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Review

Preterm patent ductus arteriosus: A continuing conundrum for the neonatologist?

Nick Evans*

Department of Newborn Care, Royal Prince Alfred Hospital and University of Sydney, Sydney, NSW, Australia

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SUMMARY

How to manage the preterm patent ductus arteriosus (PDA) remains a conundrum. On the one hand, physiology and statistical association with adverse outcomes suggest that it is pathological. On the other hand, clinical trials of treatment strategies have failed to show any long-term benefit. Ultrasound studies of PDA have suggested that the haemodynamic impact may be much earlier after birth than previously thought (in the first hours); however, we still do not know when to treat PDA. Studies that have tested symptomatic or pre-symptomatic treatment are mainly historical and have not tested the effect of no treatment. Prophylactic treatment is the best-studied regimen but improvements in some short-term outcomes do not translate to any difference in longer-term outcomes. Neonatologists have been reluctant to engage in trials that test treatment against almost never treating. Observations of very early postnatal haemodynamic significance suggest that targeting treatment on the basis of the early postnatal constrictive response of the duct may optimize benefits. A pilot trial of this strategy showed reduction in the incidence of pulmonary haemorrhage but more trials of this strategy are needed.

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1. Introduction

A conundrum is defined as an intricate and difficult puzzle; how we should manage the preterm patent ductus arteriosus (PDA) is indeed a conundrum. On the one hand, there is evidence that the preterm PDA can be pathological. First, haemodynamic studies show that the PDA facilitates shunting of large volumes of blood from the systemic to the pulmonary circulation, draining blood from the former and overloading blood into the latter. Second, observational studies that have consistently associated persistent PDA shunting with a range of adverse outcomes including necrotizing enterocolitis (NEC), peri/intraventricular haemorrhage (P/IVH), chronic lung disease (CLD) and death [1–3]. Interpretation of these studies is limited by the co-linearity between each of these outcomes, persistent PDA and immaturity, and also by the wide range of ways in which PDA has been defined using a menagerie of clinical and, latterly, echocardiographic criteria [4].

On the other hand, since PDA is causing these adverse outcomes then treating it should reduce the incidence of those outcomes. Yet amalgamations of the results of randomized trials show little evidence of consistent effect of treating PDA on outcomes [5–8]. However, again there are limitations in that, with the exception of prophylactic treatment, these trials are historically and methodologically diverse.

A purist interpretation of this conundrum would be that if treating makes no difference to outcomes then preterm PDA may not be pathological. However, lack of evidence of effect is not the same as evidence of lack of effect, and the other interpretation could be that we have not understood the natural history of the pathology of the PDA or what happens when we try to treat PDA medically. In other words, in many babies the treatment may not be doing what we want it to do.

Systematic review is important for defining the limitations of our understanding, but it is less useful for defining whether the right treatment questions have been asked in the right way. For that, you have to study the babies and their ducts with the goal of understanding what is pathological and what is not pathological about their behaviour. Good treatment strategies still depend on accurate diagnosis and an understanding of the natural history of the pathophysiology.

2. Cardiac ultrasound and the ductus

Cardiac ultrasound has been pivotal to the development of our understanding about the ductus. Ultrasound allows direct imaging

* Address: Department of Newborn Care, Royal Prince Alfred Hospital, Missenden Road, Camperdown, Sydney, New South Wales 2111, Australia. Tel.: +612 9515 8760; fax: +612 9550 4375.
E-mail address: nicholas.evans@sydney.edu.au.

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of the ductus, assessment of constriction, the shunt direction and velocity, and the disturbance to blood flow patterns in the great vessels either side of the ductus (Fig. 1).

2.1. Normal ductal physiology

In most term babies, functional closure occurs by 24 h of age [9]. Intimal ischemia and then necrosis result from the continued intense constriction of the muscular wall and the ductus eventually evolves into the ligamentum arteriosum that we all have where our ductus arteriosus used to be.

Ultrasound studies have resulted in a shift in thinking about the preterm ductus but dogma in medicine is not easy to change. There has been a long-held view that early postnatal ductal shunting is not important and that pathological ductal shunting evolves after a few days. This thinking has been the premise of many of the clinical trials, and it evolved from studies that were done in the late 1960s [10]. Whereas this may have been true in the late 1960s, it is not true now and, indeed, the reverse may be true, as early left-to-right shunting may cause more hemodynamic pathology in the early hours of circulatory transition than a few days later, even if the volume of the shunt does increase.

2.2. Early preterm ductal behaviour

The ductus does just one active thing in its postnatal life. It constricts and closes. Otherwise it is just a passive conduit for blood with flow direction determined by the pressures at either end. At all preterm gestations, there is great variation in the degree of constriction during the early postnatal hours. This varies from those with minimal constriction to those where the constriction is much as would be seen in a well term baby [2]. Figure 2 shows ductal color Doppler diameter at 5 h of age plotted against gestation in 124 babies born before 30 weeks. In most babies, the shunt is pure left-to-right or bidirectional with a dominant left-to-right component, showing that pulmonary pressures are usually subsystemic even early after birth [2]. In babies where the ductal constriction fails, there is often a large shunt moving blood from the systemic circulation and loading it into the pulmonary circulation.

