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The role of patent ductus arteriosus and its treatments in the development of bronchopulmonary dysplasia

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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 the "new bronchopulmonary dysplasia (BPD)". Although early pharmacologic closure of the PDA decreases the incidence of pulmonary hemorrhage, intraventricular hemorrhage, and the need for PDA ligation, there is little evidence from controlled, clinical trials to support or refute a causal role for the PDA in the development of BPD. On the other hand, evidence from epidemiologic, preclinical, and randomized controlled clinical trials demonstrate that early ductus ligation is an independent risk factor for the development of BPD and may directly contribute to the neonatal morbidities it is trying to prevent.

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 size 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 late spontaneous ductus closure 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 persistent 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.

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PDA, pulmonary edema, and pulmonary mechanics

The pathophysiologic features of a PDA depend on the magnitude of the left-to-right shunt and on the cardiac and 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), any increase in pulmonary blood flow 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, like 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 or precapillary resistance, like dopamine (13) or red blood cell transfusion (which increases blood viscosity) (14), respectively, can decrease the left-to-right PDA shunt and redistribute the pressure head upstream, away from the capillary bed.

In premature infants with respiratory distress syndrome, an increase in microvascular perfusion pressure has an exaggerated effect on interstitial and alveolar lung fluid accumulation because of their low plasma oncotic pressure and increased capillary permeability. 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 from the lung, during the first days after birth, 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 the 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 or the 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. Exposure to mechanical ventilation for several days decreases pulmonary capillary surface area and results in 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).

PDA and the development of BPD

The increased FiO_2 and mean airway pressure needed to overcome PDA-induced changes in pulmonary compliance may be important factors in the development of chronic lung disease (16, 26, 27); however, at this point there is little evidence from controlled, clinical trials to support or refute this hypothesis.

Although there are numerous studies demonstrating the short-term effects of a PDA on pulmonary edema and pulmonary mechanics, there is a paucity of data addressing its potential role in the development of BPD. To date, there is only one small RCT (performed over 30 years ago) that has examined the pulmonary effects of prolonged exposure to a PDA in extremely premature infants requiring mechanical ventilation (27). The investigators compared the effects of ligating the PDA, when signs of congestive failure developed, with allowing the PDA to persist indefinitely. They found that surgical closure of the PDA decreased the need for prolonged ventilation support (27). Unfortunately, the investigators could not comment on the development of BPD since the study predated our current definition of "functional" BPD (i.e., need for supplemental oxygen to maintain oxygen saturation >90% at 36 weeks corrected age (28)). Whether their findings are still applicable in the setting of modern neonatal treatment has also become a matter of controversy among neonatologists (29).

More recent RCTs were never designed to address the question of whether a PDA leads to BPD or other long-term morbidities. Rather, they were designed to assess the relationship between "timing" (initiation) of pharmacologic treatment and the success of PDA closure. These "timing" RCTs give us no information about the role of prolonged exposure to a PDA in the development of BPD. However, they do contain sufficient information to allow us to examine the effects of brief exposure to a PDA on BPD development. They demonstrate that early use of indomethacin (compared with waiting 3-4 days to initiate PDA treatment) decreases the incidence of 1) severe early pulmonary hemorrhage, 2) severe grades of IVH, and 3) the need for PDA ligation. However, there is no evidence that short-term exposure to a PDA (between 2-6 days) increases the risk of developing BPD (30-39).

Pharmacologic PDA closure and BPD

Recently, a premature baboon model of PDA was developed to examine the PDA's role in the evolution of BPD (6). The premature baboon (delivered at 125 days gestation, term=185 days) has a similar neonatal course as the premature human delivered between 26-27 weeks of gestation (40): they both develop respiratory distress and fail to close their PDA after birth. Despite surfactant treatment, total parenteral nutrition, low tidal volume ventilation, and low supplemental oxygen administration during the first 2 weeks after delivery, premature baboons develop pulmonary histopathologic changes that are similar to those described in premature human infants with BPD (41-43).

When premature baboons are treated with ibuprofen to close their PDA their pulmonary mechanics are improved compared with untreated animals with a persistent PDA. Exposure to a persistent PDA for 2 weeks does not appear to alter surfactant secretion, pulmonary epithelial protein permeability, or presence of surfactant inhibitory proteins (6). Although numerous changes in the expression of genes that regulate inflammation and tissue remodeling occur in the preterm lungs 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).

Clearance of fluid from the newborn lung requires the presence of amiloride-sensitive alveolar epithelial sodium (ENaC) channels (44). In contrast with full term newborns,

preterm newborns have diminished expression of ENaC channels and slow rates of fluid clearance from their lungs (6, 45, 46). Preterm baboons with a persistent PDA have a small but significant increase in lung water at 2 weeks after delivery compared with baboons with a closed ductus (6). The improvement in pulmonary mechanics that follows pharmacologic closure of the PDA (with ibuprofen or indomethacin) 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 (34, 35, 37-39).

