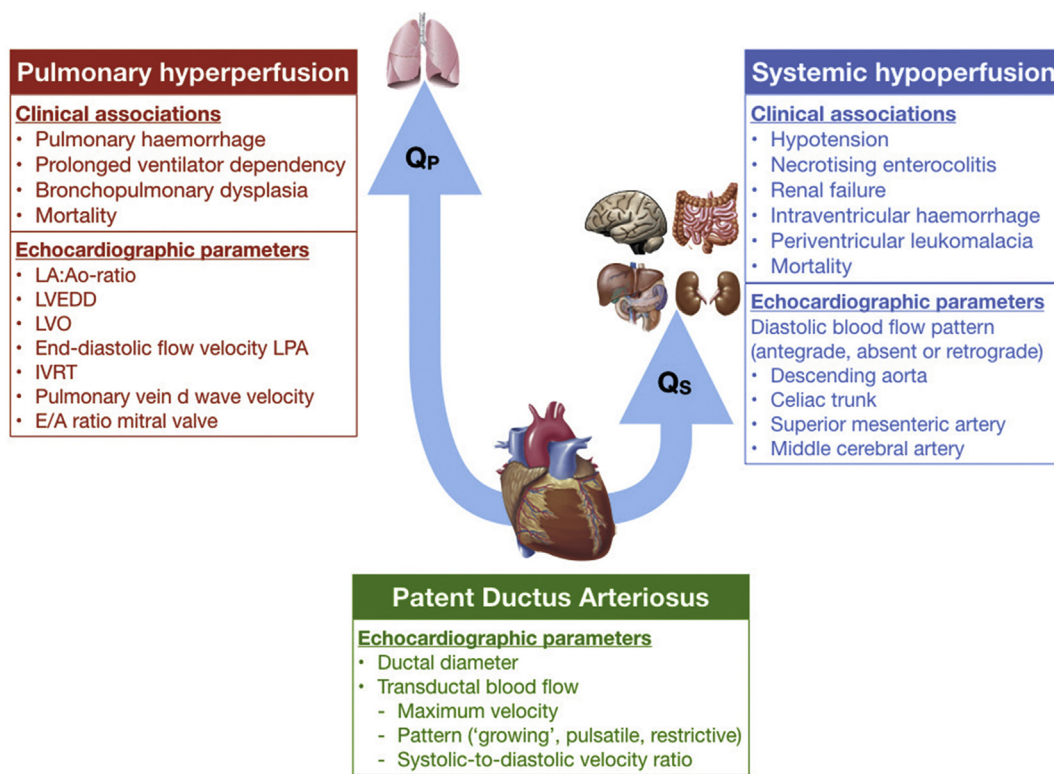
2.2. Markers of pulmonary hyperperfusion

A PDA with high-volume LtR shunt will augment pulmonary blood flow and increase the volume and pressure load of the left heart.

2.2.1. Pulmonary hyperperfusion

Increased pulmonary blood flow can be estimated by assessing end-diastolic blood flow velocity in the left pulmonary artery (V_{ED}^{LPA}) and pulmonary vein diastolic wave velocity (V_{PVdW}).

Increased transductal LtR shunting will augment pulmonary blood flow that can be objectified by measuring an increased mean and end-diastolic blood flow velocity in the left pulmonary artery from the high parasternal short-axis view. This enhanced pulmonary blood flow is clearly also reflected in pulmonary venous return by an increase in

Pulmonary hyperperfusion

Clinical associations
- Pulmonary haemorrhage
- Prolonged ventilator dependency
- Bronchopulmonary dysplasia
- Mortality

Echocardiographic parameters
- LA:Ao-ratio
- LVEDD
- LVO
- End-diastolic flow velocity LPA
- IVRT
- Pulmonary vein d wave velocity
- E/A ratio mitral valve

Systemic hypoperfusion

Clinical associations
- Hypotension
- Necrotising enterocolitis
- Renal failure
- Intraventricular haemorrhage
- Periventricular leukomalacia
- Mortality

