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ORIGINAL ARTICLE

Patent ductus arteriosus: pathophysiology and management

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Patent ductus arteriosus (PDA) in preterm newborns prior to 28 weeks of gestation has led to many challenges regarding the type and timing of treatment regimens. A PDA results in increased pulmonary blood flow and redistribution of flow to other organs. Several co-morbidities (i.e., necrotizing enterocolitis, intracranial hemorrhage, pulmonary edema/hemorrhage, bronchopulmonary dysplasia, and retinopathy) are associated with the presence of a PDA, but whether or not a PDA is responsible for their development is still unclear. The prostaglandin inhibitor, indomethacin, is effective in the treatment of PDA. Questions regarding the optimal timing of the intervention – early prophylaxis or treatment, once signs and symptoms become evident – have challenged physicians for decades. Both evidence and experience are explored in this article. Comparative physiology between the full-term and preterm newborn and the barriers preventing the necessary cascade of events leading to permanent constriction of the PDA are reviewed.

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Introduction

The ductus arteriosus is an essential component of fetal circulation allowing for communication between the pulmonary artery and the aorta. After birth, it usually closes within 48 h. A persistently patent ductus arteriosus (PDA) is diagnosed when the ductus arteriosus fails to close after 72 h.[1] Patent ductus arteriosus increases pulmonary blood flow and left atrial and ventricular volumes, and produces a redistribution of systemic blood flow. Clinical complications are dependent on the degree of left to right shunting through the ductus. Hemodynamic symptoms from a PDA are present in 55–70% of infants delivered below 1000 g or prior to 28 weeks of gestation and may require either medical or surgical intervention.[2]

There are various factors that contribute to patency of the ductus arteriosus. Similarly, there are numerous strategies in the management of these patients. Animal models have helped to unravel the pathophysiology of the PDA and to understand the factors responsible for its closure or patency after birth. The appropriate timing of prostaglandin (PG) inhibitors, such as indomethacin, is another area of debate. There is concern about early prophylaxis with indomethacin since some infants might be exposed to an unnecessary agent if the ductus would have closed on its own. On the other hand, delaying treatment until one can document that the PDA is unlikely to undergo spontaneous closure may increase the infant's chances of developing morbidities caused by the PDA and make the success of pharmacological closure less likely. This article will review both the published evidence and the experience in the management of PDA.

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Pathophysiology

In utero, low fetal systemic arterial oxygen tension (PaO_2) and elevated circulating PGs (in addition to PGs made within the ductus wall itself) play a significant role in keeping the lumen of the ductus arteriosus patent. This is necessary for fetal circulation and survival. After a full-term birth, the ductus closes within 24–48 h of delivery.[2]

The closure of the ductus arteriosus in full-term infants occurs in two steps. Initially, within the first few hours after birth, increased arterial PaO_2 and decreased circulating PGs allow the smooth muscle media of the ductus to constrict. As a result of the constriction, the inner muscle wall of the ductus arteriosus develops profound ischemic hypoxia which leads to the formation of vascular endothelial growth factor, transforming growth factor-beta, and other inflammatory mediators and growth factors that transform the ductus into a non-contractile ligament.[3]

Conversely, in preterm infants, the ductus often fails to constrict in the days following birth. Even in those preterm infants who achieve ductus constriction, the ductus frequently fails to develop the level of profound hypoxic ischemia needed to cause remodeling of the artery. As a result, many premature infants with a closed ductus can reopen their ductus and develop clinical symptoms related to the PDA.[4]

Several endogenous vasodilators made within the ductus wall (e.g., PGs and nitric oxide) are known to inhibit ductus closure. Among the prostaglandins, PGE_2 appears to be the most important in keeping the ductus patent. Reduction of PG synthesis by inhibition of cyclooxygenase (COX) produces constriction of the ductus.[1] In addition to PG, nitric oxide is produced by the ductus. Nitric oxide synthase is found in both the endothelial cells lining the ductus lumen and in the vasa vasorum that lie in the ductus adventitia. The premature ductus is more sensitive to the effects of both PGs and nitric oxide. Clinical observations reveal that PG inhibitors are more effective if given on the first day after birth and may be less effective as postnatal age increases. Animal studies reveal that nitric oxide production increases in the ductus wall after birth and may play a role in the decreasing effectiveness of indomethacin with increasing postnatal age. In both animal and human studies, a combination of indomethacin and nitric oxide synthase inhibition, several days after birth, causes more effective ductus constriction than indomethacin alone[2] (Figure 1).

