Received: 19 August 2018 | Accepted: 16 October 2018

DOI: 10.1111/chd.12702

SPECIAL ISSUE ARTICLE

WILEY Congenital Heart Disease

Effect of Patent Ductus Arteriosus on Pulmonary Vascular Disease

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Abstract

The hemodynamic effects of a patent ductus arteriosus (PDA) are well known including systemic hypoperfusion and volume overload on the left ventricle. This article aims to provide a review of the long-standing effect of a hemodynamically significant PDA on the pulmonary vasculature and the role of cardiac catheterization in preterm infants with a PDA and pulmonary hypertension.

KEYWORDS

congestive heart failure, neonatology, patent ductus arteriosus, pediatrics, preterm infant, pulmonary hypertension, pulmonary vascular resistance, surgical ligation of PDA, transcatheter closure of PDA

1 | INTRODUCTION

Patent ductus arteriosus (PDA) is a very common condition in preterm infants. By 7 days of age, the PDA remains open in around 65% preterm neonate's born between 25 and 28 weeks of gestation and 87% at 24 weeks of gestation.[1] Despite the high prevalence and multiple studies, there continues to be controversy on the management of the PDA and its long-term effects on morbidity and mortality in preterm infants.[2,3] Though there are disagreements on what is considered a hemodynamically significant PDA, from a physiologic standpoint the effects on the heart in terms of left atrial and ventricular dilation are well known. The systemic hypoperfusion effects (such as renal impairment and necrotizing enterocolitis) are also conceivable. However, what is often overlooked is the effects on the pulmonary vasculature from a high-pressure large volume shunt in a long-standing PDA. The confounding factor in preterm infants is the comorbidity of bronchopulmonary dysplasia (BPD). Pulmonary vascular disease in these cohorts of patients is a significant factor during decision making for closure of the PDA. More so, management of pulmonary hypertension in the presence of a large PDA is challenging. The main objective of this review is to remind readers of the pulmonary vascular changes associated with an untreated large PDA in a preterm infant and the role of diagnostic cardiac catheterization which may assist in decision making for PDA closure.

2 | PHYSIOLOGY

2.1 | Effect of a large PDA on pulmonary vasculature

The pulmonary vascular resistance (PVR) normally drops after birth with breathing due to lung expansion and an increase in PO_2. In addition, the systemic vascular resistance (SVR) increases with removal of the placenta and leads to an increase in pulmonary blood flow. The pulmonary arterial pressure (PAP) falls normally and the medial layer of smooth muscle becomes thin.[4] If the ductus arteriosus is widely patent, the PAP does not fall as rapidly and remains elevated. With large PDAs, there may be systemic pressures due to equalization across a large defect. The diastolic pressures in the aorta and the pulmonary artery may be similar as well. The pulmonary arterioles do not mature or thin normally and the persistence of the smooth muscle in the media delays the drop in PVR over the first 3-4 months. The PVR does not reach normal levels but falls enough to permit excess pulmonary blood flow. As the PVR decreases the

