https://doi.org/10.33472/AFJBS.6.2.2024.849-862

African Journal of Biological Sciences

Research Paper Open Access

An Overview about Patent Ductus Arteriosus Management

Ehab Abdelmoniem Elbanna, Alshaymaa Ahmed Ali, Atef Mohamed Khalil, Asmaa Reda Elsayed

Pediatrics Department, Faculty of Medicine, Zagazig University

Email: Aassmmaa156@gmail.com

Article History

Volume 6, Issue 2, April 2024

Received:19 April 2024

Accepted: 27 May 2024

Published: 27 May 2024

doi: 10.33472/AFJBS.6.2.2024.849-862

Abstract: PDA is the most common cardiovascular condition among preterm infants. The incidence of PDA decreases as gestational age at birth increases. Recent evidence suggests that over 50% of infants born before 26 weeks of gestation still have an open ductus beyond 2 months after birth. In term infants, PDAs are observed in approximately 1 in 2000 births, accounting for 5% to 10% of all cases of congenital heart disease. The hemodynamic consequences of PDA vary significantly. In infants where the pulmonary vascular resistance decreases at birth and the PDA remains open, a continuous left-to-right shunt occurs. According to the Poiseuille Law, the shunt flow is proportional to the pressure gradient between the aorta and pulmonary artery and inversely related to the resistance to flow. Among preterm infants, the presence of PDA is associated with various adverse outcomes, including death, which are not typically seen in older and more mature patients. The diagnostic assessment of PDA varies depending on the significance of the ductus. In the case of preterm infants, transthoracic echocardiography is the preferred noninvasive method for evaluating the importance of the ductus. This imaging technique utilizes 2-dimensional and color flow Doppler to assess the size, direction, and volume of the shunt. Recent evidence suggests that varied responses to pharmacological PDA treatments, such as indomethacin and ibuprofen, may be influenced by differences in developmental trajectory, genetic variability of drug-metabolizing enzymes, and drug targets. Surgical ligation of the ductus, performed through the application of a surgical clip via a left posterolateral thoracotomy, offers nearly universal achievement of ductal closure. However, rare cases of ligation of the left pulmonary artery or mainstem bronchus have been reported. Transcatheter closure has become the preferred procedure for definitive PDA occlusion in adults, children, and infants weighing 6 kg or more. In smaller preterm infants, this approach has emerged more recently. Conservative management, which involves avoiding definitive closure and waiting for spontaneous closure, has gained popularity due to the lack of long-term benefits demonstrated by randomized trials of pharmacological and surgical ligation treatments. Various strategies are employed in conservative management to manage the consequences of the ductus, such as fluid restriction, diuretics, systemic afterload reduction, and adjustments in airway pressures or hematocrit levels.

Keywords: *Patent Ductus Arteriosus*

Introduction

During normal development of the cardiovascular system, there are changes in the shape of the sixth embryonic aortic arches. These changes create connections between the main pulmonary artery and the descending aorta, located after the left subclavian artery. The upper parts of the sixth embryonic arches form the branch

pulmonary arteries, while the lower left sixth arch forms the ductus arteriosus (DA). This transformation takes place within the first 8 weeks of fetal development in humans **(1)**.

The DA is a crucial structure during fetal development, but it becomes abnormal if it remains open after the neonatal period. The DA can persist in various sizes and configurations, with different relationships to nearby structures. Understanding these anatomical factors provides insights into the resulting physiological consequences **(2)**

Mechanisms regulating fetal ductal patency and closure:

The ductus arteriosus (DA) in the fetus possesses inherent tension, necessitating the presence of dilating factors to keep it open. In the early stages of fetal development, nitric oxide (NO), produced by the endothelium, serves as the primary relaxing agent. It functions through the signaling of cyclic guanosine monophosphate (cGMP) and protein kinase G. As the fetus nears the end of gestation, the responsibility of maintaining DA patency shifts to prostaglandin E2, which originates from the placenta. Prostaglandin E2 interacts with the G-protein-coupled receptor EP4, activating the cyclic adenosine monophosphate (cAMP) and protein kinase A signaling cascade. Regardless of the specific signaling molecule involved, these pathways work together to reduce intracellular calcium levels, effectively preventing the contraction of smooth muscle cells in the DA throughout fetal life **(3)**.

Mechanisms regulating normal postnatal ductal closure:

After birth, the DA undergoes functional closure and transforms permanently into the fibrous ligamentum arteriosum. Various factors, including molecular, structural, hemodynamic, and maternal environmental/infection factors, play a role in the postnatal closure of the DA**(4)**.

Molecular Factors:

The closure of the DA after birth is facilitated by significant reductions in dilating factors and an increase in intracellular calcium levels. The onset of breathing leads to a substantial rise in alveolar PaO_2, which acts as a crucial regulator of DA closure. Recent evidence suggests that immature biochemical oxygen-sensing mechanisms contribute to maintaining the patency of the ductus arteriosus in preterm infants **(4)**.

Structural Factors:

Compared to full-term infants, preterm infants have rudimentary or absent intimal cushions, fewer fully developed contractile smooth muscle cells, and a lack of vasa vasorum, all of which contribute to the sustained openness of the DA**(5)**.