Echocardiographic parameters
Diastolic blood flow pattern (antegrade, absent or retrograde)
- Descending aorta
- Celiac trunk
- Superior mesenteric artery
- Middle cerebral artery

Patent Ductus Arteriosus

Echocardiographic parameters
- Ductal diameter
- Transductal blood flow
  - Maximum velocity
  - Pattern ('growing', pulsatile, restrictive)
 - Systolic-to-diastolic velocity ratio

Fig. 2. Clinical associations and echocardiographic indices of significant transductal left-to-right shunting. E/A ratio, E(arly) to A(trial) wave ratio; IVRT, isovolumic relaxation time; LA:Ao ratio, left atrium to aortic root ratio; LPA, left pulmonary artery; LVEDD, left ventricular end-diastolic diameter; LVO, left ventricular output; Qp, pulmonary perfusion; Qs, systemic perfusion.

Table 1
Overview of echocardiographic indices of transductal shunt volume.

Echocardiographic indices of shunt volume	Small	Moderate	Large
Characteristics of the PDA			
Absolute diameter (mm)	< 1.5	1.5–2.0	≥ 2.0
PDA:LPA diameter ratio	< 0.5	0.5–1.0	≥ 1.0
PDA diameter indexed to body weight (mm/kg)	–	–	≥ 1.4
Transductal peak systolic velocity (m/s)	> 2.0	1.5–2.0	< 1.5
Transductal systolic-to-diastolic velocity gradient	< 2.0	2.0–4.0	> 4.0
Pulmonary hyperperfusion			
End-diastolic blood flow velocity in LPA (cm/s)	< 20	20–50	> 50
Pulmonary vein diastolic (D)-wave velocity (cm/s)	< 0.3	0.3–0.5	> 0.5
LA:Ao ratio	< 1.5	1.5–2.0	> 2.0
LVEDD (Z-score)			
LVO (mL/kg/min)	< 200	200–300	> 300
Mitral valve E:A ratio	< 1	1	> 1
LV-IVRT (ms)	> 40	30–40	< 30
Systemic hypoperfusion			
Diastolic blood flow pattern in systemic arteries (DAo, MCA, PCA, CT, SMA, RA)	Antegrade	Absent	Retrograde
Qp:Qs ratio			
LVO:SVCf ratio	–	–	≥ 4.0

Ao, aortic root; DAo, descending aorta; E:A ratio, E(arly) to A(trial) wave ratio; LA, left atrium; LPA, left pulmonary artery; LV-IVRT, left ventricular isovolumic relaxation time; LVEDD, left ventricular end-diastolic dimension; LVO, left ventricular output; PDA, patent ductus arteriosus; Qp, pulmonary blood flow; Qs, systemic blood flow; SVCf, superior vena cava flow.

pulmonary vein diastolic (D) wave velocity. Blood flow pattern in the lower pulmonary veins is assessed in the high parasternal long-axis view (so-called crab view) and consists of three components, namely S
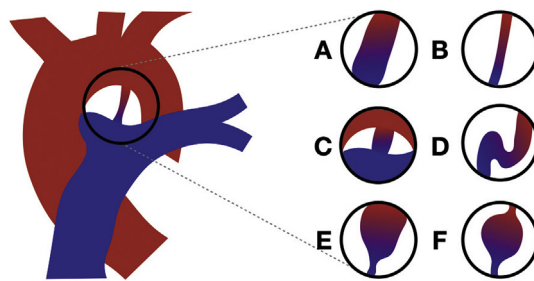
Fig. 3. Different morphology types of a patent ductus arteriosus. Schematic representation of a patent ductus arteriosus connecting the aorta (in red) with the pulmonary artery (in blue). (A) Straight-through; (B) narrow; (C) short; (D) serpentine; (E) funnel; (F) saccular.

(systolic)-wave, D (diastolic)-wave, and the A (atrial)-wave. Increased D-wave velocity suggests high transductal shunt flow [9].

2.2.2. Volume overload of the left heart

The degree of volume overload can be assessed by measuring left atrium to aortic root (LA:Ao) ratio, left ventricular end-diastolic dimension (LVEDD), left ventricular output to superior vena cava flow (LVO:SVCf) ratio.