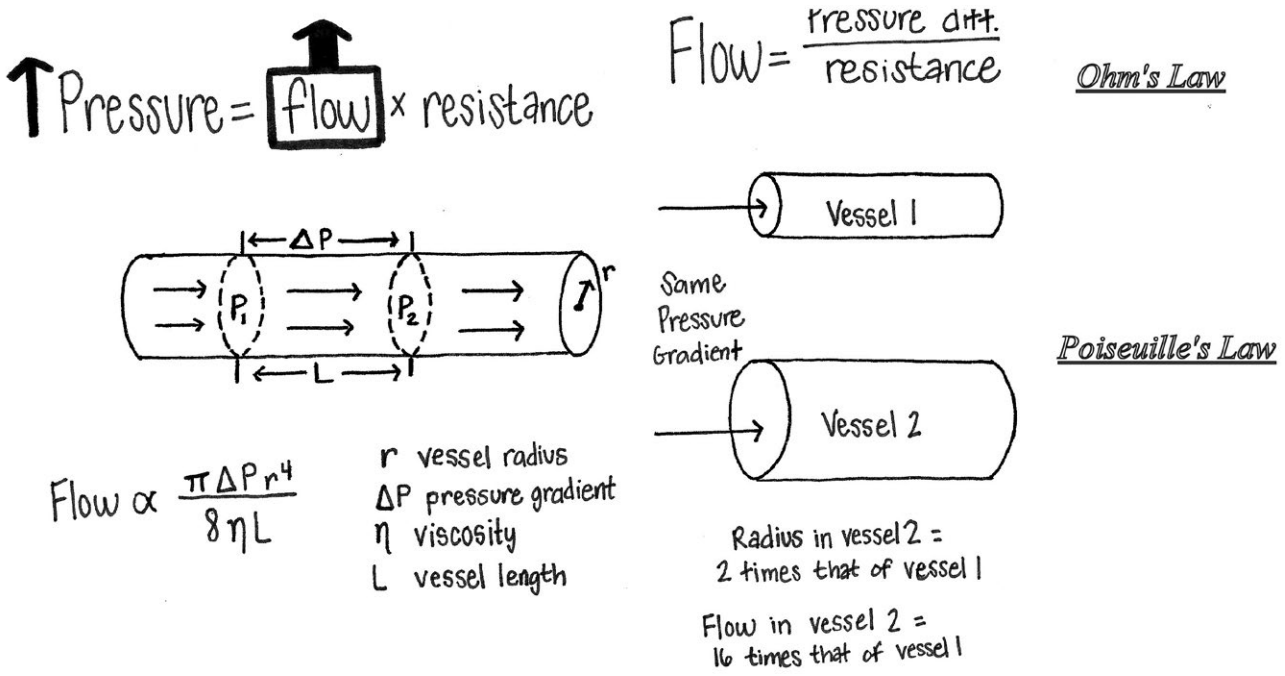

FIGURE 1 Ohm's Law (above) showing the relationship between pressure, flow, and resistance through a vascular bed. Poiseuille's Law (below) showing the impact of change in radius of the vessel

pulmonary blood flow continues to increase but the PAP remains high at systemic levels due to the large size of the PDA. This concept of high-pressure, high-flow shunting is important to understand and one must clarify the distinction between elevated PAP and high PVR. The relationship between resistance and flow is well understood by the modified Ohm's law which describes the pressure in a vascular bed as the product of the resistance and blood flow. Therefore, an elevated pressure as seen in a large PDA with equalization of pressures, more often implies a high flow large shunt as opposed to an increased resistance. In fact, an increase in the resistance through the vascular bed will result in a decrease in blood flow (Figure 1).

During early infancy as mentioned above, the predominant changes are in the media muscle layer of the pulmonary arterioles which further progresses to the peripheral arterioles. If a large PDA persists beyond a year, intimal thickening develops which can progress to fibrosis by 2-3 years of age.[4] This increases the PVR by encroaching the lumen of the vessel and decreasing the pulmonary arteriolar compliance. This reduces pulmonary blood flow and left-to-right shunting and can show temporal improvement in symptoms of heart failure. Eventually, when the pulmonary vascular changes become severe to raise the PVR to systemic levels, right-to-left shunting develops. Irreversible pulmonary vascular changes may develop in at least 50% of patients with a large PDA without intervention by 2 years of age.[5] Even when reversible, changes in PVR take time to normalize after PDA closure.[4]

