Preterm Patent Ductus Arteriosus: Controversies Overview

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For over five decades healthcare providers have argued whether to treat the patent ductus arteriosus (PDA) in preterm infants or not and if so, when and how. 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. We provide a chronicle of the evolution of knowledge about the ductus arteriosus (DA) and the varying nature of controversies concerning the determination (and definition) of hemodynamic significance PDA (hsPDA), appropriate identification of infants for therapy, selection of treatment regimen, and the exact impact of PDA treatment on meaningful short- and long-term outcomes.

Historical highlights

In the history of human medicine, the DA occupies a most singular position. The first description of a fetal vascular conduit interconnecting the aorta and the pulmonary artery without understanding its function was described by Galen in the 2nd century A.D. in his "*De usu paritum*":

"Neither vessel (*Foramen ovale* and *Ductus arteriosus*) is small or the result of an accident; on the contrary, they are very broad and have notable lumens, which could not fail to be recognized not only by anyone having eyes but even by anyone having a sense of touch, provided that he wished to busy himself with dissecting" (1). "And so it is right to admire nature here too, because when the *viscus* (the lung) needed only to grow, she supplied it with pure blood, and when it was changed so that it moved, she made its flesh light as a feather in order that it might be easily dilated and compressed by the thorax. This is the very reason, why a passageway (the *Foramen ovale*) was made connecting the *Vena cava* and the venous artery (*V. pulmonalis*) in the fetus. In as much as this vessel (the *V. pulmonalis*), however, serves as a vein for the viscus, it was necessary, I suppose, for the other one (*A. pulmonalis*) to change into the usefulness of an artery, and therefore nature also connected this one to the great artery (the aorta), but in this case, because there was a space between the vessels, she created another, small, third vessel (the *Ductus arteriosus*) to join the two" (2).

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A more accurate description of the Galen's circulatory paradigm appeared only 13 centuries later when both Servetus (3) and Colombo (4) recognized the role of the pulmonary transit (Fig. 1): "Not just air, but blood mixed with air is sent from the lung to the arteria venosa (the pulmonary vein). Therefore, the mixture occurs in the lungs...Thus the vital spirit is transfused from the left ventricle into the arteries of the whole body".

In the same year, the Italian surgeon Leonardo Botallo pretended to have discovered the *Foramen ovale* ("*Vena arteriarum nutrix* to *nullo antea notate*") in an appendix to his monograph de catarrho (5). There is no mention of the ductus arteriosus, also not in the 1641 reedition of Botallo's de via sanguinis (6-7). Due to misinterpretation of a publisher footnote, Botallo became famous and made his way into the nomina anatomica at the Basel Conference (8) in 1895.

Embryology

In normal cardiovascular development, the proximal portions of the sixth pair of embryonic aortic arches persist as the proximal branch pulmonary arteries, and the distal portion of the left sixth arch persists as the DA, connecting the left pulmonary artery with the left dorsal aorta. Normally, the distal right sixth aortic arch loses its connection to the dorsal aorta and degenerates. This process is complete by the eighth week of fetal life and is vital for normal development of fetal circulation throughout gestation (Fig. 2).

