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Patent ductus arteriosus, its treatments, and the risks of pulmonary morbidity

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ABSTRACT

A persistent left-to-right shunt through a patent ductus arteriosus (PDA) increases the rate of hydrostatic fluid filtration into the lung's interstitium, impairs pulmonary mechanics, and prolongs the need for mechanical ventilation. In preclinical trials, pharmacologic PDA closure leads to improved alveolarization and minimizes the impaired postnatal alveolar development that is the pathologic hallmark of bronchopulmonary dysplasia (BPD). Although routine prophylactic treatment of a PDA on the day of birth does not appear to offer any more protection against BPD than delaying treatment for 2–3 days, recent evidence from quality improvement trials suggests that early pharmacologic treatment decreases the incidence of BPD compared with a treatment approach that exposes infants to a moderate-to-large PDA shunt for the first 7–10 days after birth. After the first week, routine pharmacologic treatment (compared with continued PDA exposure) no longer appears to alter the course of BPD development. Evidence from epidemiologic, preclinical, and randomized controlled trials demonstrate that early ductus ligation is an independent risk factor for the development of BPD.

Introduction

Patent ductus arteriosus (PDA) are present in up to 70% of preterm infants born before 28 weeks gestation. While there is general agreement that a moderate-to-large left-to-right PDA shunt should be closed by the time a child is 1–2 years old, there is great uncertainty about whether it needs to be closed during the neonatal period. Both the high rate of spontaneous ductus closure during the neonatal hospitalization and the absence of appropriate randomized controlled trials (RCTs) that specifically address the risks of prolonged shunt exposure, have created the current confusion.

A persistent PDA increases hydraulic pressures on both the arterial and venous sides of the pulmonary capillary bed. This, in turn, leads to an increase in fluid filtration into the interstitium, a decrease in interstitial protein concentration, and "hydraulic" pulmonary edema. Although numerous epidemiologic studies show an association between the presence of a PDA and bronchopulmonary dysplasia (BPD), clear evidence demonstrating a causal role for the PDA in the development of BPD is lacking. This chapter will examine the evidence linking a PDA and its forms of treatment to the development of BPD.

PDA: pulmonary edema, pulmonary mechanics, and alveolar growth

The pathophysiologic features of a PDA depend on the magnitude of the left-to-right shunt and on the cardiac and

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pulmonary responses to the shunt. The immature fetal ventricles are less distensible than at term.[1] As a result, left ventricular distension, secondary to the left-to-right PDA shunt, produces higher left ventricular end-diastolic pressures at smaller ventricular volumes in preterm infants than at term. The increase in left ventricular pressure increases pulmonary venous pressure, which contributes to pulmonary congestion. Because the pulmonary vascular bed in the preterm newborn is already fully recruited,[2] the increase in pulmonary blood flow from the left-to-right PDA shunt produces an increase in pulmonary arterial pressure and a shift in the pulmonary pressure head downstream towards the capillary fluid filtration sites.[3] This, in turn, increases the rate of fluid transudation into the pulmonary interstitium.[4] Depending on the gestational age and the species examined, changes in pulmonary mechanics may occur as early as 1 day after birth (as they do in mice with a PDA),[5] or not before several days of exposure to the left-to-right PDA shunt.[3,6] In preterm newborns, the decreased ability to maintain active precapillary pulmonary arterial tone[7] allows the intravascular hydraulic pressure to distribute more of its force towards the downstream capillary fluid filtration sites.[3] Anything that decreases precapillary tone (e.g., intrauterine growth restriction[8] or surfactant administration[9–11]) can exacerbate the amount of left-to-right shunt, alter the distribution of pulmonary hydraulic pressures to downstream filtration sites, and lead to earlier pulmonary edema and pulmonary hemorrhage.[8,11,12] Conversely, therapies that increase precapillary vasoconstriction (e.g., dopamine[13]) or precapillary resistance (e.g., red blood cell transfusions and increased blood viscosity[14]) can decrease the left-to-right PDA shunt and redistribute the pressure head upstream, away from the capillary bed.

