Staging of PDAs

Towards rational management of the patent ductus arteriosus: the need for disease staging

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Perspective on the review by Bose and Laughon ***(see page 498)***

Patent ductus arteriosus (PDA) is common problem, with rates of 40–55% in babies born less than 29 weeks' gestation,[1 2] yet decisions related to management remain highly controversial. Despite numerous studies on the topic there remains uncertainty with respect to diagnosis, assignment of clinical importance, whether treatment is indicated and if so the preferred treatment modality. The most fundamental question remains unanswered: does a PDA cause acute physiological or clinical change that either acutely or chronically leads to organ damage, which further leads to important neonatal morbidities? Put simply is the PDA an ''innocent bystander'' or is it pathological to the extent that early detection and intervention is warranted to prevent neonatal morbidity?

It is physiologically plausible that a major systemic to pulmonary (left-to-right) shunt can lead to considerable postnatal morbidities in extremely low birthweight (ELBW) infants, either from pulmonary overcirculation (eg, chronic lung disease (CLD)) and/or systemic hypoperfusion (eg, necrotising enterocolitis (NEC), acute renal impairment).[3] The lack of evidence supporting causality,[4 5] failure of medical treatment in some cases[1] and the inherent risks of medical[6 7] or surgical treatment options[8] has led some investigators to question whether intervention is necessary. In contrast, studies of prophylactic indometacin show reduced rates of PDA ligation, early major pulmonary haemorrhage and serious (grades III–IV) intracranial haemorrhage.[9 10] This strategy does, however, expose 40% of babies, in whom spontaneous PDA closure would have occurred, to any adverse effects of treatment.

The medical community is becoming increasingly divided on the question of treatment of the PDA. Laughon and Bose highlight some important gaps in our knowledge with respect to therapeutic intervention.[11] They emphasise that recent trials of non-steroidal anti-inflammatory agents have not led to any detectable reduction in neonatal morbidities that may be related to ongoing ductal patency. They propose the need for further trials of treatment to assess risks versus beneficial effects and suggest the need for a more restrained approach to management. Although we are in agreement that refinement of target populations requiring intervention is needed, it is unlikely and potentially dangerous to consider the solution to treatment decisions through an ''all or none'' framework. The traditional definition of a PDA, which forms the basis of clinical trials conducted to date, does not take into account physiological variability or the magnitude of the clinical effects resulting from the ductal shunt. Rather, the ''pathological'' PDA probably represents a continuum of clinical effects that lead to neonatal morbidities of varying importance. Here we examine the physiological and clinical consequences of transductal shunting, highlight the challenges of current approaches to management and propose a more rational approach to treatment.

THE CHALLENGE OF DEFINING A ''PROBLEMATIC DUCTUS ARTERIOSUS''

Although some may consider this to be semantics, the difference between a PDA and a haemodynamically significant ductus arteriosus (HSDA) has not been emphasised clearly enough in the literature, so the two terms have been used synonymously. It must be remembered that ''patent ductus'' does not necessarily imply there are physiological effects leading to haemodynamic instability or indeed any clinical problem. The PDA may represent normal physiological adaptation, where it has an important role in supporting pulmonary blood flow in the transitioning lung.[12] The decision to intervene should be based on the echocardiographic documentation of an important left-to-right transductal shunt, with measurable haemodynamic effects, leading to clinical instability.

The echocardiographically significant duct

The current definition of an HSDA is problematic as it is almost entirely based on size. A transductal diameter of >1.5 mm has been proposed as significant on the basis that at this cut-off end-organ hypoperfusion occurs.[13–15] However, this definition is somewhat limited in that it does not take into account factors such as patient size or maturation, which may account for variability in the clinical presentation. For example, the clinical impact of a PDA measuring 3.0 mm in an asymptomatic 32-week infant differs markedly from a ductus of comparable size on day 2 of life in a 24-week infant with respiratory failure and haemodynamic instability. The lack of a standardised approach in assigning echocardiographic significance is a major barrier towards better understanding the clinical impact of the ductus arteriosus.

The magnitude of the transductal shunt relates not only to transductal diameter, but it is influenced by pulmonary and systemic vascular resistance, and the compensatory ability of the immature myocardium. There is thus an urgent need to develop a comprehensive protocol to assess the impact of an HSDA on myocardial performance, systemic (eg, superior vena caval flow) and/or end-organ perfusion, as well as cardiac volume overload (eg, ratio of left atrium to aortic root size). The latter is subject to considerable operator variability, however, serial measurements may prove to be more useful.[16] Transductal dimensions that are indexed to patient size or maturation need to be prospectively evaluated. To date, there has been little consideration for the magnitude of the ductal shunt in clinical trials assessing the efficacy of therapeutic intervention on neonatal morbidities.