Using superior vena cava flow as a surrogate measure of systemic blood flow, we showed a significantly negative association between duct diameter and SVC flow at 5 h of age, but this association was not significant on the subsequent studies at 12, 24 and

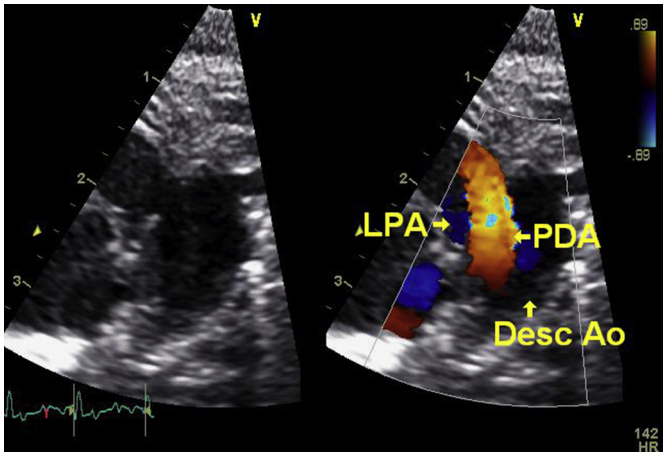

Fig. 1. Ultrasound ductal cut with two-dimensional imaging on the left and with color Doppler on the right. This wide-open duct with a mainly left-to-right shunt was found in a preterm baby just a few hours old. LPA, left pulmonary artery; PDA, patent ductus arteriosus; Desc Ao, descending aorta.

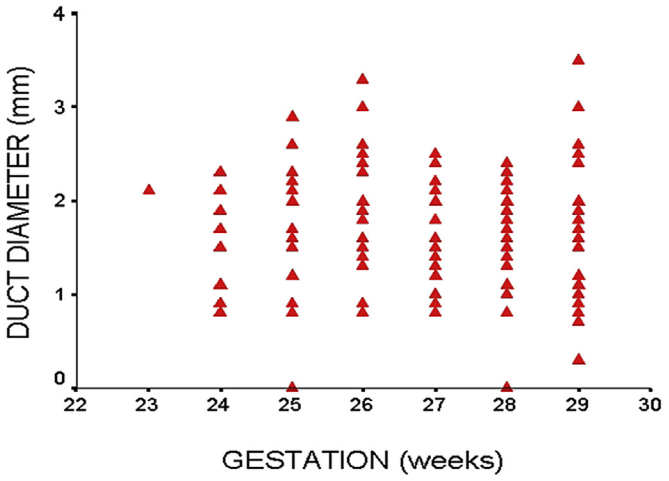

Fig. 2. Plot of ductal diameter against gestation in a cohort of 124 babies born before 30 weeks at 5 h of age.

48 h [11]. The strength of this association has not been a consistent finding in the literature; Groves et al. [12] found a similar association at 5 h in univariant analysis which became insignificant on multivariant analysis. However, existing evidence suggests that, if ductal shunting has a negative association with systemic blood flow, it does so very early after birth during this exquisitely vulnerable period of circulatory transition. After that time, in most cases, the heart seems to compensate well by increasing left ventricular output to maintain systemic blood flow in the face of this sump of blood back through the ductus. We showed a significant association between this early low systemic blood flow and development of intraventricular hemorrhage and later NEC, suggesting a possible mechanism by which PDA shunting might be part of the causation of these outcomes [11].

Whereas the heart can compensate for shunting of blood from the systemic circulation, the overload of the pulmonary circulation is passive, inevitable, and only limited by the resistance of the pulmonary vasculature. The early clinical risk of this seems to be pulmonary hemorrhage. The label ‘pulmonary hemorrhage’ is a misnomer because it is not blood but hemorrhagic pulmonary edema. In a serial hemodynamic study of 126 babies born before 30 weeks, 12 developed pulmonary hemorrhage at a mean age of 36 h [2]. Close to the time of hemorrhage, these babies had significantly higher estimated pulmonary blood flow and significantly larger ducts than the rest of the cohort, so again this clinical impact is happening early. The later role of increased pulmonary blood flow in development of ventilator dependency and chronic lung disease seems less certain and underlines the conundrum of PDA treatment. PDA features consistently as a significant risk factor for chronic lung disease but treatment of the PDA, including prophylactic treatment, makes no difference to incidence of chronic lung disease.

3. Treatment of the preterm ductus arteriosus

So should we be treating PDA in preterm babies? It has been apparent for many years from systematic review of the literature that there is no clear evidence of effect on long-term outcomes of treating PDA. The issue has been brought into sharper focus by several review articles, which have essentially re-worked the same studies and, perhaps not surprisingly, have failed to produce a clear answer. Laughon and Bose [5,6] proposed that the reason for the lack of effect might be that the patency of the preterm ductus was a

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