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# Hemodynamically significant patent ductus arteriosus and the development of bronchopulmonary dysplasia

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## Abstract

Patent ductus arteriosus (PDA) is prevalent in premature newborns and has been linked to the development of bronchopulmonary dysplasia (BPD), a serious pulmonary complication of premature birth. Although a causal relationship has not been proven, the link is greatest among infants born at lower gestational age who are treated with mechanical ventilation in the presence of a large ductal shunt. Despite strong association in epidemiological studies, treatment of a patent ductus arteriosus has not been shown to prevent BPD, and some therapies may increase the risk of BPD. We describe preclinical and clinical data demonstrating the association of a PDA with BPD, highlight the effects of surgical and pharmacological treatment, and explore the implications of recent clinical trials for the management of PDA in the premature newborn.

**KEYWORDS**
bronchopulmonary dysplasia, neonatal, patent ductus arteriosus

## 1 | INTRODUCTION

Patent ductus arteriosus (PDA) has a high prevalence in extremely low birthweight preterm infants. Epidemiological studies have linked the presence of PDA to the development of bronchopulmonary dysplasia (BPD). However, controversies in the identification of hemodynamically significant PDA (hsPDA), imprecision in the diagnosis of BPD, and heterogeneity in clinical trial design have created confusion in the literature regarding the effects of hsPDA treatment on the development of BPD. Preclinical data suggest an hsPDA alters the pulmonary fluid filtration rate in the preterm newborn leading to pulmonary edema. Reactive inflammation and changes in pulmonary vasculature maturation may further contribute to the development of BPD. Despite epidemiological studies linking the presence of hsPDA to BPD development and preclinical data demonstrating biological plausibility, evidence suggesting a clear causal role of an hsPDA is limited. Drawing a true causal relationship would allow randomized clinical trials to test clinical interventions designed to prevent BPD. In this review, we will describe evidence linking the presence of an hsPDA to the development of BPD and explore the implications of recent clinical trials for management of hsPDA in preterm infants.

## 2 | HEMODYNAMICALLY SIGNIFICANT PDA AND BPD

The development of BPD in premature infants is a multifactorial process that involves both prenatal and postnatal exposures. Changes leading to BPD begin in utero and are affected by antenatal steroids, gestational age, birthweight, gender, maternal inflammation, and maternal BMI.[1-3] BPD develops over the infant's first several weeks, influenced by mechanical ventilation, excessive oxygen exposure, postnatal infections, nutrition and growth, and certain medications.[2,4] These factors and others, share the common connection of propagation of pulmonary inflammation in the fetus and newborn.

The pulmonary tissue of the human fetus during the canalicular stage of lung development (17-27 weeks' gestation) has limited respiratory units capable of gas exchange and surfactant production. While more mature premature infants born at 28 weeks and beyond have a relatively low risk of developing BPD, infants born during the canalicular stage are often treated with mechanical ventilation and are at high risk of developing BPD. Infants born at 22-25 weeks have a greater than 50% risk of BPD, and infants born at 26-27 weeks still have greater than 30% chance of developing BPD.[5]

  

The PDA has also long been recognized as a risk factor for developing BPD, especially among those infants on mechanical ventilation beyond 48 hours.[6,7] Infants born during the canalicular stage of lung development, in addition to having an increased risk of developing BPD, are also at high risk for prolonged PDA. Spontaneous closure of the PDA occurs at a median of 13 days in infants born in the 26th and 27th weeks and a median of 71 days in infants born prior to 26 weeks.[8] Therefore, an hsPDA is often most present during the time when a premature infant is also most susceptible to lung injury leading to BPD. However, despite this temporal overlap, it remains unclear if the PDA is a true causative risk factor for BPD or simply a marker of clinical illness associated with the development of BPD.

A causative relationship between the PDA and the development of BPD is suggested by evidence that shows there is a dose-dependent correlation between ductal flow and BPD risk. El-Khuffash et al[9] derived a PDA score based on echocardiography measurements at 48 hours after birth. Variables include gestational age, PDA size, left ventricular output (a marker of increased pulmonary flow), PDA shunt velocity, and left ventricular a waves. A score of 5 or greater had a 92% positive predictive value and an 82% negative predictive value for BPD or death in a cohort of 141 infants born prior to 29 weeks' gestation. These data also show the association between PDA and BPD strengthens with both decreasing gestational age and increasing ductal flow.