In contrast to its popularity, the LA:Ao ratio is a rather inaccurate marker of volume load of the left heart due to its high intra- and interindividual variability [8]. Increased pulmonary venous return will cause an enhanced left atrial preload, ultimately resulting in dilation. The degree of LA dilation is indexed to the aortic root diameter, which is considered constant under these circumstances. Also the left ventricle will dilate secondary to this volume overload, leading to an increased LVEDD. Both LA:Ao ratio and LVEDD are assessed in the parasternal long-axis view using M-mode. It is important to understand that the above-mentioned markers of preload of the left heart are potentially
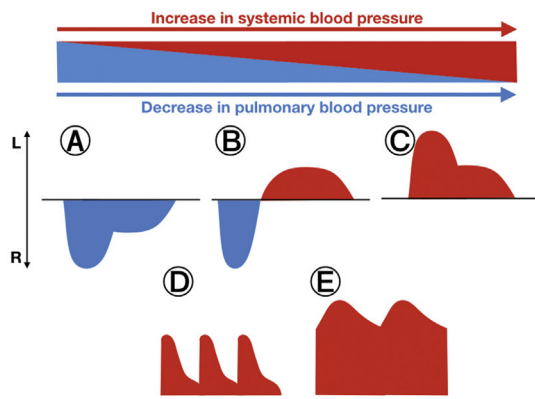
Fig. 4. Schematic representation of different transductal blood flow patterns. Transductal blood flow patterns are subdivided in (A) right-to-left (pure RtL or bidirectional with RtL component for ≥30% of the cardiac cycle), (B) growing (bidirectional with RtL component < 30% of the cardiac cycle), (C) left-to-right, that can be differentiated in (D) pulsatile or non-restrictive (LtR with V_{sys}:V_{dia} ≥ 2.0), and (E) closing or restrictive (LtR with V_{sys}:V_{dia} < 2.0).

influenced by an interatrial LtR-shunt. Significant LtR shunting through a patent foramen ovale will reduce left atrial and left ventricular volume overload, meaning that LA:Ao ratio and LVEDD might be in the "normal" range despite a significant transductal shunt volume.

Increased pulmonary venous return will elevate LVO; however, this might be ameliorated in the presence of interatrial LtR shunting or poor myocardial performance. To estimate LVO, one measures the diameter of the left ventricular outflow tract and assesses Doppler blood flow velocities (velocity time integral (VTI)) in this same area, which is needed for calculation of the cardiac output. The following formula is used for LVO estimation.

LVO (mL/kg/min) = $((\pi \times (D_{LVOT}/2)^2 \text{ (cm}^2)) \times VTI_{LVOT} \text{ (cm)} \times$ heart rate (bpm))/body weight (kg)

where D_{LVOT} is the diameter of the left ventricular outflow tract. The magnitude of transductal shunt volume can also be estimated by assessing the relation between LVO and SVCf, as SVCf will decrease as a surrogate for systemic blood flow, whereas LVO will increase secondary to rising LtR shunting. However, this is controversial, as one could also expect in some infants that SVCf is preserved in the presence of high-volume transductal shunting, since SVCf represents the venous return of the upper body, that is mainly perfused by increased LVO via preductal vessels.

A hyperdynamic left ventricle, defined as increased LV output and ejection fraction, influences the right ventricle performance secondary to impaired right ventricle preload, as indicated by lower right ventricle fractional area change (FAC) and right ventricle strain values [10].

2.2.3. Pressure overload of the left heart

Indices of pressure overload of the left heart are mitral valve E:A-wave ratio and isovolumic relaxation time (IVRT).