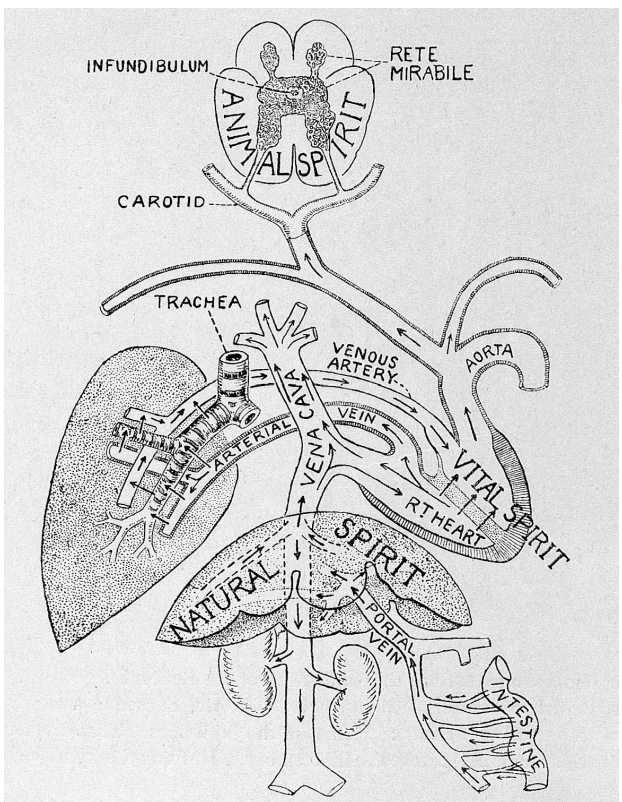

Fig. 1. *Diagram illustrating Galen's physiological scheme; with permission of the Wellcome Collections (Licensed Creative Commons Attribution CC BY 4.0).*

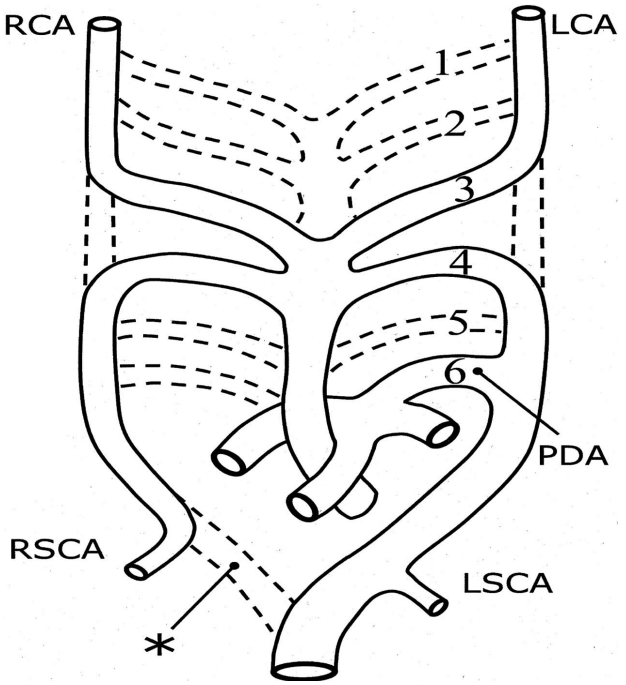

Fig. 2. *Embryonic aortic arch system. The six pairs of embryonic aortic arches are demonstrated (left-sided arches are numbered). The portions that normally involute are indicated by broken lines. The distal left sixth embryonic arch normally persists and becomes the patent ductus arteriosus (**PDA**) (*) eighth segment of the right dorsal aorta; **RCA** right carotid artery; **LCA** left carotid artery; **RSCA** right subclavian artery; **LSCA** left subclavian artery.*

Mechanisms of Normal Closure

Factors responsible for fetal patency of the DA include relatively low oxygen tension and arachidonic acid metabolites primarily prostaglandin (PGE_2), a potent relaxant of the vessel, and prostacyclin (PGI_2), (9) which are regulated by placental and

pulmonary metabolism. Postnatally, the process of DA closure occurs in two sequential steps-functional and structural. The first is due to overlapping of both physiological increase in blood oxygen tension and fall of PGE_2. Oxygen inhibits potassium and activates calcium channels, which ultimately leads to a rise in intracellular calcium concentration consequently inducing phosphorylation of the myosin light chain and thereby constriction of the spiral medial muscle layer with shortening and thickening of the ductus. Synergistically, withdrawal of PGE_2, a potent relaxant of the vessel and a prime determinant for ductal patency in utero, after elimination of the placenta contributes to its constriction.

