Received: 7 September 2018 | Accepted: 16 October 2018

DOI: 10.1111/chd.12727

SPECIAL ISSUE ARTICLE

WILEY Congenital Heart Disease

What is a hemodynamically significant PDA in preterm infants?

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Abstract

Objective: There is no consensus on the definition of a hemodynamically significant patent ductus arteriosus (hsPDA). In this review article, our objective is to discuss the main variables that one should consider when determining the hemodynamic significance of a PDA.

Results: We describe the various approaches that have been utilized over time to define an hsPDA and discuss the strengths and weaknesses of each echocardiographic index. Finally, we propose a comprehensive and individualized approach in determining the hemodynamic significance of the PDA.

Conclusion: There are several PDA-related clinical, echocardiographic, and other objective variables to take into consideration when defining an hsPDA. However, vulnerability based on gestational or chronological age is an important contributor as well.

KEYWORDS
blood flow, echocardiography, hemodynamics

1 | HISTORICAL PERSPECTIVE

In the past, an hsPDA in a newborn was diagnosed only by clinical signs, such as a systolic murmur, wide pulse pressure, bounding pulses, hyperactive precordium, pulmonary edema, and increased oxygen requirement. Then, in the 1970s, echocardiography was introduced into pediatric practice and providers began to more objectively assess the hemodynamic effects of the PDA. While the information gained from echocardiography was limited at the time, M-mode allowed for an assessment of the extra volume load due to the PDA shunt based on the diameter of the left atrium (LA) relative to a constant, the aortic root (Ao) diameter. In the 1980s, echocardiography technology advanced further as the heart structures could be visualized in two dimensions and as such the diameter of the ductus arteriosus started to be included in the assessment of hsPDA. In the late 1990s and early 2000s, neonatologists became more interested in the direct assessment of the PDA using echocardiography and other monitoring technologies. With these technological advances, it has become apparent that clinical signs of hsPDA can lag behind echocardiographic signs.[1] Thus, a more comprehensive approach in defining hsPDA has emerged.

2 | APPROACHES TO DEFINING hsPDA

Despite widespread recognition of the importance of identifying an hsPDA, there remains no consensus on its definition. There are several approaches to defining an hsPDA. One approach is to qualify and quantify the hemodynamic effects of the PDA using clinical signs, echocardiographic parameters, and other objective assessments, and define a threshold to declare a PDA as hemodynamically significant. Another approach would be to assess the need for treatment, which entails using various parameters to identify a PDA that would have high likelihood of remaining open or presenting with adverse hemodynamic effects. For example, choosing a cut-off diameter of 1.5 mm or 2 mm in an extremely preterm infant in the first couple of days of life to label it hsPDA and thus treat it. Lastly, an hsPDA could be defined based on probable outcomes. In this approach, the focus is on defining the population at risk for major complications of prematurity where the PDA is thought to play a role in the pathogenesis of said complication (eg, peri/intraventricular hemorrhage, pulmonary hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, etc.).

In defining an hsPDA, the hemodynamic effects of a PDA could be best evaluated using echocardiography, organ blood flow

Doppler, and other available modalities. Additionally, the vulnerability of a given patient or population should be taken into account, including risk factors such as of perinatal variables, gestational age, chronologic age, and genetics.

3 | ECHOCARDIOGRAPHIC DETERMINANTS IN DEFINING AN hsPDA

There are several echocardiographic indices that are helpful in evaluating for an hsPDA. These indices can be categorized into: the PDA shunt size, the extent of volume overload, the degree of pulmonary overflow, and the magnitude of systemic hypoperfusion (Figure 1).

