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ORIGINAL ARTICLE

Learning to live with patency of the ductus arteriosus in preterm infants

WE Benitz

Division of Neonatal and Developmental Medicine, Stanford University School of Medicine, Palo Alto, CA, USA

Treatment of persistent patency of the ductus arteriosus in preterm infants remains heterogeneous and controversial. Routine early treatment to induce ductal closure is not beneficial, but the potential criteria for, timing of, methods for and benefits of later ductal closure have not been determined. Management strategies for infants awaiting spontaneous closure or meeting criteria for treatment may be based on pathophysiological considerations but require evaluation in clinical trials. Better diagnostic tools allowing the identification of infants who might benefit from ductal closure, supplemented by data from clinical trials confirming realization of that potential, are urgently needed.
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> The intensity of the conviction that a hypothesis is true has no bearing on whether it is true or not.

This quote by Sir Peter Medawar, in *Advice to a Young Scientist*,[1] was posted as a handwritten note over Dr Sunshine's desk for many years.

Since delayed closure of the ductus arteriosus was first recognized as a common correlate of prematurity over 50 years ago, it has been linked to numerous adverse outcomes, including prolonged ventilation, pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis, impaired renal function, intraventricular hemorrhage (IVH), periventricular leukomalacia, cerebral palsy and death.[2] These have often been attributed to effects of a large left-to-right ductal shunt, resulting in excessive pulmonary perfusion and systemic organ ischemia. Consequently, it was widely believed that interventions that produce earlier ductal closure should be beneficial and therefore are necessary. Despite numerous controlled trials, however, no such beneficial effect has been demonstrated,[2–8] and there is increasing concern about the potential adverse effects of both surgical[9,10] and medical[11,12] treatments. This review will provide a brief overview of options for management of preterm infants with persistent patency of the ductus arteriosus. Because only a few of these interventions have been rigorously evaluated, this summary may better serve as a roadmap for testing the hypotheses that these steps may be beneficial than as a template for patient care.

Correspondence: Dr WE Benitz, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine, 750 Welch Road, Suite 315, Palo Alto, CA 94305, USA.
E-mail: benitzwe@stanford.edu

Closing the ductus

Elimination of ductal shunting and its consequences by surgical ligation or by induction of ductal constriction with cyclooxygenase (COX) inhibitors promised to ameliorate the adverse outcomes associated with ductal patency. However, neither individual randomized controlled trials nor meta-analyses of those trials[2–8] have confirmed this hypothesis. These negative results are consistent whether criteria for inclusion of trials in meta-analysis are permissive[2] or strict.[3–8] Results are the same whether trials are grouped by indication (as prophylaxis, for treatment of asymptomatic, symptomatic or any patent ductus arteriosus (PDA), or for any other indication), treatment (oral, intravenous or any indomethacin or ibuprofen, surgical ligation, or any other), postnatal age at intervention, era in which the trial was conducted (before or after availability of surfactant) or mean gestational age of the enrolled subjects.[2] These interventions are effective for achieving ductal closure. Indomethacin prophylaxis, but not treatment, is associated with a reduced risk of IVH or IVH greater than grade II, but this does not result in better long-term neurodevelopmental outcomes.[13–15] For the most important outcomes, including BPD, necrotizing enterocolitis, neurosensory impairment, death, or the combined outcomes of death or BPD and death or neurosensory impairment, the confidence intervals for odds ratios related to treatment are narrow and include 1 (no effect).[2] It is unlikely that additional trials will alter the conclusion that treatments intended to achieve early closure of the ductus fail to improve these outcomes.

Some early trials suggested that closing the ductus might shorten the duration or reduce the intensity of positive pressure ventilation or oxygen use, but those results have not been reproducible. In the sole trial comparing ligation with

non-intervention, more infants who underwent ligation required ventilation for more than 45 days[16] and more needed supplemental oxygen or continued mechanical ventilation at 36 weeks' postmenstrual age ($P<0.05$ for each outcome).[10] Similarly, controlled trials of early indomethacin prophylaxis[17,18] or therapy[19] indicate that indomethacin-treated infants require more oxygen,[17–19] higher mean airway pressures[19] and more doses of surfactant.[18] These data indicate that early use of indomethacin to close a persistent PDA fails to reduce requirements for respiratory support in the posttreatment period.