2.2 | Effects of prematurity

The preterm ductus arteriosus is very similar in morphology to the fetal ductus in that it is often tortuous and distinctively long and wide in relation to the diameter of the descending aorta.[6] There are three important considerations in preterm infants when understanding their effect and response to left-to-right shunts. The first is that premature infants with a large PDA often develop cardiac failure earlier (2-3 weeks of age) than term infants (3-6 weeks).[4] This is possibly due to the less developed response of their pulmonary vasculature to hypoxia and vasodilators. Their pulmonary arteries have a smaller amount of muscular tissue in the media with lower intrinsic tone. Therefore, they are unable to constrict appropriately and consequently develop pulmonary over-circulation faster. Secondly, they have a lower level of tolerance to left–to-right shunts as is seen in preterm infants with respiratory distress syndrome. The possible explanation for this is that in respiratory distress syndrome there is differential perfusion (ie, due to less pulmonary blood flow to poorly aerated segments, the other areas of the lungs have greater perfusion). If there is increased pulmonary blood flow due to a shunt, the perfused lung segments will have further increases in blood flow leading to pulmonary edema from transmission of arterial pressure through poorly reactive precapillary vessels. The increased pulmonary blood flow over a period of time will delay normal pulmonary vascular maturation with consequent smooth muscle retention and development of pulmonary vascular disease. The risk of BPD in preterm infants with a large PDA is thought to be higher.[4] The theoretic explanation for this is that a large PDA will have equalization of aortopulmonary pressures leading to increased pulmonary venous and left atrial pressures. Due to more permeable pulmonary capillaries in preterm infants, plasma proteins leak into air sacs and can affect surfactant function leading to reduced lung compliance. To achieve adequate oxygenation in these non-compliant lungs, mean airway pressures need to be raised which will lead to lung damage and possible BPD.[4]

