Published in final edited form as:

Semin Perinatol. 2013 April ; 37(2): 102–107. doi:10.1053/j.semperi.2013.01.006.

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

Ronald I. Clyman, MD

Professor of Pediatrics, Senior Staff, Cardiovascular Research Institute, University of California San Francisco, Departments of Pediatrics and the Cardiovascular Research Institute; the University of California San Francisco, San Francisco, CA 94143

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.

© 2013 Elsevier Inc. All rights reserved.

Corresponding author: Ronald I. Clyman, M.D., UCSF Box 0544, HSW 1408, University of California, San Francisco, 513 Parnassus Ave, San Francisco, CA 94143-0544, phone: (415) 476-4462, FAX: (415) 502-2993, clymanr@peds.ucsf.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosure: Dr Clyman has no proprietary or commercial interest in any product mentioned or concept discussed in this article

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.

Acknowledgments

Supported in part by a grant from U.S. Public Health Service (NIH HL109199) and by a gift from the Jamie and Bobby Gates Foundation.

References

1. Friedman, WF. The intrinsic physiologic properties of the developing heart. In: Friedman, WF.; Lesch, M.; Sonnenblick, EH., editors. Neonatal Heart Disease. Grune and Stratton; New York: 1972. p. 21-49.
2. Nelin LD, Wearden ME, Welty SE, et al. The effect of blood flow and left atrial pressure on the DLCO in lambs and sheep. *Respir Physiol.* 1992; 88:333-42. [PubMed: 1615230]
3. Perez Fontan JJ, Clyman RI, Mauray F, et al. Respiratory effects of a patent ductus arteriosus in premature newborn lambs. *J Appl Physiol.* 1987; 63:2315-24. [PubMed: 3436866]
4. Alpan G, Scheerer R, Bland RD, et al. Patent ductus arteriosus increases lung fluid filtration in preterm lambs. *Pediatr Res.* 1991; 30:616-21. [PubMed: 1805159]
5. Loftin CD, Trivedi DB, Tiano HF, et al. Failure of ductus arteriosus closure and remodeling in neonatal mice deficient in cyclooxygenase-1 and cyclooxygenase-2. *Proc Natl Acad Sci U S A.* 2001; 98:1059-64. [PubMed: 11158594]
6. McCurnin D, Seidner S, Chang LY, et al. Ibuprofen-induced patent ductus arteriosus closure: physiologic, histologic, and biochemical effects on the premature lung. *Pediatrics.* 2008; 121:945-56. [PubMed: 18450898]
7. Lewis AB, Heymann MA, Rudolph AM. Gestational changes in pulmonary vascular responses in fetal lambs in utero. *Circ. Res.* 1976; 39:536-41. [PubMed: 963838]
8. Rakza T, Magnenant E, Klosowski S, et al. Early hemodynamic consequences of patent ductus arteriosus in preterm infants with intrauterine growth restriction. *J Pediatr.* 2007; 151:624-8. [PubMed: 18035142]
9. Clyman RI, Jobe A, Heymann MA, et al. Increased shunt through the patent ductus arteriosus after surfactant replacement therapy. *J. Pediatr.* 1982; 100:101-07. [PubMed: 6948942]
10. Soll R, Ozek E. Prophylactic protein free synthetic surfactant for preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev.* 2010;CD001079. [PubMed: 20091513]
11. Alpan, G.; Clyman, RI. Cardiovascular effects of surfactant replacement with special reference to the patent ductus arteriosus. In: Robertson, B.; Taeusch, HW., editors. Surfactant Therapy for Lung Disease: Lung Biology in Health and Disease. Marcel Dekker, Inc.; New York: 1995. p. 531-45.
12. Raju TNK, Langenberg P. Pulmonary hemorrhage and exogenous surfactant therapy—a metaanalysis. *J. Pediatr.* 1993; 123:603-10. [PubMed: 8410518]
13. Bouissou A, Rakza T, Klosowski S, et al. Hypotension in preterm infants with significant patent ductus arteriosus: effects of dopamine. *J Pediatr.* 2008; 153:790-4. [PubMed: 18675433]
14. Fouron JC, Bard H, Riopel L, et al. Circulatory changes in newborn lambs with experimental polycythemia: comparison between fetal and adult type blood. *Pediatrics.* 1985; 75:1054-60. [PubMed: 4000779]
15. Ikegami M, Jacobs H, Jobe A. Surfactant function in respiratory distress syndrome. *J. Pediatr.* 1983; 102:443-47. [PubMed: 6687477]
16. Clyman RI. Commentary: Recommendations for the postnatal use of indomethacin. An analysis of four separate treatment strategies. *J. Pediatr.* 1996; 128:601-07. [PubMed: 8627430]
17. Shimada S, Raju TNK, Bhat R, et al. Treatment of patent ductus arteriosus after exogenous surfactant in baboons with hyaline membrane disease. *Pediatr. Res.* 1989; 26:565-69. [PubMed: 2602035]
18. Krauss AN, Fatica N, Lewis BS, et al. Pulmonary function in preterm infants following treatment with intravenous indomethacin. *Am. J. Dis. Child.* 1989; 143:78-81. [PubMed: 2910050]
19. Alpan G, Mauray F, Clyman RI. Effect of patent ductus arteriosus on water accumulation and protein permeability in the premature lungs of mechanically ventilated premature lambs. *Pediatr. Res.* 1989; 26:570-75. [PubMed: 2602036]
20. Mokres LM, Parai K, Hilgendorff A, et al. Prolonged mechanical ventilation with air induces apoptosis and causes failure of alveolar septation and angiogenesis in lungs of newborn mice. *Am J Physiol Lung Cell Mol Physiol.* 2010; 298:L23-35. [PubMed: 19854954]
21. Gerhardt T, Bancalari E. Lung compliance in newborns with patent ductus arteriosus before and after surgical ligation. *Biol. Neonate.* 1980; 38:96-105. [PubMed: 7388095]