Pharmacologic closure of the PDA is also associated with improved alveolar development in preterm baboons. In contrast to the animals with an open ductus, where impaired alveolar development (the hallmark of the new “BPD”) is noticeable by 2 weeks after birth, pharmacological closure of the PDA leads to improved alveolarization (6). However, at this point in time, it is unclear whether the improvement in alveolarization, associated with pharmacologic closure of the PDA, is due to the closure of the PDA or due to the pharmacologic agents (indomethacin and ibuprofen) used to close it. For example, inflammation of the airways and lung tissue is associated with the development of BPD (47, 48). 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 (49). 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 (50).

There is no evidence that distinguishes using indomethacin from ibuprofen for PDA closure on the development of BPD.

Surgical PDA closure and BPD

While pharmacologic closure of the PDA prevents pulmonary edema, improves pulmonary function (in humans and baboons) and promotes alveolar development (at least in baboons) (6, 23, 24, 51), there is little information to guide neonatologists in what to do when the PDA fails to close after pharmacologic treatment. PDA ligation produces immediate, permanent ductus closure and has been shown to improve pulmonary mechanics and decrease the need for prolonged ventilator support in infants with a prolonged persistent PDA (27). However, recent studies suggest that, in addition to the known surgical complications that may accompany the ligation (pneumothorax, chylothorax, scoliosis, infection, vocal cord paralysis and post-operative cardiopulmonary deterioration) (52-56) the ligation itself may directly contribute to some of the neonatal morbidities it is trying to prevent (51, 57-59).

Several population-based and cohort-controlled observational studies have suggested that early surgical ligation is an independent risk factor for the development of BPD and other neonatal morbidities (57-63). Caution must be used, however, when trying to link *causation* to *association* in these observational studies. Although the statistical models adjust for multiple factors, they cannot adjust for bias due to unmeasured potential confounders. This is a significant issue when treatment approaches are determined by the physician’s impression of the patient’s condition (e.g, degree of immaturity or illness) rather than by a specific mandated treatment protocol.

Studies in premature baboons support the concept that surgical ligation may produce detrimental effects on lung function and growth (64). Following pharmacologic ductus

closure, premature baboons have improved pulmonary mechanics and increased alveolar surface area compared with premature baboons with a persistent PDA (6). In contrast, baboons that have their PDA closed by surgical ligation show no signs of improved pulmonary mechanics or increased alveolar growth (65, 66). This raises the possibility that ductus ligation, while eliminating the detrimental effects of a PDA on lung development, may create its own set of problems that counteract any of the benefits derived from ductus closure.

Premature delivery and mechanical ventilation decrease the expression of genes involved with new vessel growth and lung remodeling and increase the expression of genes involved with pulmonary inflammation (6, 47, 67-76). Disruption of angiogenesis plays a significant role in impaired alveolarization (77). Surgical PDA closure decreases the expression of genes involved in angiogenesis (angiopoietin-2 and transforming growth factor beta 3) (78) and increases the expression of pro-inflammatory mediators (cyclooxygenase 2, tumor necrosis factor-alpha, and cells expressing CD14) (79). Surgical PDA closure also decreases the expression of pulmonary ENaC channels. The decrease in ENaC expression may contribute to the pulmonary edema, delayed fluid clearance and lack of improvement in pulmonary mechanics after PDA ligation (79). The increased expression of cyclooxygenase 2, that follows PDA ligation may account for the decreased expression of ENaC in the lungs of ligated animals (6).

At this time there is little evidence to suggest that surgical PDA closure prevents the evolution of BPD (57-61). In fact, the only RCT that examined the effects of prophylactic PDA ligation (versus delayed ligation) found a significant increase in the incidence of BPD in the group that was ligated prophylactically (59). Persistent alterations in inflammatory mediators and ENaC channels may account for the lack of improvement in pulmonary mechanics and BPD following surgical closure.

A delay in ligation appears to be beneficial since accumulating evidence suggests that several of the morbidities associated with ligation (post-ligation hypotension (55), vocal cord paralysis (53, 54), BPD (58, 59) and abnormal neurodevelopmental outcome (80)) are significantly reduced when ligation is delayed. Further investigations will be needed to determine which infants are most likely to benefit from surgical ligation and which infants might best be left untreated when pharmacologic approaches are no longer an option.

Interpretation and summary

1. Except for one clinical trial (27) prior PDA clinical trials were NOT designed to determine whether prolonged exposure to a PDA contributes to BPD.
2. A moderate/large Left-to-Right PDA shunt increases the need for ventilation support (and appears to inhibit alveolar development when left untreated in preterm baboons).
3. Tolerating the presence of a symptomatic PDA for several days does NOT increase the incidence of BPD.
4. There is no evidence to suggest that surgical PDA closure prevents the evolution of BPD.

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