Transmittal blood flow velocities are assessed from the four-chamber view using pulsed Doppler just downstream from the mitral annulus. Two phases of ventricular filling can be distinguished, the early (E), passive diastolic phase and the late, active atrial (A) contraction phase. Because of a relative low ventricular compliance in preterm infants, passive filling of the ventricle is hampered, thus leading to an E:A ratio < 1. Significant transductal shunt volume will increase left atrial pressure and therefore augment passive ventricular diastolic filling, which is reflected in an E:A ratio > 1. Since the E:A ratio usually is > 1 in mature children, this is also called pseudo-normalisation of the E:A ratio in preterm infants with significant LtR ductal shunting.

Another effect of an increased left atrial pressure is earlier opening of the mitral valve that can be objectified by measuring the time

between aortic valve closure and mitral valve opening, i.e. the left ventricular isovolumic relaxation time (LV-IVRT). Significant transductal LtR shunting will decrease IVRT.

2.3. Markers of systemic hypoperfusion

The counter-effect of an increased pulmonary blood flow secondary to significant transductal LtR shunting is decreased systemic blood flow. The effects of this stealing phenomenon can be observed in the (predominantly diastolic) blood flow pattern in several systemic arteries, such as the descending aorta, middle cerebral artery, pericallosal artery, internal carotid artery, coeliac trunk, superior mesenteric artery and the renal artery. Three different flow patterns can be observed based on antegrade, absent or retrograde diastolic blood flow. Retrograde diastolic blood flow in the postductal aorta specifically has been shown to be highly predictive of significant transductal shunt volume [11]. Recent data suggest that retrograde diastolic blood flow can also be observed in preductal systemic arteries with potential consequences for cerebral perfusion, that traditionally has been considered to be protected by an increased LVO [12].

As already mentioned earlier, reduced systemic blood flow in relation to increased pulmonary blood flow is reflected by a high LVO:SVCf ratio.

3. Role of neonatologist-performed echocardiography in the management of a patent ductus arteriosus

Neonatologist-performed echocardiography is used in the management of preterm infants with a persistent PDA to predict haemodynamic significance, to estimate the risk of presumptive PDA-related morbidity (PDA severity scores), to monitor the effect of treatment, and to evaluate possible long-term effects. In this way, it is aimed to individualise PDA management and hopefully improve outcome.

It goes without saying that it is obligatory to exclude any duct-dependent structural heart disease before commencement of therapeutic closure.

3.1. Predictive value of neonatologist-performed echocardiography for haemodynamic significance and adverse outcomes

Table 1 can be used to estimate transductal shunt volume based on echocardiographically assessed variables. However, as shown in Table 2 the predictive values of these markers for haemodynamic significance are rather disappointing [13–20]. It must be noted that the definitions of haemodynamic significance and the populations studied are highly heterogeneous in the included studies.

Different PDA scoring systems, incorporating echocardiographic and occasionally clinical parameters, have recently been described that estimate the severity of transductal shunt volume and relationship to subsequent mortality in preterm neonates in the first three days of life [13,21–25]. The PDA severity score is composed of five components (gestational age, ductal diameter, transductal peak velocity, left ventricular output, and left ventricular a′-wave by tissue Doppler imaging) and has a positive and negative predictive value of 92% and 82%, respectively, for the composite outcome chronic lung disease or mortality [24]. Although there is great similarity in the parameters, the predictive value varies according to different outcomes, such as necrotising enterocolitis and periventricular leukomalacia [25].

Retrograde diastolic blood flow in the postductal descending aorta and a non-restrictive, pulsatile transductal blood flow pattern are considered the best indicators of high-volume transductal LtR shunting [4].

Table 2
Predictive values of echocardiographic indices for haemodynamic significance of PDA.