The duration of PDA exposure may also play a role in BPD risk. Schena et al[10] followed the PDA in a group of 242 infants born prior to 29 weeks' gestation. The PDA was assessed using staging system proposed by McNamara and Sehgal[11]; this includes ductal size, flow pattern, left atrium-to-aorta ratio, end-diastolic flow pattern in the superior mesenteric artery, and filling pressure of the left ventricle. It is estimated that BPD risk increases by 70% for each additional week of exposure to an hsPDA.[10]

The canalicular stage of lung development is also remarkable for a relatively underdeveloped pulmonary vascular bed. The low cross-sectional area of the vascular system in the fetal lungs helps to maintain high pulmonary vascular resistance and limits blood flow through the lungs to approximately 25% of right ventricular output at 20 weeks postmenstrual age, increasing to 44% by 30 weeks.[12] As the fetus is born, pulmonary vascular resistance begins to drop; this allows the ductus to transition from a right-to-left shunt to a left-to-right shunt. Under these conditions, pulmonary blood flow is greater than right ventricular output, and blood return to the left side of the heart is increased. If pulmonary blood flow exceeds the capacity of the left ventricle, hydrostatic pressure increases in the pulmonary capillary bed, pushing fluid from the vascular space to the interstitial space, and contributing to pulmonary edema.

In the first few days after birth, the neonate may be protected against pulmonary edema by increased lymph flow that quickly clears excess fluid from the lungs.[13] However, if ductal flow increases or lymph drainage is impaired, the capacity of the lymph channels to clear interstitial fluid may be exceeded causing fluid to remain within the interstitial space. Interstitial edema separates the alveolar surface from the surrounding capillary bed, limiting gas exchange by increasing the distance over which gas molecules must diffuse (Figure 1). Ineffective gas exchange results in ventilation perfusion mismatch and hypoxemia, recognized at the bedside as a decline in oxygen saturation. The immediate response is to increase delivery of inspired oxygen, a strategy that may correct hypoxemia in the short term, but leads to the development of simplified alveoli, a hallmark of BPD.[14] The effect of increased oxygen exposure is illustrated in a mouse model (Figure 2), demonstrating that alveolar simplification increases with prolonged exposure to higher concentrations of oxygen.

To decrease oxygen exposure, the provider may choose to increase alveolar distending pressure (Figure 1D). This strategy can improve gas exchange, but often requires mechanical ventilation, which has also been shown in animal models to induce apoptosis of alveolar cells and leads to impaired angiogenesis within the lung.[15,16] Furthermore, mechanical ventilation induces an inflammatory cascade in the neonatal lung leading to increased microvascular permeability and increased lung fluid.[17] Such inflammation, coupled with developing fibrosis that impairs lymph drainage, compounds the problem of excessive pulmonary flow and overwhelms the neonate's ability to clear lung fluid. This process can cause PDA-related pulmonary edema several days after birth in a patient who had previously tolerated the left-to-right PDA shunt.

Over time, exposure to excessive pulmonary blood flow alters the development of pulmonary vasculature. A paucity of pulmonary vessels is a pathological feature of BPD.[18] In a preclinical rat model, persistent exposure to elevated blood flow led to an increase in pulmonary vascular resistance and alterations in alveolar structure characteristic of BPD.[19] Similar changes occur in preterm infants with pulmonary hypertension, systemic to pulmonary vascular connections, and pulmonary vein stenosis, all of which may also be related to increased vascular resistance and pulmonary overcirculation.[20]

Strategies to avoid mechanical ventilation in premature infants, especially in the first week after birth, have been shown to reduce the incidence of BPD.[21,22] These strategies, however, seem to have no effect on the diagnosis of PDA. In a trial comparing early synchronized nasal intermittent positive pressure ventilation with mechanical ventilation in infants born prior to 32 weeks, Bhandari et al[23] report a significant reduction in BPD or death (52% vs 20%, $P = .03$) despite finding no difference in rates of PDA. Similarly, Ramanathan et al[24] report a reduction in BPD in infants randomized to noninvasive ventilation vs nasal CPAP (21% vs 39%, $P = .04$), possibly due to decreased need for invasive mechanical ventilation at 7 days after birth in the noninvasive ventilation group. In this study, there was no difference in PDA diagnosis or ligation between the groups. Therefore, it is likely not the simple presence of PDA that increases the risk of BPD. Instead, it is the presence of a hemodynamically significant shunt in combination with injury induced by mechanical ventilation and oxygen toxicity that overwhelms pulmonary lymph drainage and leads to a worsening cycle of edema and reactive escalation in respiratory support that eventually leads to BPD.

