Seminars in Fetal and Neonatal Medicine xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Fetal and Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Non-pharmacological management of a hemodynamically significant patent ductus arteriosus

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ARTICLE INFO

Keywords:
Patent ductus arteriosus
Management

ABSTRACT

The association between the patent ductus arteriosus (PDA) and neonatal morbidity, mortality and poor neurodevelopmental outcome in later childhood has been the focus of intense debate for decades. The lack of evidence supporting therapeutic strategies aimed at achieving PDA closure has led to the widespread adoption of conservative management aimed at mitigating the impact of shunt volume without achieving ductal closure. In this article, we review this management approach, describe the supportive evidence and potential complications associated with this strategy.

1. Introduction

The association between the patent ductus arteriosus (PDA) and neonatal morbidity, mortality, and poor neurodevelopmental outcome in later childhood has been the focus of intense debate for decades. Despite numerous observational studies and more than 50 randomized controlled trials (RCTs), an agreed consensus on its management in the premature neonatal population remains elusive. Controversy still exists regarding the determination (and definition) of ductal hemodynamic significance, appropriate identification of infants for therapy, selection of treatment regimen, and the exact impact of PDA treatment on meaningful short- and long-term outcomes. 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 [1].

There is increasing consensus that shunt volume, rather than periodic estimates of transductal diameter, represents a more holistic and accurate measure of the hemodynamic impact of a PDA. The physiological impact of the duct is governed by Poiseuille's law which states that "At a constant driving pressure the flow rate of liquid through a tube is directly proportional to the fourth power of the radius of the tube and inversely proportional to the length and viscosity of the tube." Poiseuille's law confirms that the diameter of the blood vessel plays the greatest role of all factors in determining the rate of blood flow through a vessel, as the rate of blood flow through a vessel is directly proportional to the fourth power of the radius of that vessel. In the setting of a PDA, vessel length, the pressure gradient across the vessel, blood viscosity, and the diameter of the vessel all change constantly over the first few days following birth. This dynamic nature of the components which govern flow makes estimation of the volume of the shunt difficult at best (Fig. 1).

2. The active treatment approach

Over the first days following birth, the transition from fetal to neonatal circulation induces a fall in pulmonary vascular resistance. Shunting from the systemic to pulmonary circulation across the ductus due to this fall in pulmonary vascular resistance leads to pulmonary over-circulation and systemic hypoperfusion. This is the mechanism by which the ductus arteriosus is thought to be associated with a variety of adverse neonatal outcomes including intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and lower neurodevelopmental scores [2–4]. 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 adopted, whereby the aim was to close all ducts in all infants as early as possible, either surgically or medically by administering indomethacin or ibuprofen, regardless of an

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https://doi.org/10.1016/j.siny.2018.03.008

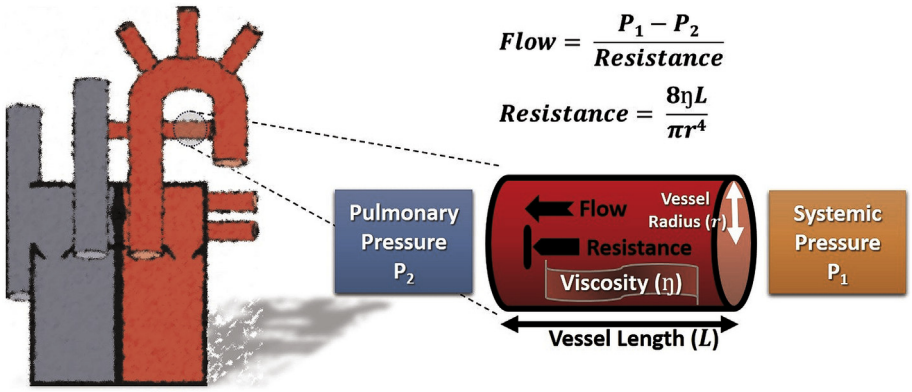

Fig. 1. Determinants of flow across the patent ductus arteriosus. Flow is proportional to the pressure gradient across the vessel and inversely proportional to the resistance of the vessel. Resistance is governed by the viscosity and length of the vessel in addition to the radius (see formulae).