Echocardiographic indices	Cut-off value	PNA at assessment	Prediction	LR +	LR–	Reference
Absolute ductal diameter	≥1.5 mm	< 31 h	hsPDA (clinical and echocardiographic) at PNA 1–15 days	5.4**	0.22**	[13]
	≥1.5 mm	3 days	Failure of closure without treatment at PNA 10 days	3.4**	0.32**	[18]
	> 2.1 mm	< 48 h	PDA ≥2 mm at PNA 1 month	6.5**	0.25**	[19]
	≥2.0 mm	7 days	Need for future PDA treatment (> PNA 7 days)	947***	0.05***	[20]
PDA diameter indexed to body weight	> 1.5 mm/kg	12–48 h	hsPDA with indication for ligation	3.5**	0.08***	[15]
	> 2.0 mm/kg	24 h	Need for subsequent treatment (clinical and echocardiographic)	2.2**	0.15**	[17]
	> 2.0 mm/kg	72 h	Need for subsequent treatment (clinical and echocardiographic)	3.0**	0.16**	[17]
PDA:LPA diameter ratio	≥0.5	< 4 days	Need for subsequent treatment (clinical and echocardiographic)	3.9**	0.28**	[16]
	≥0.5	3 days	Failure of closure without treatment at PNA 10 days	2.0**	0.15**	[18]
Transductal systolic to diastolic velocity gradient	> 1.9	< 48 h	PDA ≥2 mm at PNA 1 month	8.8**	0.13**	[19]
	≥2.0	7 days	Need for future PDA treatment (> PNA 7 days)	5.4**	0.13**	[20]
Transductal blood flow pattern	Initial "growing"	< 7 days	hsPDA (clinical, radiological and echocardiographic) at PNA < 7 days	3.4**	0.44**	[14]
	Initial "pulsatile"	< 7 days	hsPDA (clinical, radiological and echocardiographic) at PNA < 7 days	∞***	0.07***	[14]
	"Pulsatile"	24 h	Need for subsequent treatment (clinical and echocardiographic)	2.2**	0.15**	[17]
	"Pulsatile"	72 h	Need for subsequent treatment (clinical and echocardiographic)	3.0**	0.42**	[17]
LA:Ao ratio	≥1.4	24 h	Need for subsequent treatment (clinical and echocardiographic)	1.0*	1.03*	[17]
	≥1.4	72 h	Need for subsequent treatment (clinical and echocardiographic)	1.1*	0.88*	[17]
	≥1.4	3 days	Failure of closure without treatment at PNA 10 days	3.2**	0.15**	[18]
	≥1.5	< 31 h	hsPDA (clinical and echocardiographic) at PNA 1–15 days	3.2**	0.78*	[13]
	≥1.45	7 days	Need for future PDA treatment (> PNA 7 days)	3.4**	0.21**	[20]
Left ventricular output	≥300 mL/kg/min	< 31 h	hsPDA (clinical and echocardiographic) at PNA 1–15 days	3.3**	0.80*	[13]
Mitral valve E:A ratio	> 1	3 days	Failure of closure without treatment at PNA 10 days	1.1*	0.00*	[18]

***Good test: LR +, > 10–20; LR–, < 0.05–0.10.
**Intermediate test: LR +, 2–10; LR–, 0.10–0.50.
*Poor test: LR +, < 2–4; LR–, > 0.25–0.50.
E:A ratio, E(arly) to A(trial) wave ratio; hsPDA, haemodynamically significant PDA; LA:Ao ratio, left atrium to aortic root ratio; LPA, left pulmonary artery; LR +, positive likelihood ratio; LR–, negative likelihood ratio; PDA, patent ductus arteriosus; PNA, postnatal age.

3.2. Individualised patent ductus arteriosus management with the use of neonatologist-performed echocardiography

3.2.1. Reduction of the intensity of treatment

After the decision has been made to pharmacologically close a PDA based on the estimation of its haemodynamic importance, NPE can be used to titrate the number of cyclooxygenase-inhibitor doses needed for effective ductal closure. It was shown in 1999 that echocardiographically guided treatment with indomethacin in mechanically ventilated preterm infants < 1500 g was associated with a reduction in number of doses (mean: 1.6 ± 0.9 versus 3.2 ± 1.4), but also there were significantly fewer adverse effects, such as gastrointestinal haemorrhage and oliguria, without a difference in ductal closure rate [26].