The PDA shunt can be characterized by the diameter and the flow pattern through the PDA. The PDA can be visualized using the ductal view, obtained in the suprasternal or high parasternal cuts. If possible, it is ideal to view the PDA in its entirety coursing between the pulmonary artery and the descending aorta. The diameter should be measured at the narrowest portion of the PDA which often is on the pulmonary end. Traditionally, the diameter is measured using the color Doppler mode; however, with improved ultrasound technology, the visualization of the ductal wall on two-dimensional images is often possible. The diameter of the ductus is important in estimating the shunt magnitude as the flow is proportional to diameter to the power of four. Although an accurate measurement of the diameter can be challenging at times, given the greater subjectivity in defining a ductus as small, moderate, or large by the person reading the echocardiogram, measuring and reporting the ductal diameter is preferable. The flow pattern can be assessed by placing the Doppler gate within the narrowest portion of the PDA. Other than a completely right-to-left ductal flow, there are four flow patterns described by Su et al: bidirectional, growing, pulsatile, and closing (Figure 2).[2,3] The bidirectional pattern usually signifies elevated pulmonary blood pressure. The growing and pulsatile patterns indicate significant left-to-right shunt through the PDA and are thus suggestive of an hsPDA.

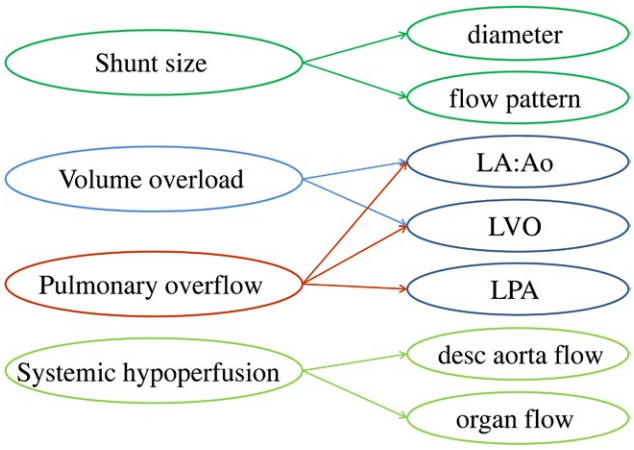

FIGURE 1 Echocardiographic indicators of an hsPDA. Each time we obtain an echocardiography, we should consider evaluating for the size of the shunt, the extent of volume overload, the degree of pulmonary overflow, and the magnitude of systemic hypoperfusion

The closing pattern in general is suggestive of ductal constriction. The diameter and the flow are related and may be complementary in identifying hsPDA. For example, one study showed that the closing pattern was most commonly seen in PDAs with smaller diameter, but there is a considerable overlap in the diameter size among the four groups.[4] Since the PDA shunt can now be described in detail

