Patent Ductus Arteriosus of the Preterm Infant

abstract

A persistently patent ductus arteriosus (PDA) in preterm infants can have significant clinical consequences, particularly during the recovery period from respiratory distress syndrome. With improvement of ventilation and oxygenation, the pulmonary vascular resistance decreases early and rapidly, especially in very immature infants with extremely low birth weight (<1000 g). Subsequently, the left-to-right shunt through the ductus arteriosus (DA) is augmented, thereby increasing pulmonary blood flow, which leads to pulmonary edema and overall worsening of cardiopulmonary status. Prolonged ventilation, with the potential risks of volutrauma, barotrauma, and hyperoxygenation, is strongly associated with the development and severity of bronchopulmonary dysplasia/chronic lung disease. Substantial left-to-right shunting through the ductus may also increase the risk of intraventricular hemorrhage, necrotizing enterocolitis, and death. Postnatal ductal closure is regulated by exposure to oxygen and vasodilators; the ensuing vascular responses, mediated by potassium channels, voltage-gated calcium channels, mitochondrial-derived reactive oxygen species, and endothelin 1, depend on gestational age. Platelets are recruited to the luminal aspect of the DA during closure and probably promote thrombotic sealing of the constricted DA. Currently, it is unclear whether and when a conservative, pharmacologic, or surgical approach for PDA closure may be advantageous. Furthermore, it is unknown if prophylactic and/or symptomatic PDA therapy will cause substantive improvements in outcome. In this article we review the mechanisms underlying DA closure, risk factors and comorbidities of significant DA shunting, and current clinical evidence and areas of uncertainty in the diagnosis and treatment of PDA of the preterm infant. *Pediatrics* 2010;125:1020–1030

AUTHORS: Shannon E. G. Hamrick, MD[a] and Georg Hansmann, MD, PhD[b]

[a]Divisions of Neonatology and Cardiology, Department of Pediatrics, Emory University, Atlanta, Georgia; and [b]Department of Cardiology, Children's Hospital Boston, Harvard Medical School, Massachusetts

KEY WORDS

ductus arteriosus, prematurity, oxygen, ion channels, platelets, cyclooxygenase, diagnosis, treatment, outcome

ABBREVIATIONS

DA— ductus arteriosus
SMC—smooth muscle cell
EC— endothelial cell
PDA—patent ductus arteriosus
CLD— chronic lung disease
BW— birth weight
VLBW—very low birth weight
ELBW— extremely low birth weight
IVH—intraventricular hemorrhage
BPD— bronchopulmonary dysplasia
NEC—necrotizing enterocolitis
DASMC— ductus arteriosus smooth muscle cell
PGE_2—prostaglandin E_2
PGI_2—prostacyclin
NO—nitric oxide
DOL— day of life
BNP—B-type natriuretic peptide
NT-pro-BNP—N-terminal-pro-BNP
CTnT— cardiac troponin T
COX— cyclooxygenase
RCT—randomized, controlled trial
VEGF—vascular endothelial growth factor
DOL— day of life
hs— hemodynamically significant

www.pediatrics.org/cgi/doi/10.1542/peds.2009-3506

doi:10.1542/peds.2009-3506

Accepted for publication Feb 22, 2010

Address correspondence to Georg Hansmann, MD, PhD, Department of Cardiology, Children's Hospital Boston, Harvard Medical School, 300 Longwood Ave, Boston, MA 02115. E-mail: georg.hansmann@gmail.com

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

The ductus arteriosus (DA) serves to divert ventricular output away from the lungs and toward the placenta in utero by connecting the main pulmonary artery to the descending aorta. A patent ductus arteriosus (PDA) in the first 3 days of life is a physiologic shunt in healthy term and preterm newborn infants.[1] In contrast, a persistently patent DA in preterm infants can have clinical consequences depending on the degree of left-to-right shunting. The increase in pulmonary blood flow in the setting of prematurity can lead to pulmonary edema, loss of lung compliance, and deterioration of respiratory status, which ultimately leads to chronic lung disease (CLD). The incidence of PDA in term infants has been estimated to be 57 per 100 000 live births,[2] whereas every third preterm infant with a birth weight (BW) of 501 to 1500 g (very low birth weight [VLBW]) can be expected to have a persistent PDA.[3] Furthermore, 55% of infants who weigh <1000 g (extremely low birth weight [ELBW]) have been described to have a symptomatic PDA that ultimately leads to medical treatment.[4,5] Although spontaneous permanent DA closure occurs in ~34% of ELBW neonates 2 to 6 days postnatally[4] and in the majority of VLBW neonates within the first year of life,[6] 60% to 70% of preterm infants of <28 weeks' gestation receive medical or surgical therapy for a PDA,[7] usually with the intention to prevent respiratory decompensation, heart failure, intraventricular hemorrhage (IVH)/brain injury, CLD/bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and death. The natural history of a PDA in premature infants cared for in today's NICUs remains unknown.

ADVANCES IN SCIENCE AND TECHNOLOGY

Mechanisms Underlying Physiologic Closure of the DA

The fetal DA appears grossly similar to the adjacent descending aorta and main pulmonary artery; however, there are essential histologic differences. The medial layer of the DA is composed of longitudinal and spiral layers of smooth muscle fibers within concentric layers of elastic tissue; in contrast, the medial layers of the aorta and pulmonary artery are primarily concentric elastic tissue.[8] The intimal layer of the DA is irregular and thick with neointimal "cushions" composed of smooth muscle and endothelial cells.[9] The DA smooth muscle cell (DASMC) is the site of oxygen-sensing, whereas the endothelium releases vasoactive substances that are important in modulating DA tone. Fetal patency is regulated by low oxygen tension and prostanoids, predominantly prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2). PGE_2 and PGI_2 levels are high in the fetus because of both placental production and diminished clearance by the fetal lungs.[8]

After birth at term, a postnatal increase in Pa_{O_2} and a decrease in circulating vasodilators such as PGE_2 and PGI_2 will induce constriction of DASMCs and, consequently, functional closure of the ductus in newborns. The mechanism by which oxygen constricts the ductus is the subject of much investigation.[10–12] Oxygen-sensing mechanisms in the DASMCs cause cell-membrane depolarization, which allows for calcium influx and contraction (Fig 1). Developmentally regulated potassium channels allow for voltage-gated calcium channels to open and increase calcium influx.[13] Immaturity of both potassium and calcium channels leads to ineffective oxygen-mediated constriction in the preterm rabbit DA.[13,14] In addition, Rho/Rho-kinase pathways can induce calcium sensitization in which sustained vasoconstriction occurs as a result of persistent myosin light-chain phosphorylation.[15,16] Rho/Rho-Kinase signaling depends on mitochondrial-derived reactive oxygen species, the generation of which may be decreased