The second, the structural phase, is a remodeling process leading to a permanent closure. It initiates antenatally and may encompass 4 distinct mechanisms: (i) development of intimal cushions; (ii) mechanical solicitation from turbulent blood flow along the narrowing lumen; (iii) intramural hypoxia due to the collapse of vasa vasorum in the constricting DA; (iv) interaction of platelets with the vessel wall (10).

Clinical epidemiology and natural history of PDA

Prompt closure of the DA after birth is essential for vascular transition to the mature circulation. In most term infants, the DA constricts in the first 72 hours after delivery (11). Failure of its closure, termed PDA, is primarily an affliction of prematurity, with the DA remaining open at 7 days of age in up to 2%, 65% and 87% of infants born respectively at 30 through 37, 25 through 28 and 24 week's gestation (12). While the DA remains open a left-to-right shunt will progressively increase as pulmonary vascular resistance declines over the first days of life. This "ductal steal" results in excessive blood flow through the lungs, predisposing to development of pulmonary congestion, pulmonary edema, and worsening respiratory failure. Similarly, diversion of blood flow from the systemic circulation may result in compromised perfusion of vital organs, including bowel, kidney, and brain. Although failure of early constriction is associated with several morbidities, i.e. bronchopulmonary dysplasia (BPD), pulmonary hemorrhage, necrotizing enterocolitis (NEC), impaired renal function, intraventricular hemorrhage (IVH), periventricular leukomalacia, and cerebral palsy, the degree to which these adverse outcomes are attributable to the hemodynamic consequences of ductal patency, has not been established (13).

Assessment of hemodynamic significance

Despite widespread use of the term, there is no consensus on the definition of hsPDA. Investigators have used ultrasound alone, or in combination with physical examination findings and biomarkers (14). Over the first days following birth, the transition from fetal to neonatal circulation induces a fall in pulmonary vascular resistance, which in turn leads to pulmonary over-circulation and systemic hypoperfusion due to systemic to pulmonary ductal shunting. The hemodynamic effects of a large left-to-right shunt associated with a PDA may be evident by physical examination, echocardiography, or measurement of serum biomarkers. Physical signs and symptoms of a PDA typically appear 3 to 4 days after delivery and are characterized by failure to wean ventilator pressures, a coarse systolic murmur at the left sternal border, increased precordial impulses, prominent peripheral pulses and either low systolic and diastolic blood pressure or low diastolic blood pressure with a widened pulse pressure (15). Often, the presence of a large ductal shunt is suspected only based on respiratory findings, such increasing requirements for supplemental oxygen, or inability to reduce mechanical ventilator support.

Echocardiography is currently the preferred tool for predicting or diagnosing ductal patency, assessing hemodynamic significance and monitoring treatment response. In an attempt to standardize the echocardiographic assessment of hemodynamic significance of a PDA, European Special Interest Group "Neonatologist-Performed Echocardiography", endorsed by the European Society for Paediatric Research and the European Board of Neonatology proposed that a comprehensive assessment of the PDA should include information on (a) PDA characteristics-diameter, flow direction, (ratio of) systolic and diastolic flow velocities; (b) Indices of pulmonary overcirculation-left ventricular output + one parameter of left-sided volume loading

OR left heart pressure loading; (c) Systemic shunt effect-Doppler flow pattern in the systemic circulation (16). The essential echocardiographic requirements for the assessment of hemodynamic significance of a PDA are summarized in Table I.

There is growing interest in exploring other biomarkers for diagnosing PDA, such as brain-type natriuretic peptide (BNP) and N-terminal pro-BNP (NTpBNP). The inactive precursor pro-BNP is released from ventricles in response to pressure or volume overload and then cleaved into the metabolically active BNP and inactive metabolite, NTpBNP (17-19) There is some evidence that in the presence of critically low diastolic arterial pressure, there is a negative effect on coronary arterial blood flow, which may lead to ischemia of the myocardium, resulting in elevated cardiac troponin T levels. Its predictive role as an exclusive biomarker in early diagnosis of hsPDA is limited and should be utilized as one component of an integrated hsPDA evaluation, which includes echocardiography and other biomarkers (20) Doppler flow measurements of the cerebral arteries are of limited value in the diagnosis of hsPDA, but in patients with low or negative end-diastolic flow, high pulsatility index or resistance indices, they may assist in earlier identification of hsPDA (21). Continuous measurement of cerebral oxygenation by near-infrared spectroscopy may be helpful in detecting a decrease in oxygenation as a sign of compromised brain perfusion due to a hsPDA (22).