22. Naulty CM, Horn S, Conry J, et al. Improved lung compliance after ligation of patent ductus arteriosus in hyaline membrane disease. *J. Pediatr.* 1978; 93:682–84. [PubMed: 702251]
23. Stefano JL, Abbasi S, Pearlman SA, et al. Closure of the ductus arteriosus with indomethacin in ventilated neonates with respiratory distress syndrome. Effects of pulmonary compliance and ventilation. *Am Rev Respir Dis.* 1991; 143:236–39. [PubMed: 1990934]
24. Yeh TF, Thalji A, Luken L, et al. Improved lung compliance following indomethacin therapy in premature infants with persistent ductus arteriosus. *Chest.* 1981; 80:698–700. [PubMed: 7307591]
25. Szymankiewicz M, Hodgman JE, Siassi B, et al. Mechanics of breathing after surgical ligation of patent ductus arteriosus in newborns with respiratory distress syndrome. *Biol Neonate.* 2004; 85:32–6. [PubMed: 14631164]
26. Brown E. Increased risk of bronchopulmonary dysplasia in infants with patent ductus arteriosus. *J. Pediatr.* 1979; 95:865–66. [PubMed: 490263]
27. Cotton RB, Stahlman MT, Berder HW, et al. Randomized trial of early closure of symptomatic patent ductus arteriosus in small preterm infants. *J Pediatr.* 1978; 93:647–51. [PubMed: 702245]
28. Walsh MC, Yao Q, Gettner P, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. *Pediatrics.* 2004; 114:1305–11. [PubMed: 15520112]
29. Bose CL, Laughon MM. Patent ductus arteriosus: lack of evidence for common treatments. *Arch Dis Child Fetal Neonatal Ed.* 2007; 92:F498–F502. [PubMed: 17951552]
30. Fowlie PW, Davis PG. Prophylactic indomethacin for preterm infants: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed.* 2003; 88:F464–6. [PubMed: 14602691]
31. Ment LR, Oh W, Ehrenkranz RA, et al. Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. *Pediatrics.* 1994; 93:543–50. [PubMed: 8134206]
32. Schmidt B, Davis P, Moddemann D, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Engl J Med.* 2001; 344:1966–72. [PubMed: 11430325]
33. Bandstra ES, Montalvo BM, Goldberg RN, et al. Prophylactic indomethacin for prevention of intraventricular hemorrhage in premature infants. *Pediatrics.* 1988; 82:533–42. [PubMed: 3174314]
34. Al Faleh K, Smyth J, Roberts R, et al. Prevention and 18-month outcome of serious pulmonary hemorrhage in extremely low birth weight infants: results from the trial of indomethacin prophylaxis in preterms. *Pediatrics.* 2008; 121:e233–8. [PubMed: 18245398]
35. Clyman RI, Chorne N. PDA treatment: Effects on pulmonary hemorrhage and pulmonary morbidity. *J Pediatr.* 2008; 152:447–48.
36. Cooke L, Steer P, Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. *Cochrane Database Syst Rev.* 2003;CD003745. [PubMed: 12804488]
37. Domanico RS, Waldman JD, Lester LA, et al. Prophylactic indomethacin reduces the incidence of pulmonary hemorrhage and patent ductus arteriosus in surfactant treated infants < 1250 grams. *Pediatr. Res.* 1994; 35:331.
38. Aranda JV, Clyman R, Cox B, et al. A randomized, double-blind, placebo-controlled trial on intravenous ibuprofen L-lysine for the early closure of nonsymptomatic patent ductus arteriosus within 72 hours of birth in extremely low-birth-weight infants. *Am J Perinatol.* 2009; 26:235–45. [PubMed: 19067286]
39. Kluckow M, Gill A, Jeffery M, et al. Ductal Echocardiographic Targeting and Early Closure Trial (DETECT): a pilot randomized controlled trial. *E-PAS.* 2012; 1675:5.
40. Clyman RI, Chan CY, Mauray F, et al. Permanent anatomic closure of the ductus arteriosus in newborn baboons: the roles of postnatal constriction, hypoxia, and gestation. *Pediatr Res.* 1999; 45:19–29. [PubMed: 9890604]
41. Coalson JJ, Winter VT, Siler-Khodr T, et al. Neonatal chronic lung disease in extremely immature baboons. *Am J Respir Crit Care Med.* 1999; 160:1333–46. [PubMed: 10508826]
42. Yoder BA, Siler-Khodr T, Winter VT, et al. High-frequency oscillatory ventilation: effects on lung function, mechanics, and airway cytokines in the immature baboon model for neonatal chronic lung disease. *Am J Respir Crit Care Med.* 2000; 162:1867–76. [PubMed: 11069828]
43. Bhatt AJ, Pryhuber GS, Huyck H, et al. 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; 164:1971–80. [PubMed: 11734454]