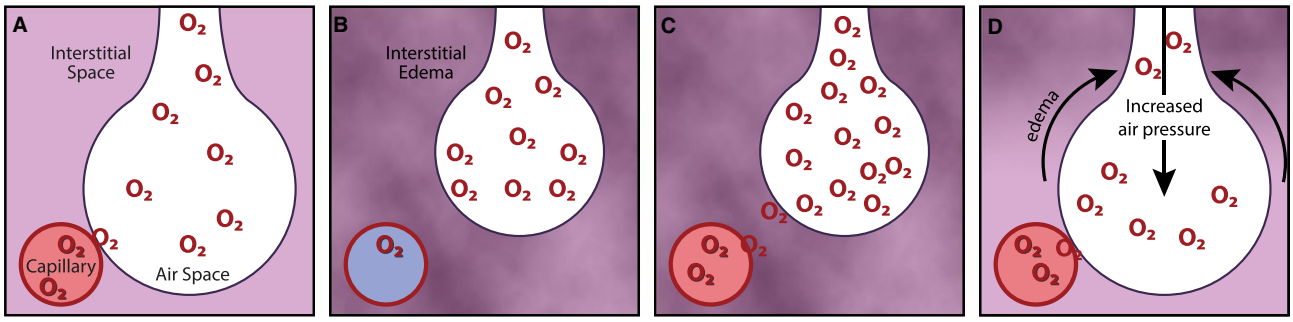


**FIGURE 1** Pulmonary interstitial edema impairs gas exchange. (A) Normal alveolar distension with oxygen transfer from the air space into the capillary. (B) Interstitial edema compresses the alveolus and separates the air space from the capillary, increasing the distance over which oxygen must diffuse. (C) Increased $FiO_2$ increases the oxygen gradient between the air space and the capillary bed, improving oxygenation. (D) Increased pressure within the air space distends the alveolus, pushes interstitial edema away from the alveolar-capillary interface, and allows for more efficient oxygen diffusion

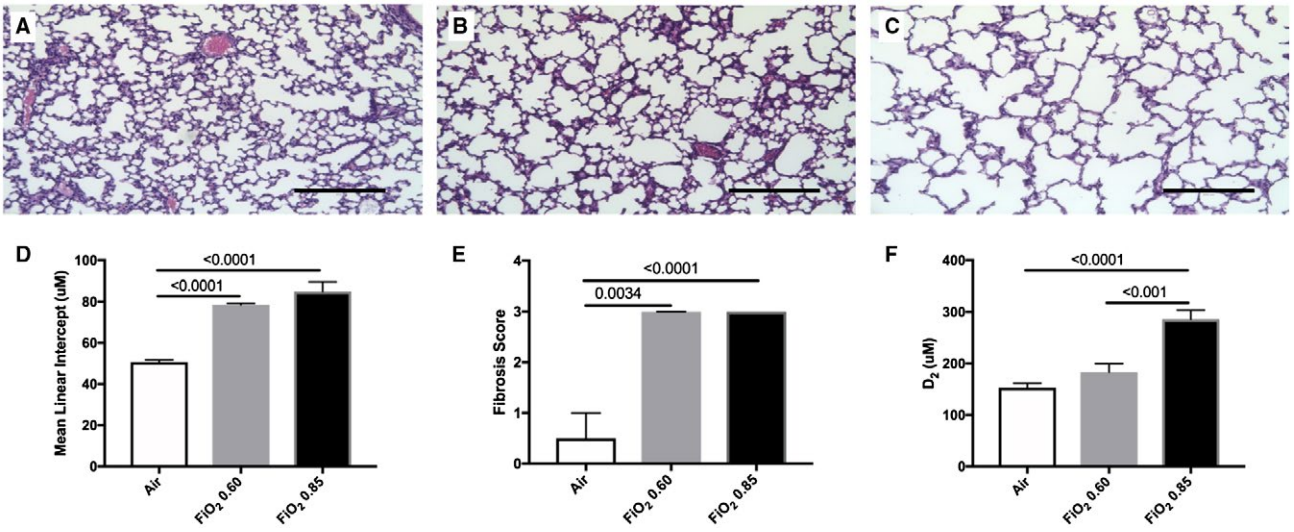


**FIGURE 2** Alveolarization in 15-day-old mouse lungs. Representative hematoxylin and eosin stained micrographs of newborn mouse lungs after exposure to either 15 days of air: (A) $FiO_2$ 0.21 or hyperoxia: (B) $FiO_2$ 0.60 (C) $FiO_2$ 0.85, demonstrating persistent alterations in lung architecture. Hyperoxia exposure during the saccular stage of lung development arrests alveolarization and leads to a heterogeneous, simplified pulmonary architecture as exemplified by significant changes in (D) the alveolar surface area to volume ratio (mean linear intercept), (E) presence of pulmonary fibrosis (fibrosis score), and (F) heterogeneity of airway area ($D_2$). Scale bar represents 200 µm. Continuous variables are expressed as mean ± standard error of the mean and analyzed by ANOVA, and categorical variables are presented as median ± interquartile range and analyzed by Kruskal-Wallis. Significance level set at $P < .05$