Table I. *Essential echocardiographic requirements for the assessment of hsPDA.*

1) PDA characteristics of dimension and flow
a) diameter flow
b) flow direction (left to right, bidirectional with right to left ≤ or > 30% of the cardiac cycle, right to left)
c) velocity in systole and diastole (m/s) and gradient
2) Indices of pulmonary overcirculation
a) LVO (ml/kg/min)
b) Left heart volume loading : choose one parameter:
i) LA/Ao, LVEDD (mm)
ii) Pulmonary vein d wave velocity (m/s)
iii) LPA diastolic velocity (m/s)
c) Left side pressure loading : choose one parameter:
i) Mitral valve E:A
ii) IVRT (m/s)
3) Indices of Systemic shunt effect
a) Flow direction in one of the following post-ductal artery
i) descendant aorta or
ii) celiac trunk
iii) middle cerebral artery (forward, absent, reversed)
Legend :Ao aortic root, IVRT isovolumic relaxation time, LA left atrium, LPA left pulmonary artery, LVEDD left ventricular end-diastolic diameter, LVO left ventricular output

Taking into consideration the heterogeneity in clinical and echocardiography significance, similar in outline to the classifications used in NEC or hypoxic-ischemic encephalopathy, a "PDA disease staging" system that incorporates clinical condition and echocardiographic findings has been suggested, but its clinical usefulness has not been evaluated (23). As recommended in a recent leader, the inclusion of important antenatal and perinatal clinical factors should also be an important part in characterizing hemodynamic significance. Lower gestational age (GA), growth restriction, lack of antenatal steroids, and other adverse perinatal events may also play a role in exacerbating the detrimental effects of PDA shunting (24). Therefore, a definition of an hsPDA must not only include echocardiographic surrogate markers of shunt volume and a comprehensive assessment of left ventricle diastolic function but must also incorporate important clinical characteristics. Any such definition should also be prospectively evaluated to determine its ability to accurately predict ductal related morbidities facilitating a more accurate identification of high-risk infants who are likely to benefit from treatment.

Treatment Options for Closure of PDA

Generally, the treatment options for PDA have been grouped into active and conservative, with the first sub-divided into medical (indomethacin and ibuprofen) and surgical. The timing of active treatment may be prophylactic, symptomatic, or early targeted treatment. Prophylactic and early targeted treatments have the potential of closing the PDA before it is symptomatic. The prophylactic treatment, once popular, has now become controversial as it unnecessarily exposes a large proportion of preterm babies to the side effects of treatment who would have closed the PDA spontaneously. Persistence of PDA is, however, associated with increase in morbidity and mortality. Early targeted treatment

seems promising as it allows selection of babies who are less likely to close the PDA spontaneously and it has the benefits of a prophylactic approach. This approach is currently being tested in large randomized trials awaiting results (see detailed discussion below).