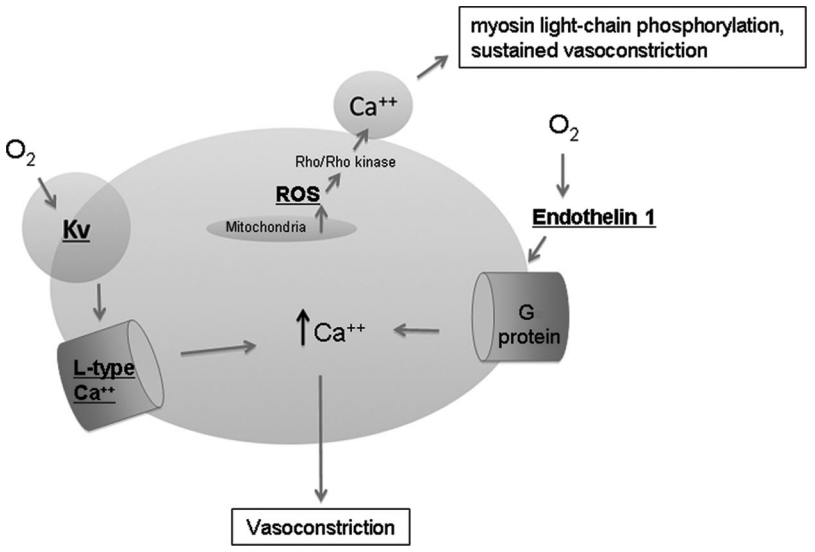

FIGURE 1

Mechanism for oxygen-induced DASMC contraction. The underlined items in bold font show developmental maturation. Potassium (K^+) channels allow for voltage-gated calcium channels to open and increase calcium influx. Rho/Rho-kinase pathways can induce calcium sensitization in which sustained vasoconstriction occurs due to persistent myosin light-chain phosphorylation, dependent on mitochondrial-derived reactive oxygen species (ROS). Oxygen also induces release of the potent vasoconstrictor endothelin-1 by the ductus, which acts to increase intracellular calcium through G-protein coupling. Kv indicates voltage-gated potassium channel, ROS indicates reactive oxygen species

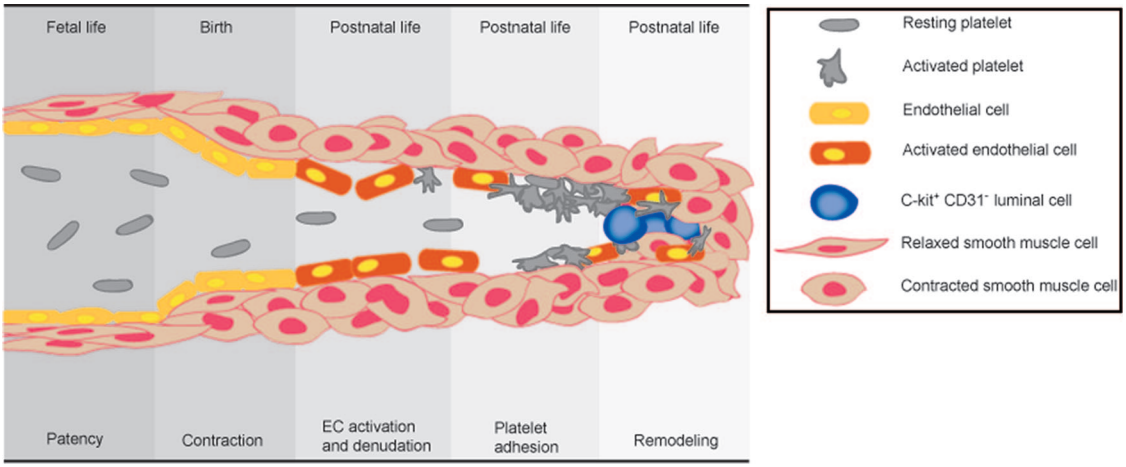

FIGURE 2

The role of platelets for sealing of the contracted DA. The scheme delineates the proposed sequence of events that contribute to postnatal DA occlusion. Echtler et al propose a model here in which reversible and incomplete DA constriction is the initial step that triggers DA closure. As a result, the luminal aspect of the DA wall adopts a prothrombotic phenotype with endothelial activation, deposition of von Willebrand factor and fibrin(ogen), and eventually endothelial cell (EC) detachment from the internal elastic lamina, which lead to collagen exposure. This process triggers the accumulation of platelets circulating in the residual DA lumen. The platelet plug that forms seals the residual lumen of the contracted DA and, together with other mechanisms, facilitates subsequent luminal remodeling. (Adapted with permission from Echtler K, Stark K, Lorenz M, et al. *Nat Med.* 2010;16[1]:75–82; supplementary figure 9.)

in the preterm DA.[15] Oxygen also induces release of the potent vasoconstrictor endothelin 1 by the ductus; endothelin 1 acts to increase intracellular calcium through G-protein coupling, although its role in closure of the DA after birth is controversial.[15,17–19]

The successful contraction results locally in a "hypoxic zone" and triggers cell death and production of hypoxia-inducible growth factors such as transforming growth factor β and vascular endothelial growth factor (VEGF), which result in vascular remodeling and anatomic DA closure, as demonstrated in newborn baboons.[9] Failure to generate the hypoxic zone in preterm infants by insufficient constriction prevents true anatomic DA closure, which explains the DA's propensity to "reopen" after echocardiographic confirmation of its closure.[20]

New Concept of Initial DA Constriction and Subsequent Platelet-Driven DA Sealing

Recently, Echtler et al[21] demonstrated by intravital confocal microscopy that platelets are recruited to the luminal aspect of the murine DA immediately after birth. Induced dysfunction of platelet adhesion or transgenic defects of platelet biogenesis ($Nfe^{-/-}$ [nuclear factor (erythroid-derived 2)] mice) led to persistent DA. It is interesting to note that nonaspirin nonsteroidal antiinflammatory drugs such as indomethacin or ibuprofen increase rather than decrease platelet-mediated thrombosis in both mice and humans,[22–24] and indomethacin actually promotes platelet accumulation after endothelial injury.[21] Lower platelet counts have been reported to be associated with a higher failure rate of indomethacin-induced PDA closure in human newborns.[25] In a retrospective, multivariate analysis of 123 premature infants born at 24 to 30 weeks' gestation, thrombocytopenia was an independent predictor of PDA with hemodynamic significance (odds ratio: 13.1; $P < .0001$).[21] Thus, platelets may be crucial for DA closure by promoting thrombotic sealing of the constricted DA and luminal remodeling (Fig 2). Similarly, infection-associated inflammatory mediators such as tumor necrosis factor α (TNF-α), are associated with late patency of the DA; prostaglandins and reactive oxygen intermediates may be inducible by TNF-α.[26] Likewise, a temporally related infection increases the odds for failure of DA closure.[26] It is possible that other proinflammatory cytokines affect platelet function and, thus, inhibit thrombotic sealing of the constricted DA.[21]

Understanding the mechanism of functional closure of the DA is important not only for the preterm infant but also for patency manipulation in the newborn with ductal-dependent congenital heart disease. The recent data on separate channels and the potentially crucial role of platelets in ductal closure introduce new options for pharmacologic intervention. Rare syndromic forms of PDA, such as the *TFAP2B* mutations in Char syndrome, have been discussed elsewhere.[27]

Mechanisms Underlying the Patency of the DA in Preterm Infants

In preterm infants, the sensitivity for oxygen is reduced (see the discussion above), but in addition, the sensitivity to PGE_2, nitric oxide (NO), and perhaps endothelin 1 is increased.[7] PGE_2 acts

through G-protein–coupled receptors that activate adenyl cyclase and produce cyclic adenosine monophosphate (cAMP) to relax the vascular smooth muscle layers. cAMP concentrations also depend on phosphodiesterase-mediated degradation. Likewise, NO activates guanyl cyclase to produce cyclic guanosine monophosphate (cGMP), which is degraded by a different phosphodiesterase isoform. In fetal sheep there is a developmental increase in phosphodiesterase activity such that the more immature animal has less ability to degrade cAMP or cGMP and, thus, more sensitivity to PGE_2 and NO.[28] This developmental regulation of vascular tone is specific to the ductus; there is no change in phosphodiesterase expression with advancing gestation in the fetal aorta.[28] Administration of cortisol to immature fetal lambs in utero will result in a ductus that responds to oxygen and prostaglandin inhibition similar to that in a mature fetus,[29] which explains the decreased incidence of a PDA in preterm humans who are born to mothers who received antenatal corticosteroids.[7,30]

In summary, the mechanisms underlying functional DA closure depend on gestational maturity. The term DA will react to oxygen and decreased concentration of circulating vasodilators by contraction; these sensing mechanisms are reduced in the preterm infant; thus, anatomic closure may not occur. The intriguing role of platelets in the closure of the DA of preterm and term infants should be explored in further experimental and prospective clinical studies.