The clinically significant duct

In an attempt to design trials that are simple and pragmatic illness severity related to the PDA is not taken into account and stratification has not been performed. This over-simplification may lead to erroneous conclusions, particularly if no benefit is found. It is possible that there may be infants with severe ''ductal disease'' in whom treatment will lead to major clinical benefits that outweigh the potential risks of treatment. On the contrary there may be infants with mild ductal disease in whom the risks of intervention outweigh any perceived benefit of ductal closure.

In response to a threefold increase in referral rates for PDA ligation in our region (Central Eastern Ontario, Canada), a system of PDA categorisation

Table 1 Proposed staging system (adapted from McNamara and Hellman, unpublished clinical triaging system for ligation of a patent ductus arteriosus (PDA)) for determining the magnitude of the haemodynamically significant ductus arteriosus (HSDA), which is based on clinical and echocardiographic criteria

Clinical	Echocardiography
C1 Asymptomatic	E1 No evidence of ductal flow on two-dimensional or Doppler interrogation
C2 Mild	E2 Small non-significant ductus arteriosus
Oxygenation difficulty (OI <6)	Transductal diameter <1.5 mm
Occasional (<6) episodes of oxygen desaturation, bradycardia or apnoea	Restrictive continuous transductal flow (DA V_{max} >2.0 m/s)
Need for respiratory support (nCPAP) or mechanical ventilation (MAP <8)	No signs of left heart volume loading (eg, mitral regurgitant jet >2.0 m/s or LA:Ao ratio >1.5:1)
Feeding intolerance (>20% gastric aspirates)	No signs of left heart pressure loading (eg, E/A ratio >1.0 or IVRT >50)
Radiologic evidence of increased pulmonary vascularity	Normal end-organ (eg, superior mesenteric, middle cerebral) arterial diastolic flow
C3 Moderate	E3 Moderate HSDA
Oxygenation difficulty (OI 7–14)	Transductal diameter 1.5–3.0 mm
Frequent (hourly) episodes of oxygen desaturation, bradycardia or apnoea	Unrestrictive pulsatile transductal flow (DA V_{max}<2.0 m/s)
Increasing ventilation requirements (MAP 9–12)	Mild-moderate left heart volume loading (eg, LA:Ao ratio 1.5 to 2:1)
Inability to feed due to marked abdominal distension or emesis	Mild-moderate left heart pressure loading (eg, E/A ratio >1.0 or IVRT 50–60)
Oliguria with mild elevation in plasma creatinine	Decreased or absent diastolic flow in superior mesenteric artery, Middle cerebral artery or renal artery
Systemic hypotension (low mean or diastolic BP) requiring a single cardiotropic agent	
Radiological evidence of cardiomegaly or pulmonary oedema	
Mild metabolic acidosis (pH 7.1–7.25 and/or base deficit −7 to −12.0)	
C4 Severe	E4 Large HSDA
Oxygenation difficulty (OI >15)	Transductal diameter >3.0 mm
High ventilation requirements (MAP >12) or need for high-frequency modes of ventilation	Unrestrictive pulsatile transductal flow
Profound or recurrent pulmonary haemorrhage	Severe left heart volume loading (eg, LA:Ao ratio >2:1, mitral regurgitant jet >2.0 m/s)
''NEC-like'' abdominal distension with tenderness or erythema	Severe left heart pressure loading (eg, E/A ratio >1.5 or IVRT >60)
Acute renal failure	Reversal of end-diastolic flow in superior mesenteric artery, middle cerebral artery or renal artery
Haemodynamic instability requiring >1 cardiotropic agent	
Moderate-severe metabolic acidosis (pH<7.1) or base deficit >−12.0	

BP, blood pressure; DA V_{max}, ductus arteriosus peak velocity; E/A, early passive to late atrial contractile phase of transmitral filling ratio; IVRT, isovolumic relaxation time; LA: Ao ratio, left atrium to aortic ratio; MAP, mean airway pressure; nCPAP, nasal continuous positive airway pressure; NEC, necrotising enterocolitis; OI, oxygenation index.
Patients should be assigned both a clinical and echocardiography stage (eg, neonate with severe oxygenation failure, pulmonary haemorrhage and a 3.2 mm unrestrictive left-to-right shunt will be C4-E4 class HSDA).
Detailed discussion of the echocardiography parameters is beyond the scope of this perspective.

was developed to facilitate triaging and case prioritisation. The classification was based predominantly on illness severity and the magnitude of cardiovascular, respiratory and gastrointestinal problems. The implementation of the system led to an improvement in access and more timely intervention for the sickest infant. The impact of this system on clinical practice and neonatal outcomes will be published in due course.