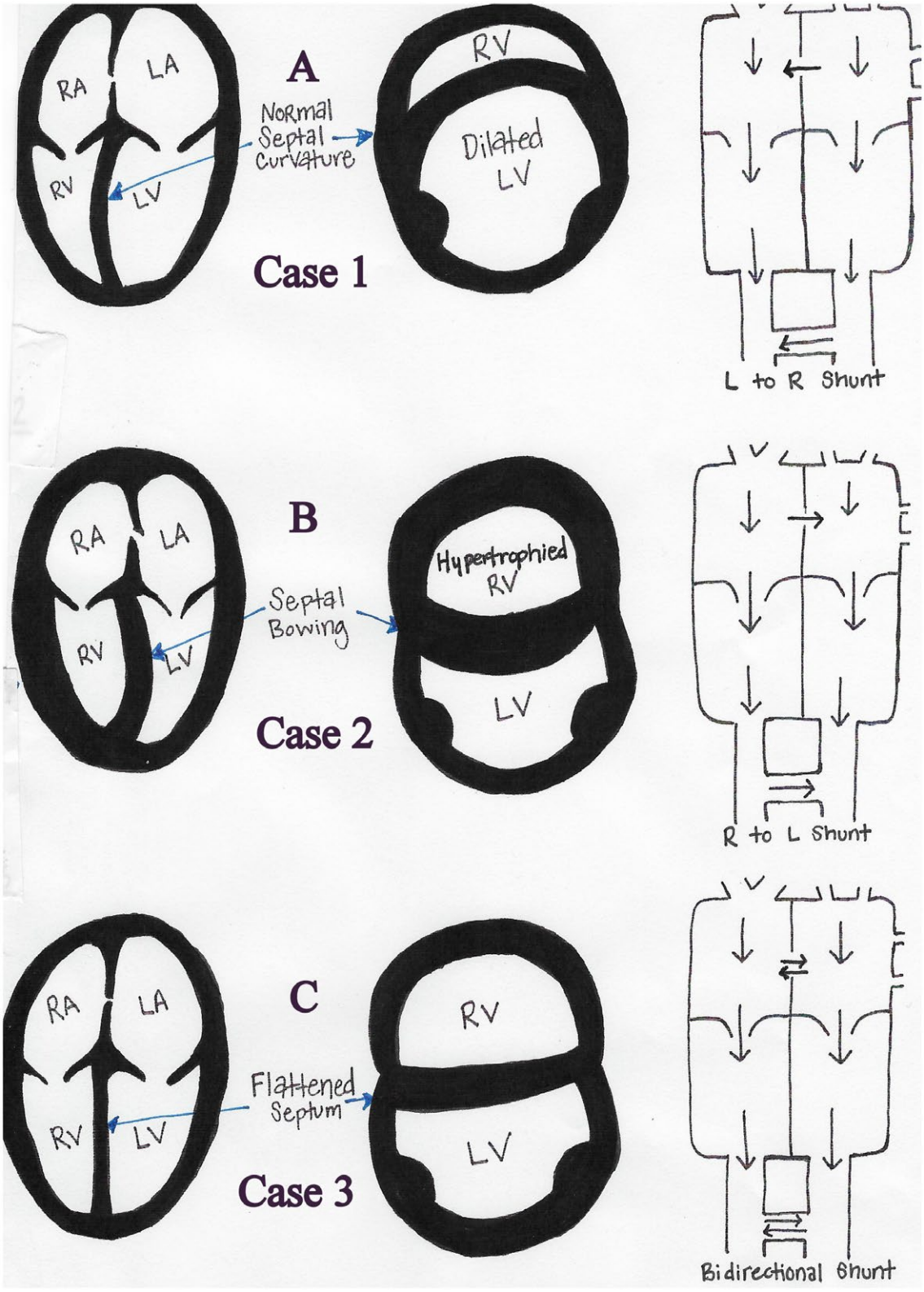

FIGURE 2 Apical 4-chamber and short-axis representation of the heart showing changes in septal curvature, wall thickness, and size in relation to pressure and volume overload in the three different case scenarios described. The companion line diagram shows direction of blood flow in each case

2.3 | Respiratory distress syndrome

Due to the alveolar hypoxia, certain parts of the lungs may have more pulmonary vasoconstriction and hence delay the fall in PVR. This will decrease the effective left-to-right shunting at the PDA. This is evidenced from the fact that with surfactant treatment in preterm infants there is enhancement of left-to-right shunting through the ductus.[7]

2.4 | Bronchopulmonary dysplasia

The pathogenesis of BPD is multifactorial but it is shown that there is destruction of angiogenic factor expression[8] which leads to earlier disruption of angiogenesis in developing lungs and impairs alveolarization.[9] Pulmonary hypertension has been associated with established BPD with reported early development[10] and this may confound the effect of a persistent large PDA in preterm infants. More importantly, the diagnosis of severe pulmonary hypertension in preterm infants with BPD is associated with increased mortality of 47% at 2 years of age[11] which should alert clinicians to early echocardiographic screening of this cohort and possibly a tailored approach to evaluation and management of a persistent PDA.

3 | CASE SCENARIOS

3.1 | Case 1

A 1-month-old 24-week preterm with left atrial and ventricular dilation on mechanical ventilation (Figure 2A).

A large left-to-right shunt from this PDA leads to increased pulmonary blood flow and consequent left atrial and ventricular dilation. This is the most common clinical scenario seen in preterm infants with a persistent large PDA. At this stage, it is safe to close the PDA from a hemodynamic standpoint as the PVR is not significantly elevated. There may be flow related pressure elevation in the pulmonary artery due to the large shunt with equalization of pressures but only mildly elevated PVR.

3.2 | Case 2

A 6-month-old 24-week preterm large PDA with severe pulmonary hypertension and right-to-left shunting (Figure 2B).

This is not very commonly seen. As shown in the figure, there is severe right ventricular hypertrophy and dilation with bowing of the interventricular septum in systole into the left ventricle due to supra-systemic right ventricular pressures. At this stage, the PDA serves as a pop-off to relieve right ventricular pressure and preserve its function. It also helps sustain cardiac output at the cost of desaturation when the pulmonary pressures are critically elevated. Closure of the PDA in this circumstance is dangerous and not recommended. Pulmonary vasodilators may be used to potentially help with reverse remodeling in the pulmonary artery vascular bed. This may help decrease the PVR in comparison to the SVR and provide a window of opportunity in the future for closure of the ductus.

3.3 | Case 3

A 4-month-old 25-week preterm with BPD, moderate-to-severe pulmonary hypertension and a large PDA (Figure 2C).