CRITICAL ASSESSMENTS

Risk Factors and Comorbidities Associated With Patency of the DA

A ductal left-to-right shunt will cause increased pulmonary blood flow. In the setting of preterm respiratory distress with low plasma oncotic pressure and increased capillary permeability, a PDA can result in interstitial and alveolar pulmonary edema and decreased lung compliance, which, in turn, will lead to higher ventilator settings, prolonged ventilation with potentially high oxygen load,[31] and probably to BPD/CLD. In ELBW (BW $<$ 1000 g) and VLBW (BW $<$ 1500 g) infants, lung injury is often combined with myocardial dysfunction due to left-sided volume overload that, together with a ductal steal phenomenon, will worsen systemic perfusion. Therefore, preterm infants born at $<$1500 g are susceptible to hypoperfusion of vital organs and resultant additional comorbidities such as IVH, periventricular leukomalacia, NEC, and (pre)renal failure. However, although a PDA is definitely associated with these morbidities, its causal role is not clear.[32] A persistently patent DA was shown to be a risk factor for increased mortality rate in a single-center, retrospective study.[33]

Chronic Lung Disease

PDA has been shown to be a risk factor for CLD after risk adjustment in a population-based study[34] and a study performed through the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Network.[35] Preterm baboons exposed to a PDA for 14 days have arrested alveolar development, which is a characteristic of the "new" BPD.[32,36] However, prophylactic PDA ligation within 24 hours of life did not decrease BPD rates.[37]

Neurologic Morbidities

Because IVH typically occurs within the first few days of life, only trials that examine PDA prophylaxis can assess this relationship.[32,38] The prophylactic surgical-ligation trial did not reveal a significant difference in IVH (although it was not powered to do so). In contrast, prophylactic indomethacin reduces IVH (trial-pooled relative risk: 0.66 [95% confidence interval: 0.53–0.82])[37,39,40] and might improve long-term neurologic outcome in boys born at (600–1250 g)[41] (see "Neurologic Outcome"). The effect of PDA on periventricular leukomalacia is unknown.

Necrotizing Enterocolitis

Preterm infants with PDA have decreased intestinal and renal blood flow and blood-flow velocity on ultrasound compared with gestational age–matched infants without PDA,[42] and these values "normalize" after ductal closure. Results of a systematic review of PDA treatment trials that delayed therapy in 1 group for at least 6 days suggested that the incidence of NEC is decreased by early treatment in infants born at $<$1000 g.[32,43] Likewise, the aforementioned trial of prophylactic ligation in the first 24 hours of life significantly reduced NEC.[37]

TREATMENT OF PDA IN THE PRETERM INFANT

When Is a PDA Hemodynamically Significant?

Echocardiography and Cerebral Doppler Sonography

There have been no stringent clinical or sonographic criteria on the need for PDA closure to date. Echocardiographically, a left atrium–to–aortic root diameter ratio of $\geq$1.4 in the parasternal long-axis view, a DA diameter of $\geq$1.4 mm/kg body weight, left ventricular enlargement, and holodiastolic flow reversal in the descending aorta indicate a significant PDA shunt.[44] Pulse-wave Doppler interrogation of the main pulmonary artery in neonates with a hemodynamically significant (hs) DA demonstrates turbulent systolic and diastolic flow[45] and abnormally high antegrade diastolic flow ($\geq$0.5 m/second).[46] Additional echocardiographic markers that indicate a hemodynamically significant PDA

shunt are reviewed elsewhere.[45,46] In accordance with the holodiastolic aortic flow reversal, some neonatologists consider a resistance index of ≥0.9 on cerebral Doppler examination of the anterior cerebral artery a sign of significant ductal shunting with adverse cerebral steal effect. Certainly, if the diameter of the PDA is as large as or even larger than the main pulmonary artery on the second day of life (DOL), then early pharmacologic or surgical treatment should be strongly considered. However, echocardiography alone at 48 hours cannot identify infants with a PDA who go on to develop severe IVH and/or die,[47] which thereby underlines the need for further clinical and biochemical criteria for risk stratification.

B-Type Natriuretic Peptide, N-Terminal-pro-BNP, and Cardiac Troponin T: Biomarkers for PDA Risk Stratification and Intervention?

A growing body of evidence suggest that elevated plasma B-type natriuretic peptide (BNP) or NT-pro-BNP levels, now more frequently used as biomarkers for heart failure[48] and congenital heart disease[49] in infants and children, may indicate a "symptomatic" PDA and guide its treatment.[50–54] In small series of preterm infants born at <28 weeks'[55] or 25 to 34 weeks'[53] gestation, plasma BNP correlated with magnitudes of the ductal shunt (ie, ductal size,[55] left atrium–to–aortic root ratio,[53,55] and diastolic flow velocity of the left pulmonary artery[53]).

In neonates of <28 weeks' gestational age, BNP levels of >550 pg/mL on the second DOL were suggested to predict PDA intervention (sensitivity: 83%; specificity: 86%); the indication for intervention in this study was based on the following combined criteria: need for ventilatory support, narrowest ductal diameter of >2 mm, and ductal left-to-right shunt.[55] In neonates born at 25 to 34 weeks' gestation, the best cutoff BNP concentrations on DOL 3 for the diagnosis of "symptomatic PDA" was determined to be 1110 pg/mL (sensitivity: 100%; specificity: 95.3%)[53]; the indication for intervention in this study was based on 2 of 5 clinical criteria plus evidence of a large PDA with left-to-right flow according to color Doppler echocardiography.[53] Similarly, plasma NT-pro-BNP levels obtained from infants born at <33 to 34 weeks' gestation were a good indicator of hemodynamically significant PDA at a suggested cutoff NT-pro-BNP concentration of 10 180 pg/mL on DOL 2 (sensitivity: 100%; specificity: 91%)[56] and 11 395 pg/mL on DOL 3 (sensitivity: 100%; specificity: 95%).[57] It is interesting to note that BNP concentrations decrease not only with age but also during the course of indomethacin therapy for PDA.[53,54] BNP-guided therapy (ie, no indomethacin administration if the BNP level is <100 pg/mL 12 or 24 hours after the first dose) reduced the number of indomethacin doses during the first course of treatment[54] and thereby may reduce comorbidities associated with indomethacin use. It is also interesting to note that plasma NT-pro-BNP and cardiac troponin T (cTnT) levels are higher in preterm infants (VLBW or <32 weeks' gestation) with a PDA who subsequently develop IVH grade III/IV or death compared with those with a PDA and without complications.[47] Nevertheless, in any neonate with suspected or confirmed significant PDA, it is the combination of frequent clinical evaluations, comprehensive echocardiographic studies, and perhaps biomarkers such as BNP, NT-pro-BNP, or cTNT that should guide timely and individualized decisions on the best treatment.