In a randomised controlled pilot study, the effect of indomethacin was echocardiographically analysed by measuring the change in ductal diameter. Early treatment was started in patients < 30 weeks gestation, when the ductal diameter measured > 2.0 mm at postnatal age < 6 h in the absence of contraindications. Only those patients who remained with a ductal diameter of > 1.6 mm received an additional dose. Adopting this policy, the exposure to indomethacin could be reduced from a median of three doses to only one dose, without any concomitant increase in the incidence of closure failure, ductal reopening, surgical ligation, or clinical outcomes, such as pulmonary haemorrhage, bronchopulmonary dysplasia, necrotising enterocolitis, or renal failure [27]. In another randomised controlled pilot study, the benefit of echocardiographically guided ibuprofen treatment was analysed in preterm neonates born at a gestational age between 24 and 34 weeks [28]. The findings were that NPE reduced the number of ibuprofen doses from a median of 3 (interquartile range (IQR): 3–4) to 2 (1–5.7) without any differences in ductal closure failure, mortality, or major

neonatal morbidities. Subgroup analysis showed, however, that the difference in number of doses of ibuprofen was more profound in infants > 28 weeks gestation.

3.2.2. Prevention of complications after ductal ligation

Another application of NPE-guided management is in the direct postoperative phase after ductal ligation. NPE can be used to identify patients at risk for the development of post PDA ligation cardiac syndrome and enables early intervention to prevent postoperative cardiorespiratory instability [29]. Left ventricular output < 200 mL/kg/min at 1 h postoperative predicted subsequent critically low cardiac output (at 8 h postoperatively), systolic hypotension and a necessity for inotropic treatment with a positive likelihood ratio of 7.3 (95% confidence interval (CI): 3.5–15.4), 3 (1.8–5.0) and 3.5 (2.3–5.4), respectively. Anticipating the development of post-ligation cardiac syndrome guided by NPE with early intervention with milrinone led to a reduction in systemic hypotension, and the need for inotropic support and reduced ventilatory failure in this study.

However, despite this prophylactic administration of milrinone in the selected patients at risk (LVO < 200 mL/kg/min) about half (51.2%) still developed oxygenation or ventilatory failure (30). Using comprehensive echocardiographic monitoring, a prolonged isovolumic relaxation time (IVRT) was identified as a risk factor for the development of oxygenation or ventilatory failure after ductal ligation in a cohort of 86 preterm infants (median gestational age of 25 weeks (IQR: 24–26) and a median birth weight of 740 g (IQR: 640–853)) [30]. An IVRT > 30 ms 1 h postoperatively, reflecting impaired diastolic left ventricular performance in response to increased LV afterload, was associated with a positive and negative likelihood ratio of 2.1 and 0.28, respectively, for respiratory instability.

3.2.3. Follow-up of asymptomatic persistent patent ductus arteriosus

There is no consensus about optimal management of preterm infants in whom ductal closure has not been documented before discharge to home, either after expectant management or after failure of pharmaceutical closure. In a retrospective observational study of 310 preterm infants with a birth weight < 1500 g who survived to discharge, 11 patients who were never treated and 10 patients with treatment failure after indomethacin administration (21/310, 6.8%) were discharged without documented ductal closure [31]. At follow-up at a median postmenstrual age of 48 weeks (IQR: 46–56), spontaneous closure of the ductus arteriosus was found in 86% (18/21) of these patients. No adverse effects of a prolonged exposure to a PDA, such as congestive heart failure, pulmonary hypertension, or bacterial endocarditis, occurred in this population. In two of the 21 (9.5%) patients, the PDA was closed by catheter intervention.

It was recently suggested in a prospective observational study in preterm infants < 30 weeks gestation, using conventional and novel echocardiographic techniques, that prolonged exposure to a PDA induces reversible, adaptive, but not pathologic cardiac remodelling [32].

This all suggests that an expectant approach towards a PDA after discharge is justified at least in some subgroups of patients.

4. Conclusions

Neonatologist-performed echocardiography enables the identification of the preterm infants with high-volume transductal blood flow who are at highest risk for adverse outcome and potentially would benefit most from timely therapeutic intervention. The choice and intensity of therapeutic interventions can be guided by NPE, thereby reducing the risks of therapy-related adverse effects.