There are several other reasons why the PDA may become less responsive to indomethacin after birth in the preterm infant. Shortly after birth, there is an inflammatory response that develops within the wall of the ductus arteriosus. This response is associated with the influx of monocytes/macrophages into the ductus wall and the induction of several cytokines such as interferon gamma and tumor necrosis factor-alpha. Several of these cytokines are potent vasodilators that act through mechanisms independent of either PGs or nitric oxide.[5]

Another reason for the diminished contractile responsiveness of the ductus to indomethacin after birth has to do with energetics within the ductus wall. In the premature ductus, even when the lumen of the ductus remains patent, energy metabolites (i.e., glucose, oxygen, and ATP) begin to fall after birth. Although this is not profound enough to cause cell death and remodeling, it does interfere with the ductus' ability to contract.[6]

It should be noted that even when the premature ductus does constrict, it remains relatively resistant to developing profound hypoxia, which is the primary signal driving the cell death and inflammatory cascade resulting in remodeling. Although the main source of nutrients in the ductus is through the lumen, a substantial amount is provided by the vasa vasorum, which supply to the outer wall of the ductus. The vasa vasorum enter the outer wall of the ductus and grow toward the lumen. They stop growing approximately 400–500 μm from the lumen. The distance between the lumen and the vasa vasorum is called the avascular zone of the vessel. The thickness of the avascular zone (400–500 μm) defines the furthest distance that two sources of nutrients can be separated and still maintain oxygen and nutrient homeostasis in the tissue. In the full-term ductus, the increased tissue pressure occurring during ductus constriction occludes the vasa vasorum and prevents any flow of nutrients to and through the outer wall of the vessel. This results in the 'effective' avascular zone expanding from 500 μm to the entire thickness of the vessel wall (approximately 1.2 mm). When this occurs, the center of the ductus wall becomes profoundly ischemic.[3]

In the premature (24 week gestation) ductus, the vessel wall is only about 200 μm in thickness (Figure 2). The scattered vasa vasorum in the vessel lie in the adventitia and do not penetrate the muscle media. The thin-walled immature ductus does not need the

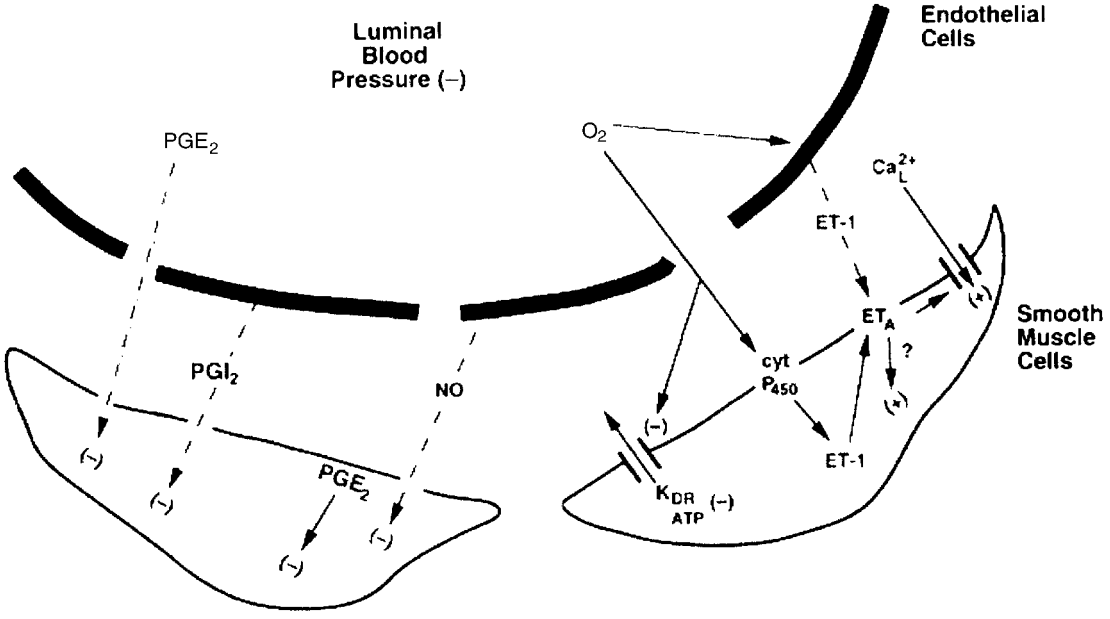

Figure 1 Factors involved in the patency of the ductus. PGE_2 = prostaglandin E_2, PGI_2 = prostaglandin I_2, NO = nitric oxide, K_{DR} = direct rectifying voltage-sensitive potassium channel, ATP = adenosine triphosphate, cyt P_{450} = cytochrome P450, ET-1 = endothelin 1, ET_A = endothelin A