Pharmacologic Ductus Closure With Cyclooxygenase Inhibitors

Nonselective cyclooxygenase (COX) inhibitors such as indomethacin or ibuprofen inhibit prostaglandin synthesis, first shown in 1976.[58,59] The efficacy of COX inhibitors depends on gestational age. COX inhibitors are less effective in severely preterm infants,[58,59] a fact often attributed to inadequate contraction of the immature DASMC but recently suggested to be a result of failure of intimal cushion formation; the latter process involves NO-mediated fibronectin synthesis[60,61] and chronic activation of the prostaglandin receptor EP4 that promotes hyaluronic acid production.[62,63] Hyaluronic acid is an extracellular matrix factor that the DASMC use to migrate inward, so blockade of prostaglandins may prevent intimal cushion formation and, thus, prevent effective closure in the most immature infants.[62] In fact, COX-1/2 knockout mice have a persistent PDA,[64] and women who take indomethacin prenatally as tocolysis for preterm labor are more likely to have an infant with a PDA.[65] Counterintuitively, COX inhibitors are much less if at all effective in term (versus preterm) newborns with a PDA.[66,67]

Most of the randomized, controlled trials (RCTs) from the 1980s evaluated 2 different treatment strategies for the closure of the DA[68]:

- prophylactic treatment, to be started in the first 24 hours of life; and
- symptomatic treatment when PDA and its shunt volume have been found to be hemodynamically relevant according to echocardiography, typically between 2 and 7 days after birth.

However, given the nature of neonatology as an ever-evolving discipline that deals with declining gestational age at birth, better survival rates, and changing practices, the above-listed strategies may not apply to today's most premature infants. Because 100% oxygen is not more effective than room air[69] and most likely harmful in near-term newborn resuscitation (higher mortality rate in 2 meta-analyses,[70,71] including a small sub-

group analysis in preterm infants),[71] more and more centers now use room air as the initial gas in the delivery room.[72,73] Oxygen concentrations as low as 30% (vs 90%) also seem to be beneficial in the resuscitation of very premature infants born at 24 to 28 weeks' gestation by reducing oxidative stress and the risk of BPD.[74] Moreover, the results of recent studies suggest that the oxygen load for VLBW infants in the NICU is underestimated[31] and that long-accepted targets of oxygen saturations for preterm infants in their first weeks of life might be too high.[75–77] It is unclear whether "tailored" oxygen resuscitation and intensive care may increase or decrease the incidence of hsPDA in VLBW infants. Two decades ago, it was demonstrated that reactive oxygen metabolites relax the lamb DA by stimulating prostaglandin production,[78] whereas the results of more recent work suggested that immaturity of mitochondrial reactive oxygen species generation is associated with reduced and delayed oxygen-mediated ductal constriction.[15] Antenatal steroids are now given to almost 90% of eligible preterm infants. Prophylactic endotracheal surfactant administration and early extubation to continuous positive airway pressure are frequently performed. Today, the minority of VLBW infants still remain intubated past DOL 3, and only a subgroup remains with severe respiratory distress for which one would question treating a PDA. Hence, the results of previous trials (discussed below) need to be interpreted carefully, and those who perform future studies need to take into account these management changes.

CURRENT EVIDENCE AND AREAS OF UNCERTAINTY

Neurologic Outcome

Although indomethacin is known to cause profound reduction in cerebral perfusion, an RCT showed that low-dose prophylactic indomethacin reduces the incidence of IVH identified by cranial ultrasound.[79] Proposed mechanisms include maturation of the cerebral vascular basement membrane, improvements in cerebral vascular autoregulation, and anti-inflammatory effects.[80,81] Ballabh et al[82] (2007) demonstrated that prenatal COX-2 inhibition decreased angiopoietin 2 and VEGF levels, as well as germinal matrix endothelial cell proliferation, and lowered the incidence of germinal matric hemorrhage (GMH = IVH grade I) in pups of pregnant rabbits. The authors speculated that by suppressing germinal matrix angiogenesis, prenatal inhibition of COX-2 (celecoxib) or VEGF receptor 2 (ZD6474) may be able to reduce both the incidence and severity of GMH in susceptible premature infants.[82] However, there are currently no human data to support this hypothesis. A larger RCT, the Trial of Indomethacin Prophylaxis in Preterms (TIPP),[38] confirmed a reduction in IVH with indomethacin therapy but failed to show a benefit in its combined primary outcome of improved survival and neurologic functional status (ie, composite of death, cerebral palsy, cognitive delay, deafness, and blindness at a corrected age of 18 months). Subsequently, authors of a Cochrane meta-analysis[39] concluded that "there is no evidence to suggest either benefit or harm in longer term outcomes including neurodevelopment" and did not recommend prophylactic use of indomethacin. However, others criticized that the primary outcome's anticipated effect size (≥20%) in the TIPP trial was too large; a smaller effect size (<3%) would have been more appropriate on the basis of the incidence of IVH in that particular population and its association with neurodevelopmental outcome.[83] Ment et al[41] reevaluated their original trial data from 1994 and found that indomethacin-treated boys had significantly less hemorrhage and higher scores in 1 neurocognitive test than girls, which suggests that the effect of indomethacin was gender specific. In the TIPP study, a negative effect of indomethacin in girls was a more prominent observation than a positive effect in boys.[84] Longer courses of indomethacin have been associated with less moderate-to-severe white matter injury on brain MRI.[85]

Pulmonary Outcome

Controversy exists as to whether ibuprofen treatment[86] or indomethacin prophylaxis (see TIPP trial results[87]) may increase the incidence of BPD/CLD in ELBW infants without PDA. So far, treatments for PDA closure have not resulted in a reduction of BPD rates.[88,89] The uncertainty about the benefits and risks of the use of COX inhibitors can only be resolved by performing an RCT that includes a placebo group in which PDA treatment is offered to infants in very limited circumstances only.[88] Also unclear is the optimal dosing and duration of COX inhibition. Authors of a 2007 Cochrane systematic review noted that a prolonged indomethacin course did not significantly improve the frequency of PDA treatment failure, CLD, IVH, or mortality.[90] A reduction in transient renal impairment was seen but countered by an increased risk for NEC: "There is a paucity of data on optimal dosing and duration of indomethacin therapy for the treatment of PDA, in particular for ELBW premature infants. It is likely that a single standard indomethacin regimen is not the ideal for every premature infant. Therefore, individual patient response should be considered and evaluated, particularly in ELBW infants. . . ."[90]

ADVERSE EFFECTS OF COX INHIBITORS

Renal failure/oliguria seems to be more frequent with indomethacin than ibuprofen (19% vs 7%; $P < .05$), although it is reversible.[91] Nonetheless, these alterations in fluid status may

affect ventilator management and supplemental oxygen use and increase the risk of CLD in treated ELBW infants without PDA.[87] Indomethacin in conjunction with postnatal corticosteroids may increase the risk of intestinal perforation.[92,93] It has been reported that prophylactic ibuprofen is associated with severe pulmonary hypertension; an RCT was halted early because of this concern ($n = 135$).[94,95] However, the association between prophylactic ibuprofen and pulmonary hypertension was not noted in a larger clinical case series of 227 preterm newborns.[96]

IBUPROFEN VERSUS INDOMETHACIN

The rate of the primary ductal closure is similar for both drugs, that is, 60% to 80% in mixed populations of premature infants (eg, 66%–70%, gestational age 24–32 weeks[91]), with decreasing efficacy and higher recurrence rates in extremely premature infants. After primary treatment failure in infants born at <1000 g or < 28 weeks' gestation, successful PDA closure after a second course of either indomethacin or ibuprofen was found in 44%[97] and 40%,[5] respectively. The lowest spontaneous or drug-induced closure rates (primary and secondary) were found in the most immature infants (ie, those born at <26 weeks' gestation).[4,20,91]