Inconsistency in the diagnosis of hsPDA may obscure the link between a PDA and BPD development. As previously described, the volume of PDA flow is a key factor in determining BPD risk.[9,10] Assessing PDA flow by echocardiogram, however, is labor-intensive and requires significant skill. Identification of a marker that is both sensitive and specific for hsPDA and less difficult to acquire than echocardiography may solidify the causality between the presence of a PDA and later BPD development. One such marker may be N-terminal probrain natriuretic peptide (NT-proBNP), which is emerging in clinical use for the diagnosis of hsPDA. A recent meta-analysis found NT-proBNP to be a more sensitive, but less specific marker for hsPDA than brain natriuretic peptide, a similar marker of atrial dilatation that has been used as a biomarker for cardiac dysfunction due to PDA.[25] NT-proBNP has been shown to have good correlation with flow patterns on echocardiography that are associated with hemodynamic significance of the PDA.[26] Recent work by Rodríguez-Blanco et al[27] suggests that for the prediction of BPD, NT-proBNP may be a superior measure of an hsPDA than echocardiography because increased NT-proBNP levels more accurately predicted the development of BPD than did the detection of an hsPDA by echocardiography alone. This relationship may explain earlier work suggesting NT-proBNP is an independent biomarker of BPD development.[28] Future trials using NT-proBNP to target early hsPDA treatment in neonates on mechanical ventilation may be able to show a reduction in BPD among infants at highest risk.

## 3 | PDA TREATMENT EFFECTS ON BPD OUTCOMES

In a preterm baboon model, early pharmacotherapy has been shown to prevent the changes of BPD. Baboons that underwent pharmacologic closure of the PDA at 3 days of life with ibuprofen were protected against deleterious changes in alveolar architecture that occurred in animals where the PDA remained open. Treated animals had improvements in the pulmonary ventilation index and did not develop alveolar arrest on histopathology at 14 days. While surfactant protein levels, expression of RNA regulating inflammatory and remodeling genes, and tracheobronchial cytokines were similar between the two groups, the lungs of treated animals were significantly drier and produced 2.5-fold more epithelial sodium channel proteins.[29]

It is still not clear, however, that interventions to close the PDA reduce the risk of BPD in humans. Multiple studies have shown the development of BPD is unchanged regardless of the PDA treatment strategy. Chock et al[30] compared 209 VLBW infants treated in a single center with historically different PDA management strategies. In the conservative management group, they found a reduction in any PDA treatment and a delay in surgical ligation without a significant rise in the rate of BPD.

Two large observational trials in North America show similar results. Lokku et al[31] report on the Canadian experience among 5824 infants born prior to 33 weeks in Canada between 2006 and 2012; conservative management of the PDA increased over time, while the rate of BPD decreased. In the United States, Bixler et al[32] report on 61 520 infants born prior to 30 weeks. They compared years 2006-2010 with 2011-2015 and show the diagnosis of PDA decreased, medical treatment for PDA decreased, and PDA ligation decreased, while the rate of BPD remained unchanged.

In pooled analysis of 30 RCTs conducted between 1980 and 2016, rates of BPD were not affected by pharmacotherapy for PDA treatment. These findings remain even when limiting analysis to those trials enrolling infants less than 29 weeks or those beginning treatment prior to 5 days.[33]

Observational studies and meta-analyses such as those described above may be criticized for having variable clinical practices and nonspecific definitions for both PDA and BPD; limitations that can only be overcome with well-designed randomized trials. Kluckow et al[34] randomized 92 infants born prior to 29 weeks to receive indomethacin or placebo for early treatment of large PDA (>1.3-1.8 mm depending on postnatal age). Secondary analysis showed there was no statistical difference in BPD rate between groups. However, the primary outcome was combined death and/or abnormal cranial ultrasound. This study was not powered to detect differences in BPD, and 40% of the placebo group received early pharmacotherapy at a median of 5 days. At the time of this writing, results of the PDA-TOLERATE trial have been published only in abstract form. Two hundred two neonates born prior to 28 weeks were randomized to receive either pharmacotherapy or conservative therapy for PDA. Randomization occurred one week after birth, and there was no difference in BPD between groups.[35,36]