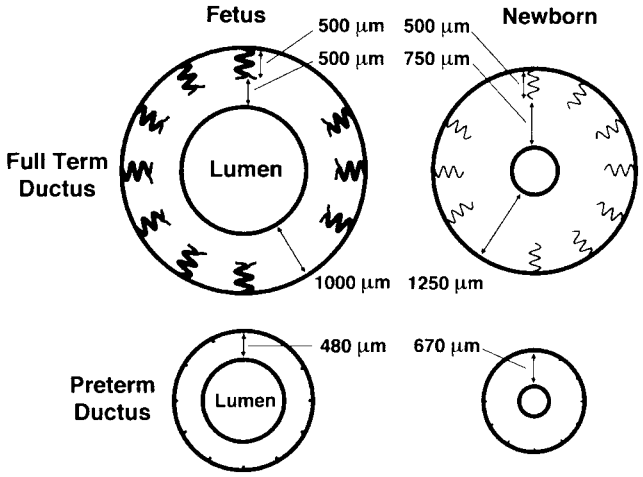

Figure 2 Ductus arteriosus in the fetus and full-term and preterm newborn.

vasa vasorum for nutrient flow because it can receive all of its nutrient flow from its lumen. As a result, during closure of the preterm ductus, there is no vulnerable region of the wall that is at risk for loss of vasa vasorum flow. Although the avascular zone of the preterm ductus wall thickens slightly after birth, it does not thicken to the extent that occurs at term. As a result, the preterm ductus arteriosus is less likely to develop the severe degree of hypoxia that is necessary for ductus remodeling.[3] In order for the preterm ductus to develop the degree of ischemia needed to set up the remodeling cascade, it is essential that it develop complete luminal obliteration and complete elimination of nutrient flow to its wall.

Clinical findings and associations

Patent ductus arteriosus is associated with several neonatal morbidities. Both animal and human studies have demonstrated alterations in blood pressure with a drop in the mean, as well as, systolic and diastolic pressures. Left ventricular output can increase by as much as 100%. In spite of this increased cardiac output, redistribution in blood flow results in increased flow to the lungs and decreased flow to the pressure passive organs like the intestines, skin, muscle, and kidneys. This redistribution may result in metabolic acidosis, necrotizing enterocolitis (NEC), and pulmonary edema/hemorrhage.

Timing is important in evaluating when different morbidities will present. Intracranial hemorrhage usually occurs within the first 3 days after birth. Similarly, marked pulmonary edema and pulmonary hemorrhage secondary to fluid shifts and ductus patency occurs within 2–3 days after birth. Necrotizing enterocolitis usually presents 5 days after birth.[7]

Treatment

Indomethacin (Indocin® IV, Merck, West Point, PA, USA) is a PG inhibitor that has been used for the closure of PDA since the late 1970s. Indomethacin has been utilized as early symptomatic therapy, late symptomatic therapy, or prophylactic therapy.[7]

There is still ongoing debate regarding when to treat a PDA in premature infants who are born before 28 weeks of gestation. Physicians for decades have weighed the pros and cons of early prophylactic therapy versus late treatment for infants who are most at risk for developing complications from a PDA. Clinical experience reveals that if a delayed treatment approach is used (waiting until hemodynamic symptoms of a PDA appear), 55–70% of infants born before 28 weeks of gestation and weighing less than 1000 g at birth ultimately will be treated for a PDA during their hospitalization. The evidence suggests that preterm infants require a tighter degree of constriction than full-term infants to develop the anatomic changes that lead to permanent ductus closure. Even minimal degrees of ductus patency after indomethacin treatment will prevent remodeling and lead to subsequent clinical reopening. Clinical and laboratory experience also indicates that PG inhibitors given as prophylaxis, early after birth, are more effective in producing tight ductus constriction than waiting several days for symptoms to develop. The delay of several days may necessitate the use of other vasoconstrictive agents, in addition to indomethacin, to produce the same degree of ductus closure. Preterm infants who are born before 28 weeks of gestation and who receive prophylaxis with indomethacin by 6–15 h after birth consistently have a lower incidence of serious pulmonary hemorrhage, intracranial hemorrhage (grade III/IV), and need for ductus ligation.[8–10]

A platelet count of at least 50 000 is necessary prior to the first dose of indomethacin. A PT and PTT should be obtained if there is any concern about bleeding. Serum creatinine and platelet count should be checked prior to second and third doses. Because of decreased gastrointestinal blood flow secondary to indomethacin, the infant is restricted to no oral intake during treatment and for 48 h after treatment is completed. Urine output should be monitored since the infant may experience a transient decrease in output requiring alterations in fluid administration. Indomethacin may be restarted when urine output is greater than 1 ml/kg/h.