Ibuprofen does not seem to be as potent a vasoconstrictor on the mesenteric, renal, and cerebral vascular beds when compared with indomethacin. In the largest prospective head-to-head study to date ($N = 74$ per group), there were no statistically significant differences in the adverse events of hemorrhage, CLD/BPD, and NEC between the 2 drugs; however, NEC was diagnosed twice as often with indomethacin treatment (8 vs 4; $P = .37$), whereas BPD occurred more frequently with ibuprofen (39 vs 29; $P = .1$) (nonsignificant trends).[91] As discussed above, prophylactic indomethacin decreases the rate of IVH,[38] although the underlying mechanisms are poorly understood. At present, the costs for treatment doses of ibuprofen are similar to those for indomethacin. Indomethacin and ibuprofen are multiple times more expensive in the United States than in Canada, Europe, and Australia.[98]

PROPHYLAXIS VERSUS SYMPTOMATIC TREATMENT

Prophylactic trials with COX inhibitors have consistently revealed a decreased need for surgical ligation, decreased incidence of pulmonary hemorrhage, and decreased incidence of serious IVH.[32] However, there is a high rate of spontaneous DA closure (60%),[99] which suggests that many infants are unnecessarily exposed to drugs with potentially serious adverse effects. Absence of major lung disease predicts spontaneous closure,[4] which may be explained by the higher pulmonary vascular resistance seen with major lung disease creating a higher-pressure transmission to the DA, which makes the constrictive mechanisms less effective.

On the basis of the current data, there is no role for ibuprofen prophylaxis in VLBW infants who are at risk for PDA.[86,99] A reduction in serious IVH with prophylactic use may justify this practice in selected high-risk patients, although the criteria are subject to debate. A recent pilot study[100] examined a new treatment strategy, based on the degree of ductal constriction by echocardiogram after the first dose of prophylactic indomethacin, that may allow for less exposure to COX inhibitors.[100] At the time when a second dose of indomethacin was due, the patients were randomly assigned to either further treatment only if the ductus was >1.6 mm (echocardiogram-directed group) or completion of the usual 3-day course of indomethacin regardless of ductal size (standard-therapy group). The authors found that the incidence of PDA closure, reopening, and ligation was not different between the 2 groups, but indomethacin exposure was significantly less in the echocardiogram-directed group (for BNP-guided PDA therapy, see ref 54). However, although not powered to assess neurologic outcomes, there was a trend toward a higher incidence of IVH in the echocardiogram-directed group.[100]

On the basis of the current clinical data, there are no benefits and possibly harm with both early use of ibuprofen (prophylaxis, treatment) in the first 24 hours of life (eg, pulmonary hypertension,[94,95,99] but see ref[96]) and prolonged courses of indomethacin for PDA treatment (eg, NEC).[90]

SURGICAL LIGATION OF THE DA

Surgical ligation is performed for PDA closure when treatment with COX inhibitors is contraindicated or fails. Beyond the fourth week of life, the success rate of pharmacologic treatment decreases rapidly as the ductal tissue matures and becomes less regulated by prostaglandins. There are low morbidity and mortality rates in experienced centers; however, adverse events are reported: recurrent laryngeal nerve damage, chylothorax (thoracic duct injury), pneumothorax, a period of left ventricular dysfunction immediately after ligation, and concerns over the development of scoliosis.[101–105] Additional data from the TIPP study have indicated that infants whose DA is ligated may be at greater risk for poor developmental outcome compared with infants treated medically,[106] but the current data are inconclusive as to whether the neonates treated surgically were particularly sick or whether PDA ligation itself con-

tributed to adverse neurodevelopment. A preterm baboon study that compared surgical ligation at DOL 6 versus no PDA treatment and evaluated brain histology at DOL 14 revealed small differences in brain weight favoring ligation with no evidence of overt injury in either group.[107] A retrospective study of 446 preterm infants revealed that surgical ligation was associated with CLD on regression analysis but not with neurodevelopmental impairment.[108] As mentioned above, a trial of prophylactic ligation in the first 24 hours of life did significantly reduce the incidence of NEC.[37] It is unfortunate that there have been no recent prospective RCTs comparing outcomes after ligation with outcomes after either placebo or medical treatment.[37,102,109,110] Therefore, the risks and benefits of surgical ligation in PDA compared with contemporary alternatives are unknown.[89] Again, the only way to resolve the benefits and risks to the use of either COX inhibitors or primary surgical ligation is by performing an RCT that includes a placebo group in which PDA treatment is offered to infants in very limited circumstances (eg, pulmonary hemorrhage, persistent cardiovascular instability, pulmonary edema necessitating high ventilator settings, severe ductal steal in the cerebral or intestinal circulation).

CONSERVATIVE TREATMENT OF PDA

Vanhaesebrouck et al[111] prospectively studied 30 neonates ≤30 weeks' gestational age. All infants with PDA were treated following a standard protocol as soon as a diagnosis of a hemodynamically important PDA (DA diameter ≥ 1.4 mm according to color Doppler) was made. Initially, conservative treatment was performed and consisted of fluid restriction (maximum: 130 mL/kg per day beyond day 3) and adjustment of ventilation (lowering inspiratory time and giving higher positive end-expiratory pressure). It was planned that infants with a PDA who did not show clinical improvement and/or deterioration, with continuing need for ventilatory support, would undergo ductal ligation. No medication for prophylactic or therapeutic treatment of PDA was given. Ten neonates developed a clinically important PDA. After conservative treatment the duct closed in all neonates, and none of them required ductal ligation or medical treatment. The rates of major complications were no higher than those reported in the literature. Hence, for a selected subgroup of VLBW preterm infants, conservative treatment consisting of fluid restriction and ventilator adjustment may be an alternative treatment, although its efficiency should be studied in larger trials.

CAN WE DEFINE OBJECTIVE AND RELIABLE CRITERIA FOR THE PREDICTION OF PDA COMPLICATIONS AND THE NEED FOR TIMELY INTERVENTION?

Sehgal and McNamara[45,112] recently suggested a staging system for PDA based on clinical and echocardiographic criteria. The aforementioned echocardiographic criteria and biomarkers such as BNP, NT-pro-BNP, and cTNT[47] may allow the creation of a clinical algorithm for identifying at-risk infants and determining indication, timing, and best mode of therapy. A future RCT on ductus intervention should investigate whether an algorithm based on predefined clinical, echocardiographic, and biochemical criteria versus an algorithm that excludes biomarkers decreases the rate of "rescue PDA ligation" and adverse outcomes such as IVH grade III + IV, BPD, NEC, and death.

CONCLUSIONS

In his article on the natural history of persistent DA, Campbell astutely predicted in 1968 that "as the years pass, more physicians will be advising operation for a persistent ductus arteriosus with no personal experience of its natural course without operation."[113] This statement seems to likewise be true for COX inhibition; it is unfortunate that today we are in that very situation.[89] Closure of the preterm PDA either by COX inhibition or surgical ligation is currently justified only by the reduction in severe IVH with prophylactic administration of indomethacin and, potentially, the reduction in NEC with prophylactic surgical ligation; however, given the risks of either therapy and the high rate of spontaneous closure, these prophylactic strategies cannot be recommended for all preterm newborns. Treatment strategies for the symptomatic PDA may be justified for select patients.