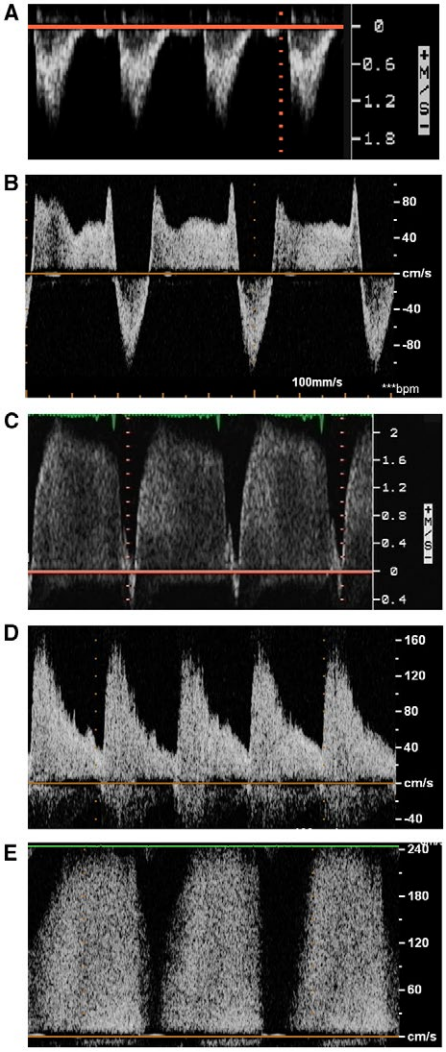

FIGURE 2 Examples of PDA flow pattern are shown. A, Pulmonary hypertension pattern with pure right-to-left shunt, indicative of suprasystemic pulmonary arterial pressure; B, Bidirectional shunt suggestive of elevated systolic pulmonary arterial pressure, with right-to-left shunting during systole and left-to-right shunting in diastole; C, Growing pattern: almost complete left-to-right shunt with minimal right-to-left, indicative of decreasing pulmonary arterial pressure; D, Pulsatile pattern, completely left-to-right shunt with a significant difference in systolic and diastolic velocities; E, Closing pattern: completely left-to-right shunt with high velocity and minimal or no difference between systolic and diastolic velocities. The flow in the closing pattern is continuous but due to the small PDA size there can be gaps (as in this example) with the cursor moving in and out of the ductus with heart motion or respiration *Source*: From Noori (2018).[3]

by measuring the diameter and the flow pattern, these parameters should be taken into account when defining an hsPDA.

The extent of volume overload can be determined echocardiographically by calculating the LA:Ao and by measuring the left ventricular dimension or output (LVO). As mentioned earlier, LA:Ao is historically the first echocardiographic index used to define a significant PDA and still is of the most common indices that is provided in an echocardiogram report. Although a cutoff of 1.4 is often used as a marker of an hsPDA, the index is an indicator of volume load and not specific to PDA. Therefore, LA:Ao can be large due to volume overload or mitral valve/left ventricular dysfunction. Conversely, in the presence of a large patent foramen ovale, the LA/Ao ratio may be small since the extra volume supplied by a PDA could "pop off" through the PFO. LVO is large in the setting of an hsPDA, as the additional volume from the PDA enters the pulmonary vasculature, returns to the left side of the heart, and then is ejected from the left ventricle. Indeed, the LVO can be 400-600 mL/kg/min (normal 150-300 mL/kg/min). However, in the presence of a significant left-to-right ductal shunt, a low-normal LVO is a more ominous sign as it indicates an inadequate compensatory increase in cardiac output. Despite the above limitations, the extent of volume overload to the left side of the heart should be taken into account when assessing whether a PDA is hemodynamically significant and requires treatment.

The degree of pulmonary overflow from an hsPDA can be determined by the LA:Ao ratio and LVO, as well as the end-diastolic velocity in the left pulmonary artery (LPA). Normally, the flow through the branched pulmonary arteries primarily occurs during the systole with absent or minimal flow during the diastole. In comparison, an hsPDA will lead to increased pulmonary blood flow, which can readily be assessed by measuring the LPA diastolic flow. End-diastolic velocity greater than 20 cm/s is often used as a marker of an increased pulmonary flow with an hsPDA.

Finally, assessment of the descending aorta and organ blood flow using Doppler may be useful in determining the magnitude of systemic hypoperfusion. Diastolic flow reversal in the descending aorta, which is reflective of steal phenomenon from a left-to-right PDA shunt, results in compromise to systemic circulation. Retrograde descending aorta flow combined with the PDA diameter greater than 1.5 mm appears to be the best echocardiographic indicator of an hsPDA.[5] However, the presence of retrograde aorta flow does not quantify the effect on systemic perfusion or shed light on maldistribution of blood flow to different vascular bed; therefore, measuring the direct flow to the end organs may also be helpful.

Cerebral blood flow is altered in the presence of an hsPDA.[6-8] Low blood flow in the splanchnic and renal arteries in the presence of an hsPDA has also been described.[9] Major arteries supplying various organs (eg, anterior or middle cerebral artery, superior mesenteric artery, and renal artery) can be assessed using Doppler. Normally, antegrade organ blood flow is detected both in the systole and diastole. In an hsPDA, decreased flow can be seen in both the systole and diastole, or diastolic blood flow may be absent or even reversed. While low organ blood flows have been noted in hsPDA, the impact of an hsPDA on regional cerebral, splanchnic, and renal oxygenation as measured by near infrared spectroscopy has been variably reported.[10-14] This variability is likely in large part due to differences in the studied population including the PDA characteristics. Further work needs to be done to clarify the effects of an hsPDA on organ perfusion and oxygenation.