Treatments designed to achieve ductal closure may have significant adverse effects. Ligation may be followed by cardiorespiratory decompensation in the immediate postoperative period.[20] Long-term sequelae include an increased risk of BPD,[9,10,21] retinopathy of prematurity [21] and neurodevelopmental impairment,[21] as well as left vocal cord paralysis,[22–24] diaphragmatic paresis[24] or eventration,[25] chylothorax[24,26,27] and scoliosis.[28] Treatment with COX inhibitors may be associated with renal impairment,[29] spontaneous intestinal perforation,[30,31] IVH[2] and changes in cerebrovascular autoregulation[32] (of uncertain significance). The risk–benefit balance for these interventions is therefore unknown.

Although this evidence indicates that routine, early treatment of persistent ductal patency in the preterm infant is of no demonstrable benefit, it does not mean that medical or surgical closure of the ductus is never appropriate or necessary, nor that persistent patency of the ductus can simply be ignored. Nearly all of the clinical trials included in the meta-analyses referred to above allowed intervention to close the ductus in 'control' subjects in whom ductal patency persisted for some time, and such interventions were frequently used. Therefore, these trials are essentially comparisons of earlier with later (and perhaps more selective) intervention rather than intervention versus non-intervention. The indications for, timing of and utility of later interventions remain indeterminate.

The common experience that severe congestive heart failure develops in some preterm infants with persistent PDA, similar to some with other large left-to-right shunts (for example, a large ventricular septal defect), indicates that active management of infants with large ductal shunts may sometimes be necessary. Appropriate treatments may include closure of the PDA. The clinical context of care for preterm infants and even the composition of the patient population itself have evolved substantially as the evidence provided by previous trials accrued; therefore, results of older trials may not be directly applicable in current practice. These facts raise important questions: What management is optimal for the preterm infant with persistent patency of the ductus? Are there infants for whom pulmonary edema, congestive heart failure or systemic steal are so severe—despite other measures—that closure of the ductus becomes necessary? If so, how can those infants be identified and how should they be treated? Have changes in the patient population (particularly increased survival of infants <26 weeks' gestation) or in practice (increased use of antenatal steroids, better modes of ventilation, inhaled nitric oxide and so on) created new cohorts of infants who might benefit from early intervention to induce ductal closure?

Management of infants with a patent ductus

Tolerating patency of the ductus while awaiting spontaneous closure or meeting of criteria for later treatment may require adoption of measures that affect pulmonary blood flow (PBF) and systemic blood flow, as pulmonary edema, systemic steal or congestive heart failure resulting from a large left-to-right ductal shunt might have significant impacts on long-term outcomes.

Preventing pulmonary edema

Pulmonary edema resulting from excessive PBF may be an important mediator of lung injury, predisposing to development of BPD.[33] Neonatal animals can tolerate large left-to-right shunts, with pulmonary-to-systemic blood flow ratios (Q_P/Q_S) at least as high as 3:1, without developing pulmonary edema, unless additionally stressed by another factor, such as excessive fluid administration, reduced serum oncotic pressures or concurrent bacterial infection. Management strategies may therefore be designed either to reduce PBF or to ameliorate concomitant predisposing factors.

Pulmonary blood flow is determined by the pulmonary vascular resistance (PVR) and the difference between pulmonary arterial (PAP) and pulmonary vascular outflow pressures. With a widely patent ductus, the PAP is essentially equal to the systemic blood pressure. PBF is increased by measures that increase systemic blood pressure, such as infusions of dopamine or epinephrine, and may be reduced by systemic afterload reducers, such as captopril, nitroprusside or milrinone. Because increased PAP recruits and distends vessels in the pulmonary vascular bed, reducing PVR, the effects of changes in PAP on PBF are magnified. The pulmonary vascular outflow pressure depends on the relationship between the extravascular and intravascular pressures, which are approximated by alveolar and left atrial pressures, respectively. If the alveolar pressure exceeds the left atrial pressure, it is the former (rather than venous pressure) that determines PBF. Therefore, increased distending pressure (PEEP or CPAP) may reduce PBF, but excessive distending pressures may compromise venous return and reduce cardiac output. At high lung volumes, stretching and narrowing of alveolar capillaries increase PVR, augmenting effects mediated by reduction of the transpulmonary intravascular pressure gradient from increased alveolar pressure. On the other hand, increased venous or left atrial pressures cause capillary recruitment and distension, reducing PVR and offsetting or outweighing the impact of reduction in the arteriovenous pressure gradient.