44. Hummler E, Barker P, Gatz J, et al. Early death due to defective neonatal lung liquid clearance in alpha-ENaC-deficient mice. *Nat Genet.* 1996; 12:325–8. [PubMed: 8589728]
45. Helve O, Pitkanen O, Janer C, et al. Pulmonary fluid balance in the human newborn infant. *Neonatology.* 2009; 95:347–52. [PubMed: 19494556]
46. Copetti R, Cattarossi L, Macagno F, et al. Lung ultrasound in respiratory distress syndrome: a useful tool for early diagnosis. *Neonatology.* 2008; 94:52–9. [PubMed: 18196931]
47. Speer CP. Inflammation and bronchopulmonary dysplasia: a continuing story. *Semin Fetal Neonatal Med.* 2006; 11:354–62. [PubMed: 16702036]
48. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 2001; 163:1723–9. [PubMed: 11401896]
49. Varsila E, Hallman M, Venge P, et al. Closure of patent ductus arteriosus decreases pulmonary myeloperoxidase in premature infants with respiratory distress syndrome. *Biol Neonate.* 1995; 67:167–71. [PubMed: 7640315]
50. Nakamura T, Takasaki J, Ogawa Y. Inflammatory changes in the lungs of premature infants with symptomatic patent ductus arteriosus. *Pediatr Int.* 2002; 44:363–7. [PubMed: 12139558]
51. Clyman RI, Chorne N. Patent ductus arteriosus: evidence for and against treatment. *J Pediatr.* 2007; 150:216–9. [PubMed: 17307530]
52. Roclawski M, Sabiniewicz R, Potaz P, et al. Scoliosis in patients with aortic coarctation and patent ductus arteriosus: does standard posterolateral thoracotomy play a role in the development of the lateral curve of the spine? *Pediatr Cardiol.* 2009; 30:941–5. [PubMed: 19597861]
53. Smith ME, King JD, Elsherif A, et al. Should all newborns who undergo patent ductus arteriosus ligation be examined for vocal fold mobility? *Laryngoscope.* 2009; 119:1606–9. [PubMed: 19507238]
54. Clement WA, El-Hakim H, Phillipos EZ, et al. Unilateral vocal cord paralysis following patent ductus arteriosus ligation in extremely low-birth-weight infants. *Arch Otolaryngol Head Neck Surg.* 2008; 134:28–33. [PubMed: 18209132]
55. Moin F, Kennedy KA, Moya FR. Risk factors predicting vasopressor use after patent ductus arteriosus ligation. *Am J Perinatol.* 2003; 20:313–20. [PubMed: 14528401]
56. Noori S, Friedlich P, Seri I, et al. Changes in myocardial function and hemodynamics after ligation of the ductus arteriosus in preterm infants. *J Pediatr.* 2007; 150:597–602. [PubMed: 17517241]
57. Kabra NS, Schmidt B, Roberts RS, et al. Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: results from the trial of indomethacin prophylaxis in preterms. *J Pediatr.* 2007; 150:229–34. [PubMed: 17307535]
58. Chorne N, Leonard C, Piecuch R, et al. Patent ductus arteriosus and its treatment as risk factors for neonatal and neurodevelopmental morbidity. *Pediatrics.* 2007; 119:1165–74. [PubMed: 17545385]
59. Clyman R, Cassady G, Kirklin JK, et al. The role of patent ductus arteriosus ligation in bronchopulmonary dysplasia: reexamining a randomized controlled trial. *J Pediatr.* 2009; 154:873–6. [PubMed: 19324366]
60. Gersony WM, Peckham GJ, Ellison RC, et al. Effects of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. *J Pediatr.* 1983; 102:895–906. [PubMed: 6343572]
61. Jhaveri N, Moon-Grady A, Clyman RI. Early surgical ligation versus a conservative approach for management of patent ductus arteriosus that fails to close after indomethacin treatment. *J Pediatr.* 2010; 157:381–87. [PubMed: 20434168]
62. Mirea L, Sankaran K, Seshia M, et al. Treatment of patent ductus arteriosus and neonatal mortality/morbidities: adjustment for treatment selection bias. *J Pediatr.* 2012; 161:689–94. e1. [PubMed: 22703954]
63. Madan JC, Kendrick D, Hagadorn JI, et al. Patent ductus arteriosus therapy: impact on neonatal and 18-month outcome. *Pediatrics.* 2009; 123:674–81. [PubMed: 19171637]
64. 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; 36:123–9. [PubMed: 22414883]
65. McCurnin DC, Yoder BA, Coalson J, et al. Effect of ductus ligation on cardiopulmonary function in premature baboons. *Am J Respir Crit Care Med.* 2005; 172:1569–74. [PubMed: 16179644]