ACKNOWLEDGMENT

We thank Dr Bernard Thébaud, University of Alberta, for critically reading the manuscript.

REFERENCES

1. Skinner J. Diagnosis of patent ductus arteriosus. *Semin Neonatol*. 2001;6(1):49–61
2. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002;39(12):1890–1900
3. Investigators of the Vermont-Oxford Trials Network Database Project. The Vermont-Oxford Trials Network: very low birth weight outcomes for 1990. *Pediatrics*. 1993;91(3):540–545
4. Koch J, Hensley G, Roy L, Brown S, Ramaciotti C, Rosenfeld CR. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. *Pediatrics*. 2006;117(4):1113–1121
5. Richards J, Johnson A, Fox G, Campbell M. A second course of ibuprofen is effective in the closure of a clinically significant PDA in ELBW infants. *Pediatrics*. 2009;124(2).

Available at: www.pediatrics.org/cgi/content/full/124/2/e287

6. Herrman K, Bose C, Lewis K, Laughon M. Spontaneous closure of the patent ductus arteriosus in very low birth weight infants following discharge from the neonatal unit. *Arch Dis Child Fetal Neonatal Ed.* 2009;94(1):F48–F50
7. Clyman RI. Ibuprofen and patent ductus arteriosus. *N Engl J Med.* 2000;343(10):728–730
8. Schneider DJ, Moore JW. Patent ductus arteriosus. *Circulation.* 2006;114(17):1873–1882
9. 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(1):19–29
10. Weir EK, Lopez-Barneo J, Buckler KJ, Archer SL. Acute oxygen-sensing mechanisms. *N Engl J Med.* 2005;353(19):2042–2055
11. Keck M, Resnik E, Linden B, et al. Oxygen increases ductus arteriosus smooth muscle cytosolic calcium via release of calcium from inositol triphosphate-sensitive stores. *Am J Physiol Lung Cell Mol Physiol.* 2005;288(5):L917–L923
12. Weir EK, Obreztchikova M, Vargese A, Cabrera JA, Peterson DA, Hong Z. Mechanisms of oxygen sensing: a key to therapy of pulmonary hypertension and patent ductus arteriosus. *Br J Pharmacol.* 2008;155(3):300–307
13. Thébaud B, Michelakis ED, Wu XC, et al. Oxygen-sensitive Kv channel gene transfer confers oxygen responsiveness to preterm rabbit and remodeled human ductus arteriosus: implications for infants with patent ductus arteriosus. *Circulation.* 2004;110(11):1372–1379
14. Thébaud B, Wu XC, Kajimoto H, et al. Developmental absence of the O_2 sensitivity of L-type calcium channels in preterm ductus arteriosus smooth muscle cells impairs O_2 constriction contributing to patent ductus arteriosus. *Pediatr Res.* 2008;63(2):176–181
15. Kajimoto H, Hashimoto K, Bonnet SN, et al. Oxygen activates the Rho/Rho-kinase pathway and induces RhoB and ROCK-1 expression in human and rabbit ductus arteriosus by increasing mitochondria-derived reactive oxygen species: a newly recognized mechanism for sustaining ductal constriction. *Circulation.* 2007;115(13):1777–1788
16. Hong Z, Hong F, Olschewski A, et al. Role of store-operated calcium channels and calcium sensitization in normoxic contraction of the ductus arteriosus. *Circulation.* 2006;114(13):1372–1379
17. Coceani F, Kelsey L. Endothelin-1 release from lamb ductus arteriosus: relevance to postnatal closure of the vessel. *Can J Physiol Pharmacol.* 1991;69(2):218–221
18. Fineman JR, Takahashi Y, Roman C, Clyman RI. Endothelin-receptor blockade does not alter closure of the ductus arteriosus. *Am J Physiol.* 1998;275(5 pt 2):H1620–H1626
19. Michelakis E, Rebeyka I, Bateson J, Olley P, Puttagunta L, Archer S. Voltage-gated potassium channels in human ductus arteriosus. *Lancet.* 2000;356(9224):134–137
20. Weiss H, Cooper B, Brook M, Schlueter M, Clyman R. Factors determining reopening of the ductus arteriosus after successful clinical closure with indomethacin. *J Pediatr.* 1995;127(3):466–471
21. Echtler K, Stark K, Lorenz M, et al. Platelets contribute to postnatal occlusion of the ductus arteriosus. *Nat Med.* 2010;16(1):75–82
22. Struthmann L, Hellwig N, Pircher J, et al. Prothrombotic effects of diclofenac on arteriolar platelet activation and thrombosis in vivo. *J Thromb Haemost.* 2009;7(10):1727–1735
23. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs: an update for clinicians—a scientific statement from the American Heart Association. *Circulation.* 2007;115(12):1634–1642
24. Sheffield MJ, Schmutz N, Lambert DK, Henry E, Christensen RD. Ibuprofen lysine administration to neonates with a patent ductus arteriosus: effect on platelet plug formation assessed by in vivo and in vitro measurements. *J Perinatol.* 2009;29(1):39–43
25. Boo NY, Mohd-Amin I, Bilkis AA, Yong-Junina F. Predictors of failed closure of patent ductus arteriosus with indomethacin. *Singapore Med J.* 2006;47(9):763–768
26. Gonzalez A, Sosenko IR, Chandar J, Hummler H, Claure N, Bancalari E. Influence of infection on patent ductus arteriosus and chronic lung disease in premature infants weighing 1000 grams or less. *J Pediatr.* 1996;128(4):470–478
27. Bökenkamp R, Deruiter MC, van Munsteren C, Gittenberger-de Groot AC. Insights into the pathogenesis and genetic background of patency of the ductus arteriosus. *Neonatology.* 2009;98(1):6–17
28. Liu H, Manganiello V, Waleh N, Clyman RI. Expression, activity, and function of phosphodiesterases in the mature and immature ductus arteriosus. *Pediatr Res.* 2008;64(5):477–481
29. Clyman RI, Mauray F, Roman C, et al. Effects of antenatal glucocorticoid administration on ductus arteriosus of preterm lambs. *Am J Physiol.* 1981;241(3):H415–H420
30. Clyman RI, Ballard PL, Sniderman S, et al. Prenatal administration of betamethasone for prevention of patient ductus arteriosus. *J Pediatr.* 1981;98(1):123–126
31. De Felice C, Bechelli S, Tonni G, Hansmann G. Systematic underestimation of oxygen delivery in ventilated preterm infants. *Neonatology.* 2009;98(1):18–22
32. Clyman RI, Chorne N. Patent ductus arteriosus: evidence for and against treatment. *J Pediatr.* 2007;150(3):216–219
33. Noori S, McCoy M, Friedlich P, et al. Failure of ductus arteriosus closure is associated with increased mortality in preterm infants. *Pediatrics.* 2009;123(1). Available at: www.pediatrics.org/cgi/content/full/123/1/e138
34. Marshall DD, Kotelchuck M, Young TE, Bose CL, Kruyer L, O'Shea TM. Risk factors for chronic lung disease in the surfactant era: a North Carolina population-based study of very low birth weight infants. North Carolina Neonatologists Association. *Pediatrics.* 1999;104(6):1345–1350
35. Oh W, Poindexter BB, Perritt R, et al. Association between fluid intake and weight loss during the first ten days of life and risk of bronchopulmonary dysplasia in extremely low birth weight infants. *J Pediatr.* 2005;147(6):786–790
36. Coalson JJ, Winter VT, Siler-Khodr T, Yoder BA. Neonatal chronic lung disease in extremely immature baboons. *Am J Respir Crit Care Med.* 1999;160(4):1333–1346
37. Cassady G, Crouse DT, Kirklin JW, et al. A randomized, controlled trial of very early prophylactic ligation of the ductus arteriosus in babies who weighed 1000 g or less at birth. *N Engl J Med.* 1989;320(23):1511–1516
38. 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(26):1966–1972
39. Fowlie PW, Davis PG. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. *Cochrane Database Syst Rev.* 2002;(3):CD000174
40. Fowlie PW, Davis PG. Prophylactic indomethacin for preterm infants: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed.* 2003;88(6):F464–F466
41. Ment LR, Vohr BR, Makuch RW, et al. Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. *J Pediatr.* 2004;145(6):832–834