This case albeit not as common as case 1, is a clinical conundrum. Pulmonary hypertension in the presence of a large left-to-right shunt is challenging to manage. Treatment strategies in this group of patients are not always straightforward. The use of supplemental oxygen to manage BPD and pulmonary hypertension may have opposing effects on pulmonary blood flow when there is a large PDA. On one hand, the pulmonary vasodilator effect may potentially increase pulmonary blood flow and left-to-right shunting thus promoting further vascular damage. The opposing vasoconstrictor effect of oxygen on the PDA itself may be minimal in preterm infants as previously mentioned. Treating with pulmonary vasodilator therapy to encourage reversal of vascular remodeling may also promote more left-to-right shunting. On the other hand, the concerns with closing the PDA are with risks of a pulmonary hypertensive crisis and right ventricular failure from increasing right ventricular afterload. In these situations, medical therapy or surgical ligation for closure of the PDA may not be ideal without a clear understanding of the hemodynamics. Echocardiography though useful in providing insight into the hemodynamics, may be misleading in terms of the pressure estimates and the PVR for which a diagnostic cardiac catheterization is warranted.

4 | ROLE OF CARDIAC CATHETERIZATION

Cardiac catheterization provides the opportunity for meticulous hemodynamic assessment as well as a therapeutic option for transcatheter closure of the PDA. It has the added advantage over medical and surgical therapy in its ability to test the hemodynamic effects of temporary occlusion of the PDA, ie, "test occlusion." It also has the benefit of being able to assess other causes of pulmonary hypertension such as pulmonary vein stenosis which is occasionally seen in BPD and is not well delineated by echocardiography. Patient selection for cardiac catheterization hemodynamic assessment should be based on the preprocedure clinical and echocardiographic concerns for elevated PVR. The working group for the pediatric pulmonary hypertension network has outlined a cardiac catheterization protocol for BPD infants.[12] Initial hemodynamics and calculations of indexed PVR, SVR, PVR/SVR, and Qp:Qs (ratio of pulmonary to systemic blood flow) are performed under baseline conditions. These are then repeated with 100% oxygen, 100% oxygen + inhaled nitric oxide (iNO) (40 ppm) to test for reactivity and then baseline hemodynamics again.

Test occlusion of the PDA during cardiac catheterization can be done either by balloon occlusion or with the device that is anticipated to be used to close the PDA. Hemodynamic changes that would indicate safe closure of the PDA are a 20% drop in the basal PAP and no change in the systemic pressure suggesting that the PDA is not required for augmenting or sustaining cardiac output.[13] If the hemodynamics are favorable showing reversibility with 100% oxygen and iNO, closure of the PDA will enable aggressive use of pulmonary vasodilator

therapy. This will decrease right ventricular afterload to preserve right ventricular systolic function and potentially help with pulmonary vascular remodeling. One must be cautioned that a small percentage of patients with a marginal drop in PAP and a mild drop in cardiac output can deteriorate after PDA closure due to non-regression of pulmonary hypertension and progression of right ventricular failure.[14] Thus, the interventional cardiologist must have a low threshold to abort device closure of the PDA if the hemodynamics with test occlusion are not ideal or if there are any signs that the PDA is significantly contributing to sustain cardiac output. One must also be aware that there are limitations in the calculation of PVR and cardiac output due to differential pulmonary blood flow from the PDA and the estimation of oxygen consumption in these infants. In addition, in this tenuous group of infants with elevated PVR, the use of iNO/100% oxygen or IV sildenafil may be beneficial in the perioperative period prior to initiation or continuation of long-term pulmonary vasodilator therapy.

From our preliminary institutional experience with transcatheter PDA closure and hemodynamic testing in preterm infants (<1 kg at birth and born less than 27 weeks of gestation) with a large PDA, it appears that those that underwent PDA closure early (<4 weeks of age, n = 27) had a higher Qp:Qs (median 2.5) and a lower indexed PVR (1.6 WUm^2) in comparison to those that underwent PDA closure after 8 weeks of age (n = 25, median Qp:Qs of 1.8, median indexed PVR of 3.3WUm^2). Though these data are retrosp ective, there may be benefit in closing a large PDA in the first 4 weeks of life prior to the onset of elevated PVR in extremely low birth weight infants.