These considerations suggest potential roles for afterload reduction and increased mean airway pressures for management of infants with hemodynamically significant PDA. These measures have not been the subject of controlled trials. One center has reported favorable results with the use of PEEP and captopril, along with avoidance of indomethacin, as a primary approach to PDA management.[34]

In addition to these mechanical factors, PVR is affected by pulmonary vascular tone, which may be altered by the local microenvironment and hormonal or pharmacological agents. Pulmonary arterioles constrict in response to lower pH, hypercarbia and alveolar hypoxia. They dilate with alkalosis, hypocarbia, increased alveolar oxygen tension and pharmacological agents, including nitric oxide, other nitrate vasodilators, calcium channel blockers, prostanoids (for example, epoprostenol, also known as prostacyclin or PGI_2), endothelin inhibitors (for example, bosentan) and phosphodiesterase-5 inhibitors (for example, sildenafil). The early postnatal increase in PBF is faster in a neutral thermal environment (32 to 33 °C) than at room temperature (25 to 26 °C),[35] suggesting that cold stress may decrease left-to-right ductal shunting. The net effect of such factors on PBF depends on their relative effects on PVR and systemic vascular resistance, with increased PBF resulting if reduction of PVR predominates and decreased PBF if reduction of SVR is predominant. Thus, infants with PDA may benefit from mild acidemia (or at least avoidance of or correction of alkalosis), permissive hypercapnia, use of minimal supplemental oxygen and avoidance of pulmonary vasodilator drugs. The recent report of a higher mortality rate among preterm infants who were managed using lower target oxygen saturations[36] suggests that minimizing supplemental oxygen must be balanced by maintenance of adequate oxygen saturations. Similarly, recent animal data showing that inhaled nitric oxide may be neuroprotective[37] or may preserve alveolar septation[38] suggest that unrelated beneficial effects may outweigh immediate adverse effects on ductal shunting.

PVR and PBF may also be significantly affected by blood viscosity, which is influenced by the hematocrit.[39] In infants with ventricular septal defects, increasing the hematocrit by red blood cell transfusion appears to have differential effects on the rheology of the pulmonary and systemic circulations, reducing left-to-right shunting and Q_P/Q_S.[40] Although transfusion has been used in neonates with left-to-right shunts through ventricular septal defects and in infants with unbalanced congenital heart defects (transposition of the great arteries, hypoplastic left heart), the role of higher hematocrits in preterm infants with PDA has not been determined. Comparative trials of liberal versus restrictive transfusion criteria have mostly focused on comparison of normal or moderately reduced versus lower hematocrit thresholds for transfusion; the most liberal thresholds were hematocrits of 45 to 46% for infants who required mechanical ventilation.[41,42] Increased oxygen carrying capacity also reduces the cardiac output necessary to sustain constant oxygen delivery, reducing PBF even at a constant Q_P/Q_S. No studies on the effects of hematocrits on Q_P/Q_S in preterm infants with PDA have been published; hence, the role of higher hematocrits in this setting is not known.

Pulmonary blood flow is just one factor placing an infant with PDA at risk of pulmonary edema. The net flux of fluid into the pulmonary interstitium is determined by the Starling relationship, which relates fluid flux to intravascular and extravascular hydrostatic and oncotic pressures. Increased PAP or venous pressure, decreased interstitial hydrostatic pressure and decreased serum oncotic pressure favor flux of fluid into the interstitial and alveolar spaces. Therefore, maneuvers that reduce PAP or left atrial pressure may be beneficial. The latter might include reduction of vascular volume (fluid restriction, diuretic therapy), increasing venous capacitance (morphine, nitrovasodilators) or cardiotonic agents. Interstitial hydrostatic pressure can be reduced by lowering the surface tension or increasing the effective radius of the alveolar air–water interface (law of Laplace); hence, correction of surfactant deficiency or inhibition with exogenous surfactant and maintenance of a sufficient functional residual capacity using PEEP or CPAP should reduce interstitial and alveolar edema. Adequate serum oncotic pressures favor mobilization of interstitial and alveolar fluid, but achieving that in extremely low birth weight infants may be difficult. Early initiation of protein in parenteral nutrition or early high-protein enteric feedings may not correct hypoproteinemia quickly. Intravenous administration of albumin to preterm infants does not produce sustained increments in serum albumin levels or serum oncotic pressures, and colloid infusions have been associated with prolongation of oxygen dependency in preterm infants.[43] A meta-analysis of trials conducted on treatment with albumin across all ages and diverse indications revealed increased mortality among albumin-treated subjects.[44] Data on use of albumin in hypoproteinemic preterm infants are not sufficient for assessment of efficacy or safety.[45] Although anecdotal experience suggests that plasma infusions along with aggressive diuretic use may raise serum albumin levels in preterm infants, this strategy has not been systematically evaluated.

