Ligation of the Patent Ductus Arteriosus in Preterm Infants: Understanding the Physiology

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The diagnosis and management of preterm neonates with a patent ductus arteriosus (PDA) that fails to close after medical management poses a major challenge. The association of prolonged ductal patency with morbidities including feeding intolerance, necrotizing enterocolitis (NEC), severe intraventricular hemorrhage (IVH), metabolic acidosis, renal failure, increased ventilator dependence, bronchopulmonary dysplasia (BPD), and pulmonary hemorrhage are well recognized.[1,2] In addition, a PDA failing medical treatment is associated with a 4- to 7-fold increase in mortality.[3] This association remains significant after adjustment for gestation, birth weight, disease severity, and other comorbidities, including IVH, NEC, and sepsis.

The decision to perform surgical PDA ligation has been challenged recently, owing to its possible association with adverse neurologic outcomes.[4,5] The magnitude of postoperative instability in some patients often dissuades neonatologists from choosing surgery.[6] Neonatologists face uncertainty regarding the optimal approach to this patient population. In this article, we outline the concerns surrounding PDA ligation, review the selection process for intervention, and discuss the perioperative physiological changes that may explain the link between ligation and adverse neurodevelopmental outcomes. In addition, we propose a postoperative management strategy aimed at minimizing hemodynamic compromise after PDA ligation.

The Ligation Decision?

The appropriateness and optimal timing of surgical ligation is the subject of much debate and recent controversy. In general, surgical intervention is contemplated if medical treatment fails and the PDA remains hemodynamically significant, based on clinical and echocardiography markers (discussed later). In some centers, surgery may be considered the first-line treatment in infants with NEC, IVH, pulmonary hemorrhage, thrombocytopenia, or severe oliguria, although there is no evidence to support this approach.[7] It is also possible that delays between attempted medical treatments and surgical ligation may contribute to complications.[3] In contrast, earlier surgery subjects patients to the adaptive risks of surgical ligation.

BPD	Bronchopulmonary dysplasia
CBV	Cerebral blood volume
IVH	Intraventricular hemorrhage
IVRT	Isovolumic relaxation time
LV	Left ventricular
LVO	LV output
NEC	Necrotizing enterocolitis
NIRS	Near-infrared spectroscopy
PDA	Patent ductus arteriosus
PLCS	Postligation cardiac syndrome
SVR	Systemic vascular resistance
TOI	Tissue oxygenation index
VCFc	Velocity of circumferential fiber shortening

Cardiovascular Adaption to PDA Ligation

Surgical ligation of a PDA leads to sudden changes in cardiovascular physiology, specifically a rise in left ventricular (LV) afterload and a fall in LV preload (**Figure 1**), with a resulting sudden drop in LV output (LVO).[8-10] The relative contributions of altered preload and altered afterload to postoperative instability require further characterization. This may enable the identification of more physiologically appropriate treatments.

Our understanding of postligation cardiovascular physiology has improved substantially over the last 2 decades. The physiological factors contributing to cardiovascular instability were first characterized in premature baboons. Specifically, a temporal relationship between impaired LV performance and increased systemic vascular resistance was identified, coinciding with changes in arterial pressure.[11] Subsequent prospective observational studies in human neonates have also demonstrated declining LV performance in the immediate postoperative period, coinciding with decreased pulmonary venous return (preload) and increased systemic vascular resistance (afterload). The clinical effects of this low cardiac output state become apparent usually at 6-12 hours after ligation.[10-12]

The recent prospective observational study conducted at our center is the largest to date, and the first to characterize myocardial performance at the peak time of clinical stability.[6] Impairment in indices of LV systolic performance, namely LV shortening fraction and the velocity of circumferential fiber shortening (VCFc), was identified 8 hours after surgical intervention, which coincided with clinical deterioration. Given that the effect of preload change is greatest within the first 1-2 hours after surgery, this change is unlikely the major determinant of this deterioration. An increase in the

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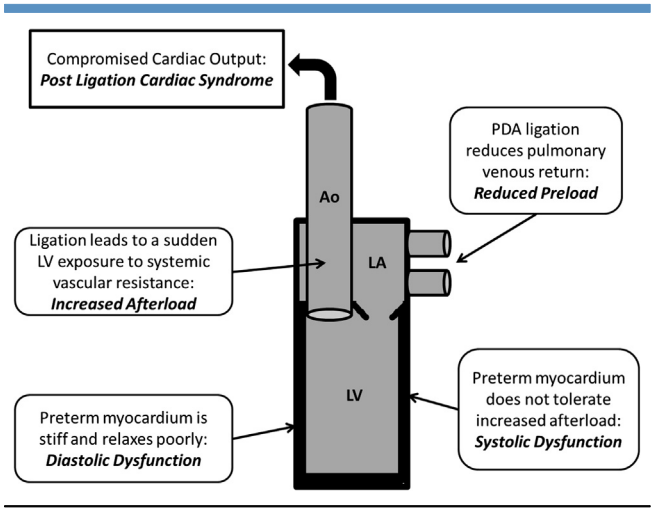