66. Chang LY, McCurnin D, Yoder B, et al. Ductus arteriosus ligation and alveolar growth in preterm baboons with a patent ductus arteriosus. *Pediatr Res.* 2008; 63:299–302. [PubMed: 18287969]
67. McCurnin DC, Pierce RA, Willis BC, et al. Postnatal estradiol up-regulates lung nitric oxide synthases and improves lung function in bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 2009; 179:492–500. [PubMed: 19151197]
68. Pierce RA, Joyce B, Officer S, et al. Retinoids increase lung elastin expression but fail to alter morphology or angiogenesis genes in premature ventilated baboons. *Pediatr Res.* 2007; 61:703–9. [PubMed: 17426644]
69. Maniscalco WM, Watkins RH, Pryhuber GS, et al. Angiogenic factors and alveolar vasculature: development and alterations by injury in very premature baboons. *Am J Physiol Lung Cell Mol Physiol.* 2002; 282:L811–L23. [PubMed: 11880308]
70. Naik AS, Kallapur SG, Bachurski CJ, et al. Effects of ventilation with different positive end-expiratory pressures on cytokine expression in the preterm lamb lung. *Am J Respir Crit Care Med.* 2001; 164:494–8. [PubMed: 11500356]
71. Vozzelli MA, Mason SN, Whorton MH, et al. Antimacrophage chemokine treatment prevents neutrophil and macrophage influx in hyperoxia-exposed newborn rat lung. *Am J Physiol Lung Cell Mol Physiol.* 2004; 286:L488–L93. [PubMed: 12588706]
72. Kotecha S, Wilson L, Wangoo A, et al. Increase in interleukin (IL)-1 beta and IL-6 in bronchoalveolar lavage fluid obtained from infants with chronic lung disease of prematurity. *Pediatr Res.* 1996; 40:250–6. [PubMed: 8827773]
73. Tullus K, Noack GW, Burman LG, et al. Elevated cytokine levels in tracheobronchial aspirate fluids from ventilator treated neonates with bronchopulmonary dysplasia. *Eur J Pediatr.* 1996; 155:112–6. [PubMed: 8775225]
74. Groneck P, Gotze-Speer B, Oppermann M, et al. Association of pulmonary inflammation and increased microvascular permeability during the development of bronchopulmonary dysplasia: a sequential analysis of inflammatory mediators in respiratory fluids of high-risk preterm neonates. *Pediatrics.* 1994; 93:712–8. [PubMed: 8165067]
75. Ikegami M, Jobe AH. Postnatal lung inflammation increased by ventilation of preterm lambs exposed antenatally to *Escherichia coli* endotoxin. *Pediatr Res.* 2002; 52:356–62. [PubMed: 12193667]
76. Jobe AH, Kramer BW, Moss TJ, et al. Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. *Pediatr Res.* 2002; 52:387–92. [PubMed: 12193673]
77. Thebaud B, Abman SH. Bronchopulmonary dysplasia: where have all the vessels gone? Roles of angiogenic growth factors in chronic lung disease. *Am J Respir Crit Care Med.* 2007; 175:978–85. [PubMed: 17272782]
78. Jain RK. Molecular regulation of vessel maturation. *Nat Med.* 2003; 9:685–93. [PubMed: 12778167]
79. Waleh N, McCurnin DC, Yoder BA, et al. Patent ductus arteriosus ligation alters pulmonary gene expression in preterm baboons. *Pediatr Res.* 2011; 69:212–6. [PubMed: 21131894]
80. Wickremasinghe AC, Rogers EE, Piecuch RE, et al. Neurodevelopmental Outcomes Following Two Different Treatment Approaches (Early Ligation and Selective Ligation) for Patent Ductus Arteriosus. *J Pediatr.* 2012