4.1. Practice points

The primary goals of NPE in the assessment and management of a PDA are:

- Confirmation of normal cardiac anatomy and shunt directionality.
- Appraisal of shunt volume using characteristics of the PDA and indirect markers of pulmonary hyperperfusion and systemic hypoperfusion.
- Evaluation of the role of the PDA in relation to heart function (pathological or supportive).
- Guidance of the choice and intensity of therapeutic interventions.

4.2. Research directions

- The results of pending randomised controlled trials comparing early active treatment versus an expectant management approach are awaited.
- Delineation of clinical and echocardiographic variables capable of identifying patients at highest risk of PDA-related morbidity and mortality.

Conflicts of interest

None declared.

Funding sources

None.

References

[1] Zonnenberg I, de Waal K. The definition of a haemodynamic significant duct in randomized controlled trials: a systematic literature review. Acta Paediatr 2012;101:247–51.

[2] Skelton R, Evans N, Smythe J. A blinded comparison of clinical and echocardiographic evaluation of the preterm infant for patent ductus arteriosus. J Paediatr Child Health 1994;30:406–11.

[3] Alagarsamy S, Chhabra M, Gudavalli M, Nadroo AM, Sutija VG, Yugrakh D. Comparison of clinical criteria with echocardiographic findings in diagnosing PDA in preterm infants. J Perinat Med 2005;33:161–4.

[4] Jain A, Shah PS. Diagnosis, evaluation, and management of patent ductus arteriosus in preterm neonates. JAMA Pediatr 2015;169:863–72.

[5] O'Rourke DJ, El-Khuffash A, Moody C, Walsh K, Molloy EJ. Patent ductus arteriosus evaluation by serial echocardiography in preterm infants. Acta Paediatr 2008;97:574–8.

[6] de Boode WP, Singh Y, Gupta S, et al. Recommendations for neonatologist performed echocardiography in Europe: consensus statement endorsed by European society for paediatric research (ESPR) and European society for neonatology (ESN). Pediatr Res 2016;80:465–71.

[7] Sehgal A, McNamara PJ. Does echocardiography facilitate determination of hemodynamic significance attributable to the ductus arteriosus? Eur J Pediatr 2009;168:907–14.

[8] Van Laere David, Van Overmeire Bart, Gupta Samir, El Khuffash Afif, Savoia Marilena, McNamara Patrick J, Schwarz Christoph E, de Boode Willem P. Application of neonatologist performed echocardiography in the assessment of a patent ductus arteriosus. Pediatr Res 2018. (Provisionally accepted).

[9] Martins F, Jain A, Javed H, McNamara PJ. Echocardiographic markers of hemodynamic significance of persistent ductus arteriosus (PDA): beyond ductal size (abstract). San Diego, CA, USA: Pediatric Academic Societies; 2015.

[10] Breatnach CR, Franklin O, James AT, McCallion N, El-Khuffash A. The impact of a hyperdynamic left ventricle on right ventricular function measurements in preterm infants with a patent ductus arteriosus. Arch Dis Child Fetal Neonatal Ed 2017;102:F446–50.

[11] Broadhouse KM, Price AN, Durighel G, et al. Assessment of PDA shunt and systemic blood flow in newborns using cardiac MRI. NMR Biomed 2013;26:1135–41.

[12] Breatnach CR, Franklin O, McCallion N, El-Khuffash A. The effect of a significant patent ductus arteriosus on Doppler flow patterns of preductal vessels: an assessment of the brachiocephalic artery. J Pediatr 2017;180:279–81. e1.

[13] Kluckow M, Evans N. Early echocardiographic prediction of symptomatic patent ductus arteriosus in preterm infants undergoing mechanical ventilation. J Pediatr 1995;127:774–9.

[14] Su BH, Watanabe T, Shimizu M, Yanagisawa M. Echocardiographic assessment of patent ductus arteriosus shunt flow pattern in premature infants. Arch Dis Child Fetal Neonatal Ed 1997;77:F36–40.