The risk of BPD is substantially increased when PDA coincides with bacteremia.[46] This association may follow from compromised integrity of the pulmonary capillary endothelial barrier by inflammatory mediators, resulting in extravasation of fluid and colloid into the interstitium. Therefore, strategies for prevention of sepsis may ameliorate potential adverse effects of ductal patency. The prenatal inflammatory response to chorioamnionitis may reduce the rate or severity of respiratory distress syndrome, but increase the risk of BPD if mechanical ventilation is necessary.[47] Interactions between systemic inflammatory responses and the effects of a PDA remain largely unexplored, and interventions to moderate the effects of inflammatory response on lung water have not been developed.

Limiting the effects of systemic steal

Because preterm infants have a limited ability to increase cardiac output in response to hemodynamic stress, runoff through a left-to-right ductal shunt may decrease systemic blood flow, compromising the perfusion of vital organs, including bowel, liver, kidneys and brain. Measures that reduce PBF, as discussed above, will therefore be helpful in sustaining systemic perfusion and in reducing the potential for ischemic injuries to those tissues. Augmenting preload and providing inotropic support may help ensure the sufficiency of systemic perfusion in the face of an elevated Q_P/Q_S. Providing sufficient preload without producing either fluid overload or elevated venous pressures may require a careful balancing of these objectives, possibly requiring invasive monitoring of central venous pressures or frequent echocardiographic hemodynamic assessments. Support of blood pressure with dopamine and/or hydrocortisone may also be of value, but optimal blood pressure levels for extremely low birth weight infants have not been established. Increasing blood pressure through systemic vasoconstriction will simply increase Q_P/Q_S.

Adverse effects of organ ischemia may be exacerbated by coincident insults or physiological stresses or moderated by their avoidance. For example, brain ischemia will be augmented by alkalosis, cerebral oxygen delivery reduced by anemia and white matter injury increased by inflammatory cytokines. Nephrotoxic drugs, including COX and angiotensin-converting enzyme inhibitors, compound the effects of renal ischemia. Presence of a moderate PDA limits the normal postprandial increment in mesenteric arterial blood flow,[48] but withholding feedings from preterm infants with PDA has not been found to reduce the risk of necrotizing enterocolitis.[49] On the contrary, low rates of necrotizing enterocolitis and ductal ligation have been reported from a center utilizing a standardizing feeding regimen and avoiding indomethacin.[34] Trials of continued enteral feeding during medical therapy to close the patent ductus will not be informative with respect to safety of feeding in the presence of an untreated PDA; trials of early versus deferred feeding of infants with untreated PDA are needed to answer this question.

Managing congestive heart failure

The approach to treatment of congestive heart failure resulting from a PDA does not fundamentally differ from that for congestive heart failure in infants in general: preload reduction (fluid restriction, diuretics), inotropic support (digoxin, catecholamines, milrinone) and afterload reduction (angiotensin-converting enzyme inhibitors, nitrovasodilators). Of these interventions, only digoxin and furosemide have been systematically evaluated as a treatment for PDA. Digoxin is ineffective,[50,51] and furosemide promotes continued patency of the ductus.[52] Measures designed to reduce PBF and Q_P/Q_S, as discussed above, should also be effective for prevention or management of CHF.

Prolongation of ductal patency

Recognition that early medical closure of the ductus is not beneficial does not imply that delaying spontaneous ductal closure is harmless. Several common therapies may prolong ductal patency, and it may be prudent to avoid them. Excessive fluid administration is associated with prolonged PDA,[53] but the optimal fluid intake and criteria for adjustment of intake are not well defined. The greatest impacts on ductal patency were observed in trials in which the 'liberal' fluid groups received, on average, 170 (see ref. 54) to 180 ml kg^{-1} per day (see ref. 55) of fluid by the beginning of the second week. Trials with less-generous intakes in the 'high fluid' group did not demonstrate significant prolongation of PDA.[43,56] Thus, modest fluid restriction with intakes no greater than 80 ml kg^{-1} per day on the first day and increasing to 150 ml kg^{-1} per day by the second week may avoid prolongation of PDA. Use of diuretics to limit fluid excess or to permit incremental caloric intake may not be a good alternative. Furosemide dilates the ductus in neonatal rats,[57] and preterm infants treated with furosemide are more likely than those treated with chlorothiazide to have PDA.[52] The effects of both classes of diuretics are mediated by prostaglandin production; hence, thiazides also may not be innocuous in this respect. Optimal fluid management for preterm infants with PDA beyond the third postnatal day probably consists of balancing fluid restriction and avoiding diuretic therapy, if possible, with provision of sufficient protein calories and protein to support growth. The optimal strategy for achieving these goals has not been delineated.