On the other hand, a reduction in BPD may be found with aggressive PDA closure in the first few days of life. In a cohort study, Liebowitz and Clyman evaluated 397 infants born prior to 28 weeks. Group 1 received prophylactic indomethacin within 15 hours of birth followed by continuation of therapy if the ductus remained patient based on echocardiography. In Group 2, PDA treatment was based on echo findings and clinical status, but no infant was treated prior to 7 days of age. As expected, PDA was more likely to be permanently constricted in the indomethacin group (77% vs 29%, $P < .05$). This was associated with a significant decrease in BPD (RR 0.68, 95% CI 0.46-0.89) and combined BPD or death (RR 0.78, 95% CI 0.62-0.95) among infants treated with prophylactic indomethacin. However, among those infants who still had a moderate-to-large PDA at 7 days, there was no difference in BPD outcomes between groups.[37] These data suggest that closure of a moderate-to-large PDA may reduce the risk of BPD, but only if it is successfully closed within the first week, generally before the onset of clinical signs.

One proposed explanation for the lack of benefit from PDA treatment is that commonly available therapies for PDA may independently increase the risk of BPD, obscuring benefits achieved from reducing PDA exposure. An early small study randomized infants born less than 1500 g to receive three doses of indomethacin or placebo beginning 12 hours after birth and showed the indomethacin group had a reduction in PDA but required longer respiratory support.[38] A possible explanation for this can be found in secondary analysis of the Trial of Indomethacin Prophylaxis in Preterms (TIPP). In this study, prophylactic indomethacin successfully reduced the incidence of PDA among extremely low birthweight infants. However, infants in the indomethacin group had higher oxygen exposure over the first week and lower urine output over the first three days.[39] Prostaglandin E2 (PGE2) plays a major role in regulating urine output by binding to prostaglandin receptors within the nephron; and COX-2 inhibitors such as indomethacin and ibuprofen reduce urine output by blocking PGE2 production.[40,41] Lower urine output associated with indomethacin treatment in the TIPP trial may have increased intravascular volume and worsened pulmonary congestion. The increased need for oxygen seems to be independent of fluid balance, and while the effect has also been reported by other studies, the mechanism remains unclear.[39]

Surgical ligation of the PDA also may increase the risk of developing BPD. As noted in preterm baboon models, animals that underwent surgical ligation at 6 and 7 days after birth had none of the beneficial biochemical changes associated with pharmacological treatment. There were no significant differences in pulmonary mechanics or histology after 14 days. However, they noted a significant increase in expression of *COX-2*, *TNF-α*, and *CD14*, genes involved with pulmonary inflammation, as well as a decrease in sodium channel expression.[42,43] These findings support the hypothesis that inflammation resulting from surgical ligation is responsible for blunting the clearance of pulmonary fluid and obscuring any benefit from closure of the PDA.

Human data also suggest increased inflammation related to surgical ligation may increase the risk for adverse pulmonary outcomes.

In a large population-based Finish trial, both medical and surgical treatments were associated with the development of severe BPD.[44] Surgical ligation was also associated an increased risk of necrotizing enterocolitis and intraventricular hemorrhage—both diagnoses associated with increased inflammation. These morbidities are increased despite surgical ligation having a low associated mortality in extremely low birthweight newborns and promoting more rapid termination of mechanical ventilation.[45] In contrast, a recent study of 308 infants from tertiary centers in Canada was unable to show that surgical ligation was associated with BPD. However, post-ligation cardiac syndrome, a recognized serious complication of surgical closure, is strongly associated with more severe BPD.[46] Recognition of the risks associated with surgical ligation and other improvements in neonatal care may be related to the decline in the number of surgical ligations performed in the United States over the last several decades.[47] It remains to be seen if alternatives to surgical closure such as percutaneous closure will be associated with improvement in rates of chronic lung disease.

## 4 | CONCLUSION

Epidemiological studies demonstrate a strong association between the presence of a PDA and the development of BPD. A causal relationship has yet to be proven, and trials investigating either pharmacological or surgical treatment of the PDA have generally failed to prevent the development of BPD. It may be that PDA treatment is beneficial only in select patients with extreme prematurity, high ductal flow rates, and mechanical ventilation in the first week after birth. However, current available therapies may independently increase the risk of BPD in this high-risk population. Future trials may be able to clarify this conundrum by better diagnosing hsPDA, standardizing "conservative" therapies, and considering the role of novel therapies.

### CONFLICT OF INTEREST

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### AUTHOR CONTRIBUTIONS

Dr. Willis and Dr. Weems each contributed to the original draft, revisions, and approval of this manuscript.

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