Figure 1. Physiological determinants of PLCS in preterm infants. *Ao*, aorta; *LA*, left atrium.

slope of the inverse relationship between end-systolic wall stress and VCFc suggests that the changes in myocardial performance are related to LV afterload. The timing of the clinical deterioration (8-12 hours after surgery) coincides with the period of maximal afterload exposure.[6] Infants weighing <1000 g were at greatest risk of compromise, which is biologically plausible, considering that the preterm myocardium is not conditioned to handle substantial changes in either preload or afterload. Both animal and preterm human data have shown that VCFc, a load-dependent measure of contractility, is inversely proportional to end-systolic wall stress, a measure of LV afterload.[13,14] Clinical studies of therapeutic interventions provide biological validation for the role of LV afterload in the pathogenesis of disease. In a retrospective cohort study, Lemyre et al[15] found that intraoperative volume support did not reduce the need for postoperative inotropic agents. In contrast, in another study, early administration of milrinone, an inotropic drug with vasodilator properties, to infants with low cardiac output led to a reduction in postoperative hemodynamic instability.[9]

Pulmonary Adaption to PDA Ligation

The presence of prolonged left-to-right shunting across the PDA leads to altered pulmonary compliance. Preterm baboons (125 days [67%] gestation) exposed to a moderated-size PDA demonstrated impaired pulmonary function and arrested alveolar development and surface area compared with age-matched fetuses (140 days gestation).[16] Several human studies have demonstrated decreased lung compliance in preterm infants with PDA compared with controls, without changes in airway resistance. Infants treated with indomethacin demonstrated improved lung compliance after successful medical PDA closure.[17-19] The changes in lung compliance after PDA ligation are more profound. In a group of 16 preterm infants, dynamic lung compliance improved, coupled with increases in tidal volume and minute ventilation.[20] It is prudent to consider these changes after ligation, given that lung overdistention could possibly further compromise vena cava and pulmonary venous flow, leading to impaired ventricular filling and contributing to decreased cardiac output.

Immediate and Short-Term Surgical Complications

Changes in cardiopulmonary physiology after surgery may lead to a postligation cardiac syndrome (PLCS) in up to 50% of infants.[21] In this prospective observational study, we defined PLCS as systolic blood pressure below the 3rd percentile expected for gestational age requiring 1 or more cardiotropic agents and accompanied by ventilation or oxygenation failure. This definition may be too restrictive, however; PLCS is likely a spectrum disorder of varying severity, with some infants developing profound hypotension and others suffering exclusively from ventilation and oxygenation failure. Onset is typically 6-12 hours after ligation and is related to increased afterload.[6,22] A recent study reported higher mortality in infants with PLCS compared with controls (33% vs 11%).[21]

Several preoperative risk factors for PLCS have been identified. In an earlier study, we found that younger postnatal age at the time of ligation was associated with increased need for postoperative cardiotropic support.[22] Other studies have reported an increased risk of PLCS in infants born at <26 weeks' gestation or at a birth weight of <750-1000 g.[23-25] In addition, compared with infants weighing >1000 g, those weighing <1000 g are more likely to develop low postoperative LVO (defined as <170 mL/kg/minute in this study), lower shortening fraction, systolic blood pressure below the 3rd percentile, and an increased need for inotropic agents (30% vs 4%).[6] Some investigators have attempted to use echocardiography to predict PLCS. PDA size before ligation was found to have a negative correlation with postoperative LVO,[10] and an inverse correlation between peak velocity across the PDA and postoperative ventilator dependence has been reported.[24] Our group recently reported that LVO <200 minute/kg/minute measured within 1 hour after PDA ligation predicted 100% of infants who subsequently developed PLCS.[9]

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.[26] In a large series of 306 ligations, Mikhial et al[27] reported a 2% incidence of intraoperative bleeding, a <5% incidence of air leaks, and no direct surgery-related deaths.

Long-Term Complications

Intraoperative Cerebral Hemodynamic Changes

Reports linking PDA ligation with adverse long term neurodevelopmental outcomes are conflicting.[4,28] Nevertheless, it is important for clinicians to understand the intraoperative and postoperative physiological alterations that may affect