We therefore propose a ''PDA staging'' system that recognises the heterogeneity in clinical and echocardiography significance, similar in outline to the classifications used in NEC or hypoxic-ischaemic encephalopathy (table 1). This classification recognises that HSDA is a clinical continuum in which the spectrum of disease ranges from mild to severe, depending on the magnitude of the ductal shunt. The merits of a staging system for illness severity is again well illustrated in the trial of selective head cooling, in which clinical benefit was shown in neonates with moderate but not severe hypoxic-ischaemic encephalopathy.[17]

IMPACT OF TREATMENT OF AN HSDA ON NEONATAL MORBIDITY

Although an HSDA has been linked to important neonatal morbidities such as CLD and NEC,[18–20] there remains little evidence that treatment improves either short-term or long-term outcomes. A recent study in premature baboons showed altered pulmonary mechanics and arrested alveolarisation after 14 days of exposure to a moderate-sized ductus[21]; Pharmacological intervention led to improvement in lung mechanics and increased alveolarisation. Why therefore have the benefits of ductal closure seen in animal models not been translated into improved outcomes for human neonates?

The current approaches to treatment include non-steroidal anti-inflammatory agents and surgical ligation. The lack of a perceived benefit may relate to the lack of consideration of the spectrum of ductal disease as outlined above, the marked variability in therapeutic strategies for medical intervention or operator-dependent factors for surgical ligation. It may also relate to the multifactorial nature of the primary outcome studied. The failure of treatment for an HSDA to decrease the rate of CLD in ELBW infants is widely proposed as one argument against intervention. This lack of clinical impact in human neonates is not surprising for two main reasons. First, the definition of CLD does not take into account the heterogeneity of the disease state or illness severity; neonates on low-flow oxygen are categorised the same as those requiring high-frequency ventilation or inhaled nitric oxide, which may lead to diluting of any real benefit. Second, the pathogenesis of CLD is multifactorial which makes it highly improbable that any one treatment will prove to be the ''magic bullet''. The lack of benefit of inhaled nitric oxide[22] and high-frequency ventilation[23] in reducing rates of CLD bears this out. Likewise the pathogenesis of NEC is multifactorial. A single randomised trial of early surgical ligation did show a reduction in the rate of NEC,[24] however, most studies fail to show an appreciable benefit of treatment. Clyman has shown that early medical intervention with

indometacin (day 1–3) is preferable to late (day 7–12) as the risk of NEC or pulmonary morbidity and need for ligation is markedly reduced.[9] Clinical trials which consider the heterogeneity of ductal disease are needed.

IMPACT OF TREATMENT OF AN HSDA ON ACUTE NEONATAL PHYSIOLOGY

The effects of the HSDA on acute physiological change and short-term clinical outcomes are also variable. These effects of the HSDA are usually related to altered pulmonary (Qp) to systemic (Qs) blood flow, leading to pulmonary overcirculation and systemic hypoperfusion. Although improved lung function, coinciding with ductal closure, has been shown with both indometacin treatment and surgical ligation,[25 26] others have found no difference in compliance in neonates with respiratory distress syndrome.[27] Oftentimes, the primary presenting problem of the HSDA may be early systolic and diastolic hypotension.[28] Inadvertently these babies are commonly treated with cardiotropic agents, such as dopamine or dobutamine, in an attempt to increase the blood pressure.[29] These agents may be of benefit if there is coexisting myocardial dysfunction, however, they may also promote left-to-right ductal shunting by increasing systemic vascular resistance.

Refinement of intensive care practice requires a combination of careful clinical monitoring and early focused echocardiographic assessment. The presence of absence or reversal of diastolic flow in the renal, superior mesenteric and middle cerebral arteries, due to the ''ductal steal'' phenomenon, is well documented.[30 31] The relationship between end-organ hypoperfusion and neonatal morbidity, however, is less clearly defined. Large ducts themselves have been shown to be associated with all grades of intracranial bleeds.[32] Development of acute renal failure or an acute (NEC-like) abdomen in the presence of a large PDA is not an unexpected clinical finding. Anecdotally there is clinical resolution after ductal treatment, but the impact of intervention in this critically ill population has not been studied. In a prospective study of 20 premature infants undergoing PDA ligation, we have recently identified low coronary blood flow. This finding is not unexpected as coronary perfusion pressure is, in part, dependent on low diastolic pressure. In addition, low preoperative diastolic coronary flow was strongly correlated with systolic hypotension, impaired myocardial performance and the need for cardiotropic support after the operation (personal observations). These data emphasise another potential adverse consequence of transductal flow leading to suboptimal coronary blood flow and myocardial perfusion. The question of whether early therapeutic intervention to minimise pulmonary overcirculation or end-organ hypoperfusion impacts on neonatal morbidity remains unanswered.

DOES TREATMENT FOR AN HSDA CAUSE HARM?