In infants less than 28 weeks gestation, a Doppler exam of the ductus should be obtained between the second and third indomethacin dose. If the Doppler study reveals any lumen patency, even if the vessel is constricted, there is at least an 80% chance of reopening. In contrast, if the ductus is closed on Doppler, there is less than 15% chance that it will reopen in the future. Therefore, if there is evidence of ductus patency, regardless of clinical signs, an additional three doses of indomethacin (0.1 mg/kg) should be administered at 24 h intervals. This additional treatment will significantly increase the likelihood of permanent ductus closure.[11] An additional Doppler should be

Table 1 Contraindications to the administration of indomethacin[12]

Active bleeding
Active or suspected necrotizing enterocolitis
Creatinine $\geqslant$2.0 mg/dl
Urine output $<$0.6 ml/kg/h
Platelet count $<$50 000
Active and untreated infection
Suspected congenital heart disease
Known gastrointestinal or renal anomaly

Table 2 Indomethacin dosing[12]

Birth weight	*Regimen*		
	First dose	*Second dose*	*Third dose*
Gestational age $\geqslant$ *28 weeks, with clinical manifestations of PDA*			
$>$1250 g	0.2 mg/kg	0.2 mg/kg 12 h after first dose	0.2 mg/kg 24 h after second dose
1000–1250 g	0.2 mg/kg	0.1 mg/kg 12 h after first dose	0.1 mg/kg 24 h after second dose
Gestation $<$ *28 weeks, prophylactic 6–15 h after birth*			
	0.2 mg/kg	0.1 mg/kg 24 h after the first dose	0.1 mg/kg 24 h after the second dose

conducted after the sixth dose of indomethacin.[12] This Doppler reading will provide information about the likelihood of subsequent reopening. Table 1 lists the contraindications against indomethacin use.

Current evidence suggests that infants with a high chance of developing a pulmonary hemorrhage, grade III/IV intracranial hemorrhage, or the need for surgical ligation may benefit from early prophylactic treatment with indomethacin. As for others, treatment can be delayed until alterations in pulmonary compliance or gastrointestinal morbidities are likely to occur. In infants who are born at 28 weeks gestation or later, a PDA is usually not treated until two or more hemodynamic signs and symptoms are present, that is, increased pulse volume or widened pulse pressure, hyperactive precordium, increased pulmonary vascular markings on chest X-ray, or echocardiographic findings of left ventricular enlargement, and/or holodiastolic reversal of flow in the descending aorta. Table 2 summarizes one approach for the dosing of indomethacin based upon birth weight and gestation.

Limited evidence-based outcomes with regard to direct comparative strategies impede the ability to reach the depth of consensus needed when treating a PDA in infants who are born at 28 weeks gestation or later. While the PDA clearly plays a role in the development of the *reversible* changes in pulmonary mechanics that result from pulmonary edema, its role in producing other long-term *irreversible* pulmonary morbidities, like pulmonary remodeling and chronic lung disease, have yet to be demonstrated. Similarly, its role in the development of NEC is based on limited clinical data acquired more than 20 years ago. Additional clinical trials should be designed and conducted in order to gather the evidence needed to determine ideal treatment parameters. One approach to evaluate the role of a PDA in pulmonary and gastrointestinal morbidities might compare early prophylaxis with indomethacin to no treatment or delayed treatment (after 2–3 weeks), when the presence of a moderate PDA is firmly established and the exposure to the left to right shunt is of chronic duration. At that point, the two groups can be compared to determine the presence or lack of morbidities, and whether the ductus or the indomethacin played a role in the outcomes.

Conclusions

Patent ductus arteriosus is a significant health risk to the preterm infant. Proper understanding of the mechanisms responsible for its delayed closure at birth is necessary for better treatment strategies. The role of indomethacin is well established; however, the best timing of therapy to prevent morbidity is still an unanswered question.

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