42. Shimada S, Kasai T, Hoshi A, Murata A, Chida S. Cardiocirculatory effects of patent ductus arteriosus in extremely low-birth-weight infants with respiratory distress syndrome. *Pediatr Int.* 2003;45(3):255–262
43. Clyman RI. Recommendations for the postnatal use of indomethacin: an analysis of four separate treatment strategies. *J Pediatr.* 1996;128(5 pt 1):601–607
44. Tacy TA. Abnormalities of the ductus arteriosus and pulmonary arteries. In: Lai WL, Mertens LL, Cohen MS, Geva T, eds. *Echocardiography in Pediatric and Congenital Heart Disease*. West Sussex, United Kingdom: Wiley-Blackwell; 2009:283–296
45. Sehgal A, McNamara PJ. Does echocardiography facilitate determination of hemodynamic significance attributable to the ductus arteriosus? *Eur J Pediatr.* 2009;168(8):907–914
46. El Hajjar M, Vaksmann G, Rakza T, Kongolo G, Storme L. Severity of the ductal shunt: a comparison of different markers. *Arch Dis Child Fetal Neonatal Ed.* 2005;90(5):F419–F422
47. El-Khuffash A, Barry D, Walsh K, Davis PG, Molloy EJ. Biochemical markers may identify preterm infants with a patent ductus arteriosus at high risk of death or severe intraventricular haemorrhage. *Arch Dis Child Fetal Neonatal Ed.* 2008;93(6):F407–F412
48. Ohuchi H, Takasugi H, Ohashi H, et al. Stratification of pediatric heart failure on the basis of neurohormonal and cardiac autonomic nervous activities in patients with congenital heart disease. *Circulation.* 2003;108(19):2368–2376
49. Law YM, Hoyer AW, Reller MD, Silberbach M. Accuracy of plasma B-type natriuretic peptide to diagnose significant cardiovascular disease in children: the Better Not Pout Children! study. *J Am Coll Cardiol.* 2009;54(15):1467–1475
50. Holmström H, Hall C, Thaulow E. Plasma levels of natriuretic peptides and hemodynamic assessment of patent ductus arteriosus in preterm infants. *Acta Paediatr.* 2001;90(2):184–191
51. Sanjeev S, Pettersen M, Lua J, Thomas R, Shankaran S, L'Ecuyer T. Role of plasma B-type natriuretic peptide in screening for hemodynamically significant patent ductus arteriosus in preterm neonates. *J Perinatol.* 2005;25(11):709–713
52. Flynn PA, da Graca RL, Auld PA, Nesin M, Kleinman CS. The use of a bedside assay for plasma B-type natriuretic peptide as a biomarker in the management of patent ductus arteriosus in premature neonates. *J Pediatr.* 2005;147(1):38–42
53. Choi BM, Lee KH, Eun BL, et al. Utility of rapid B-type natriuretic peptide assay for diagnosis of symptomatic patent ductus arteriosus in preterm infants. *Pediatrics.* 2005;115(3). Available at: www.pediatrics.org/cgi/content/full/115/3/e255
54. Attridge JT, Kaufman DA, Lim DS. B-type natriuretic peptide concentrations to guide treatment of patent ductus arteriosus. *Arch Dis Child Fetal Neonatal Ed.* 2009;94(3):F178–F182
55. Czernik C, Lemmer J, Metze B, Koehne PS, Mueller C, Obladen M. B-type natriuretic peptide to predict ductus intervention in infants <28 weeks. *Pediatr Res.* 2008;64(3):286–290
56. Nuntnarumit P, Khositseth A, Thanomsingh P. N-terminal probrain natriuretic peptide and patent ductus arteriosus in preterm infants. *J Perinatol.* 2009;29(2):137–142
57. Farombi-Oghuvbu I, Matthews T, Mayne PD, Guerin H, Corcoran JD. N-terminal pro-B-type natriuretic peptide: a measure of significant patent ductus arteriosus. *Arch Dis Child Fetal Neonatal Ed.* 2008;93(4):F257–F260
58. Heymann MA, Rudolph AM, Silverman NH. Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. *N Engl J Med.* 1976;295(10):530–533
59. Friedman WF, Hirschklau MJ, Printz MP, Pitlick PT, Kirkpatrick SE. Pharmacologic closure of patent ductus arteriosus in the premature infant. *N Engl J Med.* 1976;295(10):526–529
60. Mason CA, Bigras JL, O'Blenes SB, et al. Gene transfer in utero biologically engineers a patent ductus arteriosus in lambs by arresting fibronectin-dependent neointimal formation. *Nat Med.* 1999;5(2):176–182
61. Mason CA, Chang P, Fallery C, Rabinovitch M. Nitric oxide mediates LC-3-dependent regulation of fibronectin in ductus arteriosus intimal cushion formation. *FASEB J.* 1999;13(11):1423–1434
62. Yokoyama U, Minamisawa S, Quan H, et al. Chronic activation of the prostaglandin receptor EP4 promotes hyaluronan-mediated neointimal formation in the ductus arteriosus. *J Clin Invest.* 2006;116(11):3026–3034
63. Ivey KN, Srivastava D. The paradoxical patent ductus arteriosus. *J Clin Invest.* 2006;116(11):2863–2865
64. 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(3):1059–1064
65. Norton ME, Merrill J, Cooper BA, Kuller JA, Clyman RI. Neonatal complications after the administration of indomethacin for preterm labor. *N Engl J Med.* 1993;329(22):1602–1607
66. McCarthy JS, Zies LG, Gelband H. Age-dependent closure of the patent ductus arteriosus by indomethacin. *Pediatrics.* 1978;62(5):706–712
67. Takami T, Yoda H, Kawakami T, et al. Usefulness of indomethacin for patent ductus arteriosus in full-term infants. *Pediatr Cardiol.* 2007;28(1):46–50
68. Knight DB. The treatment of patent ductus arteriosus in preterm infants: a review and overview of randomized trials. *Semin Neonatol.* 2001;6(1):63–73
69. Saugstad OD, Rootwelt T, Aalen O. Resuscitation of asphyxiated newborn infants with room air or oxygen: an international controlled trial: the Resair 2 study. *Pediatrics.* 1998;102(1). Available at: www.pediatrics.org/cgi/content/full/102/1/e1
70. Davis PG, Tan A, O'Donnell CP, Schulze A. Resuscitation of newborn infants with 100% oxygen or air: a systematic review and meta-analysis. *Lancet.* 2004;364(9442):1329–1333
71. Saugstad OD, Ramji S, Vento M. Resuscitation of depressed newborn infants with ambient air or pure oxygen: a meta-analysis. *Biol Neonate.* 2005;87(1):27–34
72. O'Donnell CP, Davis PG, Morley CJ. Neonatal resuscitation: review of ventilation equipment and survey of practice in Australia and New Zealand. *J Paediatr Child Health.* 2004;40(4):208–212
73. Hansmann G. Neonatal resuscitation on air: it is time to turn down the oxygen tanks [published correction appears in *Lancet.* 2005;365(9457):386]. *Lancet.* 2004;364(9442):1293–1294
74. Vento M, Moro M, Escrig R, et al. Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease. *Pediatrics.* 2009;124(3). Available at: www.pediatrics.org/cgi/content/full/124/3/e439
75. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. *N Engl J Med.* 2003;349(10):959–967
76. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed.* 2001;84(2):F106–F110

77. Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. *Pediatr Res*. 2001;50(6):712–719
78. Clyman RI, Saugstad OD, Mauray F. Reactive oxygen metabolites relax the lamb ductus arteriosus by stimulating prostaglandin production. *Circ Res*. 1989;64(1):1–8
79. Ment LR, Oh W, Ehrenkranz RA, et al. Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. *Pediatrics*. 1994;93(4):543–550
80. Edwards AD, Wyatt JS, Richardson C, et al. Effects of indomethacin on cerebral haemodynamics in very preterm infants. *Lancet*. 1990;335(8704):1491–1495
81. Ment LR, Stewart WB, Ardito TA, Huang E, Madri JA. Indomethacin promotes germinal matrix microvessel maturation in the newborn beagle pup. *Stroke*. 1992;23(8):1132–1137
82. Ballabh P, Xu H, Hu F, et al. Angiogenic inhibition reduces germinal matrix hemorrhage. *Nat Med*. 2007;13(4):477–485
83. Clyman RI, Saha S, Jobe A, Oh W. Indomethacin prophylaxis for preterm infants: the impact of 2 multicentered randomized, controlled trials on clinical practice. *J Pediatr*. 2007;150(1):46–50.e2
84. Ohlsson A, Roberts RS, Schmidt B, et al. Male/female differences in indomethacin effects in preterm infants. *J Pediatr*. 2005;147(6):860–862
85. Miller SP, Mayer EE, Clyman RI, Glidden DV, Hamrick SE, Barkovich AJ. Prolonged indomethacin exposure is associated with decreased white matter injury detected with magnetic resonance imaging in premature newborns at 24 to 28 weeks' gestation at birth. *Pediatrics*. 2006;117(5):1626–1631
86. Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database Syst Rev*. 2005;(4):CD003481
87. Schmidt B, Roberts RS, Fanaroff A, et al. Indomethacin prophylaxis, patent ductus arteriosus, and the risk of bronchopulmonary dysplasia: further analyses from the Trial of Indomethacin Prophylaxis in Preterms (TIPP). *J Pediatr*. 2006;148(6):730–734
88. Bose CL, Laughon M. Treatment to prevent patency of the ductus arteriosus: beneficial or harmful? *J Pediatr*. 2006;148(6):713–714
89. Bose CL, Laughon MM. Patent ductus arteriosus: lack of evidence for common treatments. *Arch Dis Child Fetal Neonatal Ed*. 2007;92(6):F498–F502
90. Herrera C, Holberton J, Davis P. Prolonged versus short course of indomethacin for the treatment of patent ductus arteriosus in preterm infants. *Cochrane Database Syst Rev*. 2007;(2):CD003480
91. Van Overmeire B, Smets K, Lecoutere D, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. *N Engl J Med*. 2000;343(10):674–681
92. Watterberg KL, Gerdes JS, Cole CH, et al. Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. *Pediatrics*. 2004;114(6):1649–1657
93. Attridge JT, Clark R, Walker MW, Gordon PV. New insights into spontaneous intestinal perforation using a national data set: (1) SIP is associated with early indomethacin exposure. *J Perinatol*. 2006;26(2):93–99
94. Gournay V, Savagner C, Thiriez G, Kuster A, Roze JC. Pulmonary hypertension after ibuprofen prophylaxis in very preterm infants. *Lancet*. 2002;359(9316):1486–1488
95. Gournay V, Roze JC, Kuster A, et al. Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364(9449):1939–1944
96. Mosca F, Bray M, Stucchi I, Fumagalli M. Pulmonary hypertension after ibuprofen prophylaxis in very preterm infants. *Lancet*. 2002;360(9338):1023–1024
97. Keller RL, Clyman RI. Persistent Doppler flow predicts lack of response to multiple courses of indomethacin in premature infants with recurrent patent ductus arteriosus. *Pediatrics*. 2003;112(3 pt 1):583–587
98. Jobe AH. Drug pricing in pediatrics: the egregious example of indomethacin. *Pediatrics*. 2007;119(6):1197–1198
99. Shah SS, Ohlsson A. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database Syst Rev*. 2006;(1):CD004213
100. Carmo KB, Evans N, Paradisis M. Duration of indomethacin treatment of the preterm patent ductus arteriosus as directed by echocardiography. *J Pediatr*. 2009;155(6):819–822.e1
101. Mandhan P, Brown S, Kukkady A, Samarakkody U. Surgical closure of patent ductus arteriosus in preterm low birth weight infants. *Congenit Heart Dis*. 2009;4(1):34–37
102. Malviya M, Ohlsson A, Shah S. Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants. *Cochrane Database Syst Rev*. 2008;(1):CD003951
103. Spanos WC, Brookes JT, Smith MC, Burkhart HM, Bell EF, Smith RJ. Unilateral vocal fold paralysis in premature infants after ligation of patent ductus arteriosus: vascular clip versus suture ligature. *Ann Otol Rhinol Laryngol*. 2009;118(10):750–753
104. Moin F, Kennedy KA, Moya FR. Risk factors predicting vasopressor use after patent ductus arteriosus ligation. *Am J Perinatol*. 2003;20(6):313–320
105. Seghaye MC, Grabitz R, Alzen G, et al. Thoracic sequelae after surgical closure of the patent ductus arteriosus in premature infants. *Acta Paediatr*. 1997;86(2):213–216
106. Kabra NS, Schmidt B, Roberts RS, Doyle LW, Papile L, Fanaroff A. 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(3):229–234, 234.e1
107. Loeliger M, Inder TE, Dalitz PA, et al. Developmental and neuropathological consequences of ductal ligation in the preterm baboon. *Pediatr Res*. 2009;65(2):209–214
108. Chorne N, Leonard C, Piecuch R, Clyman RI. Patent ductus arteriosus and its treatment as risk factors for neonatal and neurodevelopmental morbidity. *Pediatrics*. 2007;119(6):1165–1174
109. Mosalli R, Alfaleh K. Prophylactic surgical ligation of patent ductus arteriosus for prevention of mortality and morbidity in extremely low birth weight infants. *Cochrane Database Syst Rev*. 2008;(1):CD006181
110. Gersony WM, Peckham GJ, Ellison RC, Miettinen OS, Nadas AS. Effects of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. *J Pediatr*. 1983;102(6):895–906
111. Vanhaesebrouck S, Zonnenberg I, Vandervoort P, Bruneel E, Van Hoestenberghe MR, Theyskens C. Conservative treatment for patent ductus arteriosus in the preterm. *Arch Dis Child Fetal Neonatal Ed*. 2007;92(4):F244–F247
112. McNamara PJ, Sehgal A. Towards rational management of the patent ductus arteriosus: the need for disease staging. *Arch Dis Child Fetal Neonatal Ed*. 2007;92(6):F424–F427
113. Campbell M. Natural history of persistent ductus arteriosus. *Br Heart J*. 1968;30(1):4–13