assessment of the hemodynamic impact of the duct to the infant [5]. Although surgical and medical prophylaxis demonstrated short-term benefits, including a reduction in severe NEC and a decreased incidence of severe IVH, neither strategy was found to decrease the frequency of significant, long-term neonatal morbidities such as chronic lung disease (CLD) at 36 weeks postmenstrual age (PMA) and neurodevelopmental impairment at 18 months corrected age in extremely low birth weight infants [6]. A serious concern of such a universal approach is that it exposes all infants to potentially harmful therapies which may be unnecessary. Treatments with non-steroidal anti-inflammatory medications are known to have potential side-effects including intestinal perforation and renal impairment, whereas surgical ligation may cause vocal cord paresis, chylothorax and post-ligation cardiac syndrome [7–10]. Additionally, for neonates with unrecognized persistent pulmonary hypertension (PPHN) the PDA may be acting as a vital 'pop-off valve' to alleviate right ventricular afterload, and treatment in this cohort may be detrimental [10].

Although PDA is significantly associated with many adverse neonatal outcomes, further evidence emerged which consistently demonstrated that prophylactic application of pharmacological agents only ameliorated immediate PDA effects through increased ductal closure rates, decreased frequency of symptomatic PDA and the reduced requirement for surgical ligation. There was, however, no associated improvement in critical outcomes such as mortality, retinopathy of prematurity (ROP), or BPD [7,11]. Additionally, high rates of spontaneous PDA closure in neonates born at > 28 weeks gestation (73%) and infants born at 26–29 weeks gestation who did not have respiratory distress syndrome (93%) were reported [12,13]. Therefore, over time, scepticism arose regarding the utility and benefit of active PDA treatment and support for the prophylactic regimen waned. The conservative or permissive approach gained traction and studies began to investigate its potential benefits [14,15]. This trend toward conservative management was reflected in a 2017 study of 280 neonatal intensive care units across the USA which reported a decline in PDA diagnosis and a reduction in the use of indomethacin, ibuprofen and PDA ligation in infants born prematurely between 23 and 30 weeks gestation from 2006 to 2015. Such findings are mirrored in other American and Canadian reports which document a falling incidence of pharmacological and surgical interventions for PDA closure over this timeframe [16–18].

3. Conservative management strategies

Conservative PDA management amalgamates various clinical strategies to mitigate the degree of left-to-right ductal shunting without pursuing active PDA closure through medical or surgical means. This is based on the premise that most PDAs eventually close spontaneously in premature infants prior to hospital discharge. 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 [19]. Echocardiography assessment of a PDA is an integral component of the conservative approach and should be carried out to assess the duct's impact on the circulation. Once identified, this strategy aims to ameliorate the consequences of ductal shunting via fluid restriction, diuretics, modifications to neonatal ventilation support, permissive hypercapnia, targeting lower oxygen saturation ranges, tolerance of metabolic alkalosis, and maintaining a higher hematocrit [11,20]. Such strategies aim to actively manage the consequences of a high-volume shunt through an increase in pulmonary vascular resistance (PVR) and/or a decrease in pulmonary arterial blood flow in order to limit left-to-right ductal shunting.

3.1. Fluid intake restriction

Fluid restriction to ≤130 mL/kg/day is widely reported as a suitable approach to PDA management [21]. The physiological rationale is that fluid restriction minimizes left-heart volume loading and pulmonary over-circulation, thereby potentially reducing the risk of pulmonary edema. This practice became more widespread following a 2008 Cochrane review (updated in 2014) of five RCTs which reported a reduced incidence of PDA when fluid restriction was undertaken. This, however, did not result in a reduction of other morbidities including CLD, IVH, or death [22]. There was a higher incidence of weight loss and an increased risk of dehydration associated with this strategy. The long-term impact of this strategy is currently unknown. Adequate nutrition is essential for brain development and reducing intake without optimizing caloric content, and maintaining adequate weight gain could result in adverse neurodevelopmental outcomes [23]. The majority of those studies were conducted in the early 1980s and 1990s, and therefore this practice remained untested in the modern era. A recent small prospective observational study of 18 infants with a mean gestation of 24.8 weeks found that fluid restriction (from 145 to 108 mL/kg/day) did not have beneficial effects on the pulmonary or systemic hemodynamics in preterm infants [24]. There was a significant reduction in superior vena cava flow and left ventricular output, suggesting a reduction in systemic blood flow. A judicious approach to fluid restriction is recommended, particularly in the subgroup of patients with compromised systemic perfusion.

3.2. Diuretic medication

Diuretic medications are often used to alleviate PDA-associated pulmonary edema and left-heart volume loading. Therapy is usually reserved for infants in whom fluid restriction alone fails to alleviate