Since the recognition of the PDA as an important entity in the hemodynamic physiology of the premature neonate in the 1960s, a wide variety of diagnostic and treatment strategies have been implemented. From the 1970s to the mid-2000s the prophylactic approach to PDA management was widely accepted, whereby the aim was to close all DA in all low birth weight and gestation preemies as early as possible, either surgically or medically regardless of an assessment of the hemodynamic impact of the duct to the infant. In the 1980s, several small, single-center, randomized controlled trials (RCTs) suggested that prophylactic administration of indomethacin, within the first 24 hours after birth, reduced the incidence of severe grades of intracranial hemorrhage, symptomatic PDA, and surgical PDA ligation (25-30). This led to a widely publicized multicenter RCT, the Ment trial, (31) that confirmed the benefits previously observed in the smaller, single-center RCTs. The TIPP trial conducted a few years later, (32) although confirmed the beneficial effects of early intervention in reducing the incidence of severe intracranial hemorrhage and PDA in extremely low birth weight , failed to find a benefit in its primary outcome (improved survival/neurodevelopmental outcome) and may have discouraged, therefore, the prophylaxis use of indomethacin (33).

Early targeted treatment is an attractive potential option, as only those infants likely to develop a significant PDA are treated. The echocardiography in extreme preterm infants in the first 72hrs should use criteria that have a high sensitivity for diagnosing PDA that is unlikely to close spontaneously. It should take account of the transitional circulation and be able to identify babies who have impending or established pulmonary hypertension. There is little evidence using this approach, with few studies, all small sample sizes. The results of the Australian double-blind randomized controlled prematurely withheld (34) have shown in preemies treated with indomethacin a reduction in early pulmonary haemorrhage and later medical treatment but no effect on the primary outcome of death or abnormal cranial ultrasound.

Currently, there are ongoing large randomised trials including RCT-Baby OSCAR, the French TRIOCAPI, the Dutch BeNEDuCTUS and the Australian U-PDA aiming to study the impact of early-targeted active medical treatment and supportive care alone of large PDA in very preterm infants. With these limited data and the absence of long-term outcomes it is difficult to draw any meaningful conclusions. The ongoing substantial heterogeneity in clinical practice regarding PDA management was recently highlighted by the European Population-Based Cohort Study (EPICE) study, which reported that PDA treatment varied from 10% to 39% between regions, and that this difference could not be explained by differences in perinatal characteristics (35).

Both indomethacin and ibuprofen reduce prostaglandin-mediated vasodilatation by inhibition of the cyclo-oxygenase and peroxidase sites on prostaglandin H_2 synthetase (PGHS) inhibitors. Efficacy decreases postnatally as the balance of vasodilators changes (36). When used prophylactically, intravenous indomethacin and ibuprofen appear to have similar efficacy (37-38), but only the first significantly reduces the risk of IVH (39). A recent meta-analysis Cochrane review reports equivalent efficacy with indomethacin with reduced incidence of NEC, but this may be related to heterogeneity of gestation, dosage and administration route (40). Greater efficacy with higher ibuprofen doses (20, 10 and 10 mg/kg) has been reported at low GA (41). The optimal age-appropriate dosing schedule is still under consideration since the effects of ibuprofen on total and free serum bilirubin concentrations raise concerns about the safety of some of the higher dose options. Enteral ibuprofen may offer benefits, possibly because of its longer half-life, even at lower GA and birth weights (42-43).

Major concerns with indomethacin and ibuprofen are their detrimental effects on the gastrointestinal tract and kidneys. Spontaneous intestinal perforation has been associated with both indomethacin and

ibuprofen, particularly if given in the first week or with comorbid hypotension or glucocorticoids (44). The meta-analysis of RCTs that compared oral ibuprofen to indomethacin suggests that oral ibuprofen treatment may be associated with a lower incidence of NEC than indomethacin (40). Detrimental effects on renal function include oliguria and decreased creatinine clearance (45). Usually, these can be managed with anticipatory fluid restriction, but PGHS inhibitors should be avoided in patients with hypotension or renal impairment. Moreover, there is biological variability in response to all therapies; longer courses of treatment may be required in some infants, but exposure to PGHS can be minimized by echocardiographic evaluation of individual treatment response (46).