The trials conducted to date, although not designed to assess harm, do provide some useful information on adverse effects of non-steroidal treatment. Transient alterations in cerebral perfusion[6] during indometacin administration have been shown, but prophylactic treatment is more likely to decrease the incidence of periventricular leucomalacia[10] and led to improved long-term outcome at 4.5 and 8 years.[33] In addition, any renal impairment during medical treatment is entirely reversible.[7] These studies do not provide any plausible rationale for complete avoidance of medical intervention. The adverse effects of PDA ligation are well recognised and include both reversible complications, such as pneumothorax, infection or haemorrhage, and irreversible complications, including chylothorax and vocal cord paralysis,[34] which may lead to major patient morbidity and even mortality. Not uncommonly the postoperative course is characterised by a post-ligation cardiac syndrome consisting of oxygenation failure due to pulmonary oedema, systolic hypotension and the need for cardiotropic support, which typically occur 8–12 hours after the procedure.[35] Previously we have shown that surgical intervention was associated with myocardial dysfunction secondary to increased left ventricular afterload coinciding with the clinical deterioration. Kabra *et al* have recently highlighted an association between PDA ligation and an increased risk of bronchopulmonary dysplasia, severe retinopathy of prematurity and neurosensory impairment.[36] It is impossible to determine whether this relationship reflects causality or whether need for PDA ligation is merely a marker for illness severity. Unfortunately their study did not consider the heterogeneity of clinical and echocardiographic changes that may occur with varying severity of ductal disease.

In summary, the stage at which the physiological effects of the ductus arteriosus change from benefit to harm remains unclear. Future clinical trials of treatment should be less pragmatic but more focused with strict inclusion criteria that ensure infants are randomised only if there is clear clinical and echocardiographic evidence of an HSDA. Recruited infants should be stratified according to the severity of ductal disease, in a fashion as suggested in table 1. The desired endpoints should be more tangible and reflective of the nature of the primary problem—for example, hypotension, duration of ventilation. The phenomenon of the ''HSDA'' is a continuum from physiological normality to a pathological disease state with clinical instability and varying effects on bodily organs. Although the overall desire is to improve long-term outcomes, the starting point should be to provide excellence in intensive care, focused cardiorespiratory monitoring and early targeted intervention.

With this backdrop, we propose an individualistic and rational approach in which information obtained from echocardiographic assessment is analysed in conjunction with clinical parameters to make more focused clinical decisions.

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Interventional parenting programmes

A good idea that doesn't work: the Parent Baby Interaction Programme

Martin P Ward Platt

Perspective on the paper by Glazebrook *et al* (***see page 438***)

It is impossible to work with parents and children for any length of time without coming across situations where mothers, fathers, or both seem to need help with parenting. It has long been known that there are associations between the quality of parenting and children's outcomes. Additional difficulties with establishing appropriate parenting styles are imposed on families as a result of their baby needing intensive care. It is therefore important to find out which interventions, provided in the setting of a neonatal intensive care unit (NICU), might "improve" parenting; and whether this in turn could mediate better outcomes for babies, and their parents, in families to which such interventions are given.

Over the past 20 years a great deal of work has evaluated interventions to improve parenting, and it is fortunate that many of the published studies have been randomised controlled trials. This in turn has allowed for two related Cochrane reviews, one in 2003[1] on child outcomes, and one in 2004[2] for maternal outcomes. For children, such programmes seem to lead to improvements in attachment and behaviour; and for mothers, indices of mental health, such as depression, show improvements. These effects seem to be mediated by increased maternal sensitivity towards the baby that in turn allows more secure attachment for the child, and perhaps a more rewarding relationship for the mother. So there seems to be reasonable evidence that, in general, some of these interventions work: but which, and for whom? And what is the best way to evaluate the efficacy of such interventions?

The paper by Glazebrook *et al*, evaluating the Parent Baby Interaction Programme (PBIP) in a NICU setting, is another randomised controlled trial that further contributes to the literature on interventional parenting programmes. It is important for two reasons: its demonstration that this particular intervention programme was ineffective, and the rigour of the methodology with which that finding was demonstrated. The authors discuss the possible reasons for the ineffectiveness of the PBIP, and I will not repeat them here. But is worth emphasising just how similar the measured outcomes were in the subjects and controls, given that the study was strongly powered to detect clinically relevant group differences. This demonstration of complete ineffectiveness undermines the suggestion that more intervention would have thrown up an appreciable advantage for the index babies over the controls, and strongly suggests that PBIP simply does not work.

Finding that things do not work is good for healthcare because it prevents the enthusiastic adoption, on the basis of theoretical plausibility or extrapolation from other work, of programmes that have no benefit. Indeed a programme that is plausibly beneficial may even turn out to be harmful when properly studied. New programmes will either carry a new direct cost (for instance, the establishment of a new post to deliver or coordinate the programme) or impose opportunity costs (for instance, if nurses deliver a new kind of care they may have