[15] Kwinta P, Rudziński A, Kruczek P, Kordon Z, Pietrzyk JJ. Can early echocardiographic findings predict patent ductus arteriosus? Neonatology 2009;95:141–8.

[16] Ramos FG, Rosenfeld CR, Roy L, Koch J, Ramaciotti C. Echocardiographic predictors of symptomatic patent ductus arteriosus in extremely-low-birth-weight preterm neonates. J Perinatol 2010;30:535–9.

[17] Harling S, Hansen-Pupp I, Baigi A, Pesonen E. Echocardiographic prediction of patent ductus arteriosus in need of therapeutic intervention. Acta Paediatr 2011;100:231–5.

[18] Thankavel PP, Rosenfeld CR, Christie L, Ramaciotti C. Early echocardiographic prediction of ductal closure in neonates ≤30 weeks gestation. J Perinatol 2013;33:45–51.

[19] Smith A, Maguire M, Livingstone V, Dempsey EM. Peak systolic to end diastolic flow velocity ratio is associated with ductal patency in infants below 32 weeks of gestation. Arch Dis Child Fetal Neonatal Ed 2015;100:F132–6.

[20] Yum SK, Moon CJ, Youn YA, Lee JY, Sung IK. Echocardiographic assessment of patent ductus arteriosus in very low birthweight infants over time: prospective observational study. J Matern Fetal Neonatal Med 2018;31:164–72.

[21] El Hajjar M, Vaksmann G, Rakza T, Kongolo G, Storme L. Severity of the ductal shunt: a comparison of different markers. Arch Dis Child Fetal Neonatal Ed 2005;90:F419–22.

[22] Sehgal A, Paul E, Menahem S. Functional echocardiography in staging for ductal disease severity: role in predicting outcomes. Eur J Pediatr 2013;172:179–84.

[23] Schena F, Francescato G, Cappelleri A, et al. Association between hemodynamically significant patent ductus arteriosus and bronchopulmonary dysplasia. J Pediatr 2015;166:1488–92.

[24] El-Khuffash A, James AT, Corcoran JD, et al. A patent ductus arteriosus severity score predicts chronic lung disease or death before discharge. J Pediatr 2015;167:1354–61. e2.

[25] Fink D, El-Khuffash A, McNamara PJ, Nitzan I, Hammerman C. Tale of two patent ductus arteriosus severity scores: similarities and differences. Am J Perinatol 2018;35:55–8.

[26] Su BH, Peng CT, Tsai CH. Echocardiographic flow pattern of patent ductus arteriosus: a guide to indomethacin treatment in premature infants. Arch Dis Child Fetal Neonatal Ed 1999;81:F197–200.

[27] Carmo KB, Evans N, Paradisis M. Duration of indomethacin treatment of the preterm patent ductus arteriosus as directed by echocardiography. J Pediatr 2009;155:819–22. e1.

[28] Bravo MC, Cabanas F, Riera J, et al. Randomised controlled clinical trial of standard versus echocardiographically guided ibuprofen treatment for patent ductus arteriosus in preterm infants: a pilot study. J Matern Fetal Neonatal Med 2014;27:904–9.

[29] Jain A, Sahni M, El-Khuffash A, Khadawardi E, Sehgal A, McNamara PJ. Use of targeted neonatal echocardiography to prevent postoperative cardiorespiratory instability after patent ductus arteriosus ligation. J Pediatr 2012;160:584–9. e1.

[30] Ting JY, Resende M, More K, et al. Predictors of respiratory instability in neonates undergoing patient ductus arteriosus ligation after the introduction of targeted milrinone treatment. J Thorac Cardiovasc Surg 2016;152:498–504.

[31] Herrman K, Bose C, Lewis K, Laughon M. Spontaneous closure of the patent ductus arteriosus in very low birth weight infants following discharge from the neonatal unit. Arch Dis Child Fetal Neonatal Ed 2009;94:F48–50.

[32] de Waal K, Phad N, Collins N, Boyle A. Cardiac remodeling in preterm infants with prolonged exposure to a patent ductus arteriosus. Congenit Heart Dis 2017;12:364–72.