Because the postnatal increase in oxygen tension stimulates ductal constriction, there has been concern that lower inspired oxygen concentrations during resuscitation or lower target oxygen saturations might subsequently increase the risk of persistent ductal patency. Oxygen restriction immediately after birth does not predispose to subsequent persistence of PDA.[58] A recent retrospective analysis suggested that lower target saturation ranges increased the prevalence of early hemodynamically significant PDA, but not the ultimate closure rate or need for surgical ligations.[59] No differences in PDA or medical or surgical treatment for PDA were observed in a randomized trial comparing target ranges of oxygen saturation of 85 to 89% or 91 to 95% in preterm infants between 24 and 27 weeks' gestation.[36] Avoidance of unnecessary oxygen supplementation appears to be desirable[60] and does not increase the incidence of PDA.

Recent publications have raised concern about a potential undesired effect of COX inhibitors. In animals, formation of a platelet plug in the closing ductus appears to be an essential component of definitive closure.[61] COX inhibitors may either promote or impede platelet adherence or aggregation,[62] depending on both the actions of the particular drug and the biological context. Indomethacin prolongs the bleeding time in preterm infants,[63] suggesting that it may interfere with platelet plug

formation in the closing ductus. Antenatal exposure to indomethacin (used for tocolytic effects) increases the rates of persistent ductal patency[64,65] and ductal ligation.[64–66] Observational data from preterm infants who were discharged home with a patent ductus suggest that failure to achieve late spontaneous closure may be more common among those who had been treated with indomethacin.[67] However, ibuprofen does not appear to prolong bleeding times in preterm infants, leading to speculation that it may be preferable to indomethacin for this indication.[68] Although these observations are not definitive, they raise concern that treatment with indomethacin (and possibly with other COX inhibitors) could ultimately increase the number of infants who require ductal ligation, despite inducing early ductal constriction.

Deciding when ductal closure is indicated

With one exception,[16] trials of ductal closure effectively compare early and late intervention; hence, potential benefits of late interventions, as compared with management of disordered hemodynamics while tolerating persistent ductal patency, remain unstudied. The ductus eventually closes spontaneously in most preterm infants, but prolonged patency is not unusual, especially among infants with birth weights <1000 g. Recent reports suggest that less-aggressive approaches to intervention are associated with good clinical outcomes.[34,69,70] Nevertheless, some infants with large left-to-right shunts through a PDA that has failed to constrict after an extended period of conservative management may need intervention to correct that disordered physiology. The challenge lies in determining when and how those infants can best be identified. Delay in ascertainment reduces the potential utility of COX inhibitors, which become progressively less effective for inducing ductal closure after the first postnatal week, leaving surgical ligation as the most reliable therapeutic option.

A method for early prediction of persistent PDA leading to cardiorespiratory compromise would be ideal, but that tool is elusive. In its absence, criteria for late intervention are urgently required. A staging system incorporating clinical and echocardiographic findings has been proposed by McNamara and Sehgal,[71] who have critically reviewed the use of echocardiographic measurements to quantify the hemodynamic significance of PDA.[72] El-Kuffash *et al.*[73] have found elevated serum levels of N-terminal pro-B-type natriuretic peptide and cardiac troponin T at 48 h of age in preterm infants with PDA and grade III/IV IVH or death, as compared with infants with PDA without those complications or those with a closed ductus. Those authors did not find differences in echocardiographic measurements of PDA size, left atrial to aortic ratio or left and right ventricular outputs between the PDA groups with and without complications. It is not clear whether the more comprehensive evaluation proposed by McNamara and Sehgal, or perhaps serial echocardiographic evaluations beyond 48 h of age, might better predict adverse outcomes. Development of tools to identify infants at risk for adverse outcomes attributable to a hemodynamically significant PDA must be followed by intervention trials to determine whether closure of the PDA can avert those outcomes. Until the results of such trials are available, the decision to intervene to close a PDA in a preterm infant who is not doing well will remain highly subjective.

Conclusions

Five decades after the recognition of delayed closure of the ductus in preterm infants, management remains heterogeneous and controversial. Routine early treatment to close the ductus does not appear to be beneficial, but selective later treatment may still prove valuable. The timing, criteria, objectives and methods for such treatments remain to be established. Potential strategies for minimizing the adverse effects of PDA while awaiting spontaneous closure or achievement of treatment criteria need careful evaluation in clinical trials. Medawar's reminder that those hypotheses must be subjected to rigorous testing is as timely now as it was when Dr. Sunshine posted it above his desk many years ago.

Conflict of interest

The author declares no conflict of interest.

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