4 | POPULATIONS VULNERABLE TO hsPDA

In deciding which PDAs are hemodynamically significant, in addition to the PDA characteristics, vulnerability of the specific patient or population must be taken into account. Among the many risk factors that may contribute to the development of hsPDA, gestational age and chronological age are key contributors.

PDA occurs commonly in infants born less than 29 weeks of gestation, with an incidence of 40%-55%.[15] Premature infants have physiologic impairment of spontaneous closure due to poor intrinsic tone caused by a thin muscular layer in the ductus.[16] In addition, the balance of vasoconstrictors and dilators favors patency.[17,18]

Given the known impairment of spontaneous ductal closure in premature infants, it is important to know how often extremely preterm infants are able to close the ductus without medical or surgical treatment. Koch et al prospectively studied the natural course of the ductus in very preterm infants with birth weight < 1000 grams.[19] Only 42 (34%) of the 122 studied subjects experienced spontaneous ductal closure by day 10 of life. Additionally, they found that those more likely to close the ductus were on average 27 weeks, and those less likely to have spontaneous closure were on average 25.6 weeks. Therefore, the younger group is at a higher risk for persistent PDA. A larger retrospective study by Semberova et al described the natural course of PDA in very low birth weight infants using conservative management.[20] Eighty-five percent of infants experienced spontaneous closure prior to discharge. However, it is important to note that infants <26 weeks of gestation, which is the age group at the highest risk of complications of prematurity, took the longest to close the ductus, with a median of 71 days. Additionally, 33 infants were excluded from the study due to death during the study period. Etiology of death included infection, severe intraventricular hemorrhage, necrotizing enterocolitis, and pulmonary hemorrhage, and many of these infants had a documented presence of a PDA. Therefore, spontaneous closure rate is lower in extremely premature infants (<26 weeks) and even when the ductus does close without treatment, it takes many weeks. As these extremely preterm infants are at a greatest risk for complications of prematurity, one should have a lower threshold of treating ductus in this population.

Another factor in determining the significance of a PDA is chronological age. The potential consequences of an hsPDA on different organ systems depend somewhat on chronological age. Peri/intraventricular hemorrhage (PIVH) occurs most often in the first few days of life, at a time when the PDA shunt is potentially large. As mentioned earlier, cerebral blood flow is altered in the presence of

an hsPDA and this impairment in cerebral blood flow may play a role in the pathogenesis of PIVH.[21-23]

PDA is also implicated in the development of pulmonary hemorrhage, a life-threatening complication that can occur in preterm infants usually in the first few days of life. As pulmonary vascular resistance begins to fall after birth, the shunt volume across a significant PDA increases, which leads to increased pulmonary blood flow, pulmonary edema and congestion, and eventually pulmonary hemorrhage.[24] A placebo-controlled randomized trial by Kluckow et al demonstrated that preterm infants <29 weeks with a large PDA who received indomethacin versus placebo within 12 hours of birth had significantly less early pulmonary hemorrhage (2% vs 21%).[25]

While PIVH and pulmonary hemorrhage are life-threatening conditions associated with PDA that are usually faced within days after birth, there is also an association between PDA and the development of bronchopulmonary dysplasia (BPD) over time. The body may be able to compensate initially to this increase in pulmonary blood flow, but eventually pulmonary edema develops, leading to increased ventilatory support and supplemental oxygen, which are additional risk factors for BPD.[26] Although the pathogenesis of BPD is multifactorial, there is evidence that prolonged exposure to moderate-large PDA contributes to the development of BPD.[27-29]

Table 1 summarizes the major factors to be considered when designating a PDA as hemodynamically significant. While the most commonly used echocardiographic indices in the table are useful in defining an hsPDA, the clinical factors, the risk category based on gestational age, and the risk of a particular organ injury based on the chronological age need to be incorporated in this definition, especially when considering pharmacological or surgical treatment.