Increased microvascular pressure in preterm infants with respiratory distress syndrome has an exaggerated effect on interstitial and alveolar fluid accumulation due to their low plasma oncotic pressures and increased capillary permeability. Subsequent leakage of plasma proteins into the alveolar space inhibits surfactant function and increases surface tension in the immature air sacs,[15] which are already compromised by surfactant deficiency.

Even though preterm animals with a PDA have increased fluid and, to a lesser extent, protein filtration into the lung's interstitium, the excess fluid and protein appear to be cleared by a simultaneous increase in lung lymph flow.[4] This compensatory increase in lung lymph acts as an "edema safety factor", which inhibits fluid accumulation in the lungs and minimizes changes in pulmonary mechanics.[3,16–19] The delicate balance between PDA-induced fluid filtration and lymphatic fluid clearance probably accounts for the observation, that PDA patency or closure during the first day after birth in human infants, has little effect on pulmonary mechanics and need for ventilatory support. However, if lung lymphatic drainage is overwhelmed or impaired, as it is in the presence of pulmonary interstitial emphysema or fibrosis, the likelihood of edema increases dramatically.

After several days of exposure to mechanical ventilation there is a decrease in pulmonary capillary surface area, which causes both an increase in pulmonary microvascular pressure and an increase in hydraulic fluid filtration.[20] As a result, it is not uncommon for infants with a persistent PDA to develop pulmonary edema and alterations in pulmonary mechanics at 7–10 days after birth from the same size PDA shunt that could be accommodated on the first day after delivery. In these infants, closure of the PDA consistently results in improvement in lung compliance.[16,21–25]

The preterm baboon newborn (delivered at 67% term gestation) has been used as a preclinical model to examine the role of the PDA in the development of BPD.[6,26–28] Premature delivery and mechanical ventilation of the newborn baboon decrease the expression of genes involved with new vessel growth and lung remodeling and increase the expression of genes involved with pulmonary inflammation.[6,29–40] Although numerous changes in gene expression occur during the first 2 weeks after birth, the presence of an open ductus does not appear to alter the expression of any of the pro-inflammatory or tissue remodeling genes that have been examined.[6] Nor does persistent exposure to the PDA alter surfactant secretion, pulmonary epithelial protein permeability, or presence of surfactant inhibitory proteins.[6]

In addition to its effects on pulmonary vascular fluid filtration,[4] pharmacologic PDA closure alters fluid clearance from the alveolar space. Clearance of fluid from the newborn lung requires the presence of amiloride-sensitive alveolar epithelial sodium (ENaC) channels.[41] In contrast with full-term newborns, preterm baboons have diminished expression of ENaC channels and slow rates of fluid clearance from their lungs.[6,42,43] Pharmacologic closure of the PDA (with ibuprofen or indomethacin) is associated with a small but significant decrease in lung water compared with baboons with an open ductus.[6] The improvement in pulmonary mechanics that follows pharmacologic closure of the PDA is associated with increased pulmonary expression of ENaC channels and increased lung water clearance.[6] The effects of ibuprofen and indomethacin on ENaC expression appear to be due to their inhibition of cyclooxygenase activity, rather than their effect on ductus closure.[6] This finding may account for the decreased incidence of significant pulmonary edema/hemorrhage in infants that are treated prophylactically with indomethacin or ibuprofen shortly after birth.[44–48]

Pharmacologic closure of the PDA is also associated with improved alveolar development in preterm baboons. In contrast to animals with an open ductus, where impaired alveolar development (the hallmark of the BPD) is noticeable by 2 weeks after birth, pharmacological closure of the PDA leads to improved alveolarization.[6] Whether the improvement in alveolarization is due to closure of the PDA or to the pharmacologic agents (indomethacin and ibuprofen) used to close it is uncertain at this time. Inflammation plays a significant role in the development of BPD.[33,49] Infants with a PDA have elevated concentrations of activated neutrophils in their tracheal fluid and indomethacin-induced closure of the PDA is associated with a decline in activated neutrophils.[50] However, the decrease in neutrophil concentration occurs in both those who close their ductus after indomethacin as well as in those whose PDA fails to close after indomethacin.[51]

The improvements in pulmonary mechanics and alveolar surface area that accompany pharmacologic closure of the PDA have not been observed after surgical ligation of the PDA. In premature baboons surgical PDA closure decreases the expression of genes involved in angiogenesis (angiopoietin-2