Paracetamol has been less extensively studied but appears to have similar efficacy without side effects (47-48). PDA closure is probably mediated by inhibition at the peroxidase site of PGHS (49). Paracetamol has been used for rescue therapy in extremely premature infants after failed response to indomethacin, resulting in 46% of infants having a smaller or closed DA (50). When used as primary treatment, the efficacy ranges from 70% to 81% (51-52). Efficacy appears to be affected by both gestational age and postnatal age, with improved efficacy noted when treatment was started within the first week (53). The paracetamol dose used in most case series and trials was 15 mg/kg dose every 6 hours for 3 days (52).

The appropriateness and optimal timing of surgical ligation is the subject of much debate and controversy. Broadly, surgical intervention is contemplated if medical treatment fails and the PDA remains hemodynamically significant, based on clinical and echocardiography markers. However, in some centers, although there is no evidence to support this approach, surgery is considered the first-line treatment in infants with NEC, IVH, pulmonary hemorrhage, thrombocytopenia, or severe oliguria (54). Ligation is typically performed with an open thoracic approach, and either using a metal clip or tying off the vessel.

Direct surgery-related complications include intraoperative bleeding, pneumothorax, vocal cord paralysis, chylothorax, scoliosis, and phrenic nerve injury. The collective incidence of these complications is usually low (55). Sudden changes in cardiopulmonary physiology after surgery may lead to a post-ligation cardiac syndrome (PLCS) in up to 50% of infants. Post-ligation cardiac syndrome, defined as hypotension requiring inotropic support and failure of oxygenation and ventilation, may occur 6-12 hours following ligation due to left ventricular systolic and diastolic failure, respectively. Implement of perioperative strategies aimed to reduce the frequency of post-ligation may improve outcomes for neonates in this vulnerable patient population (56).

Early PDA ligation is an independent risk factor for BPD (57) and worse neurodevelopment compared with ligation at a later age (58). Reexamined data from the Trial of Indomethacin Prophylaxis suggest that surgical PDA ligation may be associated with increased risks of BPD, severe retinopathy of prematurity and neurosensory impairment in extremely low birth weight infants (59). In retrospective cohort study of 754 preterm infants younger than 28 weeks gestational age, PDA ligation there were no differences in chronic lung disease, retinopathy of prematurity, or neurodevelopmental impairment among survivors. Therefore, previously reported poor outcomes after PDA ligation may be overestimated by trial design (60), suggesting that surgical approaches deserve full consideration for infants with refractory, symptomatic PDA. More recently, transcatheter PDA closure has been described as a viable option in very low weight infants. Over the last few years, interventional catheterization has emerged as an alternative to surgery for closure of a PDA in very low weight infants. To prevent complications, it requires a perfect selection of the device and an accurate positioning. However, further studies are needed to optimize the indications and timing of hsPDA closure and their consequences on clinical outcome (61).

The concept of a conservative approach has been fraught with much controversy and has led to confusion due to variability in its interpretation and application. The approach suggested by Benitz et al. is based on the premise that most PDAs eventually

close spontaneously in premature infants prior to hospitalization and may not require active medical or surgical closure management. Rather, modulation of trans-ductal flow by optimizing the determinants of Poiseuille's law, namely trans-ductal pressure or viscosity, may be preferable (62).

The strategies used to limit the consequences of a high-volume left-to right ductal shunting include fluid restriction, diuretics, modifications to neonatal ventilation support, permissive hypercapnia, targeting lower oxygen saturation ranges, tolerance of metabolic alkalosis, and maintaining a higher hematocrit (63-64). It is, however, prudent to recognize that the conservative approach does not imply "ignoring" the presence of a PDA, nor does it preclude active assessment and management of the PDA or permit that the known consequences of significant ductal patency on neonatal morbidity may be ignored (65).

As in other medical issues controversies depended upon the status of the cumulative contemporary medical knowledge, changing patient population characteristics, and mostly, the authoritative position of the persons offering opinions. We believe that understanding the natural history of the DA pathophysiology, relying on the combination of ultrasound findings and clinical markers, may be useful to clinicians in recognizing the selected PDA that should be closed to avoid adverse outcomes.

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