5 | CONCLUSIONS

A large PDA causes a delay in the normal physiologic drop in the PVR. Prematurity and BPD further confound the effect of the PDA. Pulmonary hypertension is a late hemodynamic consequence of a large PDA. The management of PH in the presence of a large PDA is challenging. Cardiac catheterization is a diagnostic and therapeutic armament for patient selection for safe ductal closure. By eliminating the left-to-right shunt, it may also offer the opportunity for aggressive pulmonary vasodilator therapy for vascular remodeling in infants with elevated PVR. Early closure within the first 4 weeks of life prior to the onset of significantly elevated PVR, may be of benefit.

DISCLOSURES OF GRANTS OR OTHER FUNDING

None.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

All listed authors fulfilled authorship criteria: (1) substantial contributions to research design, or the acquisition, analysis, or interpretation of data; (2) drafting the paper or revising it critically; and (3) approval of the submitted and final versions.

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REFERENCES

1. Hamrick SE, Hansmann G. Patent ductus arteriosus of the preterm infant. *Pediatrics*. 2010;125(5):1020-1030.
2. Clyman RI, Couto J, Murphy GM. Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all? *Semin Perinatol*. 2012;36(2):123-129.
3. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? *J Perinatol*. 2010;30(4):241-252.
4. Rudolph AM. *Congenital Diseases of the Heart: Clinical-Physiologic Considerations*. 3rd ed. San Francisco: Wiley-Blackwell; 2009.
5. Rosenzweig EB, Barst RJ. Congenital heart disease and pulmonary hypertension: pharmacology and feasibility of late surgery. *Prog Cardiovasc Dis*. 2012;55(2):128-133.
6. Philip R, Waller BR 3rd, Agrawal V, et al. Morphologic characterization of the patent ductus arteriosus in the premature infant and the choice of transcatheter occlusion device. *Catheter Cardiovasc Interv*. 2016;87(2):310-317.
7. Shimada S, Kasai T, Konishi M, Fujiwara T. Effects of patent ductus arteriosus on left ventricular output and organ blood flows in preterm infants with respiratory distress syndrome treated with surfactant. *J Pediatr*. 1994;125(2):270-277.
8. Bhatt AJ, Pryhuber GS, Huyck H, Watkins RH, Metlay LA, Maniscalco WM. Disrupted pulmonary vasculature and decreased vascular endothelial growth factor, Flt-1, and TIE-2 in human infants dying with bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001;164(10 Pt 1):1971-1980.
9. Stenmark KR, Abman SH. Lung vascular development: implications for the pathogenesis of bronchopulmonary dysplasia. *Annu Rev Physiol*. 2005;67:623-661.
10. Mourani PM, Sontag MK, Younoszai A, et al. Early pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2015;191(1):87-95.
11. Khemani E, McElhinney DB, Rhein L, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. *Pediatrics*. 2007;120(6):1260-1269.
12. Krishnan U, Feinstein JA, Adatia I, et al. Evaluation and management of pulmonary hypertension in children with bronchopulmonary dysplasia. *J Pediatr*. 2017;188(24-34):e1.
13. Niu MC, Mallory GB, Justino H, Ruiz FE, Petit CJ. Treatment of severe pulmonary hypertension in the setting of the large patent ductus arteriosus. *Pediatrics*. 2013;131(5):e1643-e1649.
14. Feng J, Kong X, Sheng Y, Yang R. Patent ductus arteriosus with persistent pulmonary artery hypertension after transcatheter closure. *Ther Clin Risk Manag*. 2016;3(12):1609-1613.

How to cite this article: Philip R, Nathaniel Johnson J, Naik R, et al. Effect of patent ductus arteriosus on pulmonary vascular disease. *Congenital Heart Disease*. 2019;14:37–41. https://doi.org/10.1111/chd.12702