5 | PREDICTING THE OUTCOMES OF AN hsPDA

Several scoring systems combining risk factors, clinical findings, and echocardiographic measurements have been developed to help define and predict outcomes of an hsPDA. El-Khuffash et al described the use of troponin, B-type natriuretic peptide, and echocardiographic indicators at 48 hours of life in premature infants with a PDA in predicting death before discharge or neurodevelopmental outcomes at 2 years of age.[30] Seghal et al devised a scoring system of echocardiographic indices of PDA in which higher composite scores are associated with increased odds of developing chronic lung disease.[31] The scoring system created by Gursoy et al indicates that by 72 hours of life, clinical factors including the presence of a PDA can predict the development of BPD.[32] Although the echocardiographic and clinical parameters linking a PDA to complications of prematurity require further refinement, the above scoring systems highlight the fact that PDA is not a binary variable.

TABLE 1 Echocardiographic makers of a hemodynamically significant PDA and incorporation of gestational age- and chronological age-based risk factors for consideration of treatment

Echocardiographic indicators	Non-hsPDA	hsPDA
Ductal features		
Diameter (mm)	<1.5 (GA ≤ 26 wks)	≥1.5 (GA ≤ 26 wks)
	<2.0 (GA ≤ 30 wks)	≥2.0 (GA ≤ 30 wks)
	or	and
Shunt pattern	Closing, bidirectional	Growing, pulsatile
Degree of pulmonary overflow		
LA:Ao[a]	<1.4	≥1.4
LVO (mL/kg/min)[b]	≤300	>300
LPA EDV (cm/s)	≤20	>20
Magnitude of systemic hypoperfusion		
Descending aortic flow	Antegrade	Retrograde
Organ blood flow (MCA, RA, SMA, CA)	Normal (antegrade flow in systole and diastole)	Low antegrade flow in systole or diastole Absent/reversed diastolic flow
Clinical factors	**Increased likelihood of hsPDA**	
Cardiovascular	Vasopressors/ inotropes	
Respiratory	Ventilatory support + pulmonary edema	
Gastrointestinal	Feeding intolerance	
Renal	Rising creatinine or high level for age	
Risk—gestational age-based	**GA**	
High	≤25 wks	
Moderate	26-28 wks	
Low	>28 wks	
Risk—chronological age-based	**Disease**	
Day 1-2	PIVH	
Day 1-3	Pulmonary hemorrhage	
Day 1-14	BPD	
Day 1-?	Others	

Abbreviations: BPD, bronchopulmonary dysplasia; CA, celiac artery; GA, gestational age; LA:Ao, left atrium to aortic root ratio; LPA EDV, left pulmonary artery end-diastolic velocity; LVO, left ventricular output; MCA, middle cerebral artery; PIVH, peri/intraventricular hemorrhage; RA, renal artery; SMA, superior mesenteric artery.

[a]LA:Ao can be small if there is a significant left-to-right shunt at the patent foramen ovale level.

[b]In the presence of a large PDA with a left-to-right shunt, a low-normal (150-200 mL/kg/min) can be a sign of inadequate compensation and therefore inadequate systemic flow.

6 | CONCLUSION

The definition of an hsPDA continues to evolve. The hemodynamic significance of a PDA should be interpreted by considering the gestational and chronological age, and by assessing the vulnerability of organs at risk for overflow (the lungs), or hypoperfusion (eg, the brain, intestines, and kidneys). Assessment of multiple echocardiographic indices with organ blood flow Doppler is helpful in evaluating the hemodynamic significance of a PDA. Further work is needed to reach a consensus of how to define and manage an hsPDA.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Both Drs. Shepherd and Noori contributed to the first draft and the final version of the manuscript.

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How to cite this article: Shepherd JL, Noori S. What is a hemodynamically significant PDA in preterm infants?. *Congenital Heart Disease*. 2019;14:21–26. https://doi.org/10.1111/chd.12727