Hemodynamic Factors:

Recent findings indicate that biomechanical factors, particularly among preterm infants, may also play a role in regulating DA tone. While the data are mixed, some researchers have observed a connection between thrombocytopenia (low platelet count) and delayed closure of the DA in very preterm infants. Interestingly, platelet transfusions do not accelerate the closure of the DA in thrombocytopenic premature infants. These observations have led healthcare professionals to speculate that platelet function, rather than platelet count, may influence the status of the preterm DA **(5)**.

Maternal Environmental/Infection Factors:

Postnatal patency of the DA can be influenced by factors such as congenital rubella syndrome and emerging infectious causes like the Zika virus. In addition to infections, exposure to prenatal teratogens is associated with an increased incidence of DA patency. For example, the use of cannabis during pregnancy and the resulting concentrations of tetrahydrocannabinol have been linked to a higher occurrence of patent ductus arteriosus **(6)**.

Genetic Contributors:

The presence of a patent ductus arteriosus has a complex and multifactorial genetic basis. Evidence suggests that there are two overlapping disorders: preterm PDA, resulting from structural and physiological immaturity, and term PDA, arising from genetic alterations. PDA is commonly observed in dysmorphic syndromes

associated with congenital heart disease, with approximately 10% of PDA cases being associated with chromosomal abnormalities. PDA can exist in syndromic and nonsyndromic forms, with syndromic cases more prevalent in term infants and associated with chromosomal aneuploidy and microdeletion syndromes. Among term infants, siblings have an increased risk of PDA recurrence (2% to 4%) **(7)**.

Epidemiology of PDA

PDA is the most common cardiovascular condition among preterm infants. The incidence of PDA decreases as gestational age at birth increases. Recent evidence suggests that over 50% of infants born before 26 weeks of gestation still have an open ductus beyond 2 months after birth. In term infants, PDAs are observed in approximately 1 in 2000 births, accounting for 5% to 10% of all cases of congenital heart disease. Longitudinal cohort studies indicate that the incidence of "silent" PDA, cases discovered through cardiac imaging without clinical symptoms, is approximately 1 in 20 births **(8)**.

Pathophysiology of PDA

The hemodynamic consequences of PDA vary significantly. In infants where the pulmonary vascular resistance decreases at birth and the PDA remains open, a continuous left-to-right shunt occurs. According to the Poiseuille Law, the shunt flow is proportional to the pressure gradient between the aorta and pulmonary artery and inversely related to the resistance to flow. The impact of changes in pulmonary and systemic resistances is more pronounced in patients with a larger ductus and less resistance to flow compared to those with a smaller ductus and greater resistance to flow. Modifiable factors such as PaO2 and pH also affect the transductal flow by influencing pulmonary vascular resistance **(9)**.

Unlike adults, neonates have almost fully recruited and poorly compliant pulmonary vascular beds, which means increased pulmonary blood flow leads to elevated pulmonary arterial pressure and a shift in the pulmonary pressure head, resulting in pulmonary interstitial edema, reduced lung compliance, and impaired oxygenation. Larger ductal shunts can further increase left atrial volume and pressure overload, exacerbating pulmonary venous pressure and leading to alveolar edema, deterioration in respiratory mechanics and function, and surfactant dysfunction **(3)**.

Defining the hemodynamically significant PDA:

Among preterm infants, it can be challenging for healthcare providers to determine if the PDA is causing adverse outcomes or if it is merely associated with them. Therefore, contemporary definitions of a hemodynamically significant PDA (HSPDA) go beyond echocardiographic indicators of atrial or ventricular chamber enlargement. They encompass various clinical and echocardiographic parameters that aim to identify preterm infants in whom the estimated shunt volumes through the ductus are primary contributors to physiological instability **(10)**.

Table 1: Comprehensive grading schema for HSPDA among preterm infants **(10)**.

Clinical	HSPDA	Echocardiography
Asymptomatic	No PDA	No evidence of ductal flow on 2D or Doppler interrogation
Mild symptoms • MAP <8 mmHg (on respiratory support of NCPAP or mechanical ventilation) • Feeding intolerance	Small, non-HSPDA	- Transductal diameter <1.5 mm - Restrictive continuous transductal flow (DA Vmax >2.0 m/s) - No signs of left heart volume loading (eg, mitral regurgitant jet >2.0 m/s or LA:Ao >1.5:1) - No signs of left heart pressure loading (eg, E/A ratio <1.0 or IVRT <50)

Moderate symptoms • MAP 9–12 mmHg (ventilation requirement) • Evidence of abdominal distention and/or persistent emesis	Moderate, HSPDA	• Transductal diameter 1.5–3.0 mm • Unrestrictive pulsatile transductal flow (DA Vmax <2.0 m/s) • Mild-moderate left heart volume loading (eg, LA:Ao 1.5–2.1) • Mild-moderate left heart pressure loading (eg, E/A ratio ≥1.0 or IVRT 50–60) • Decreased or absent diastolic flow in the superior mesenteric, middle cerebral, and/or renal arteries
Severe symptoms • MAP >12 mmHg (high ventilation requirements or HFOV) • Marked abdominal distention and/or erythema	Large HSPDA	• Transductal diameter >3.0 mm • Unrestrictive pulsatile transductal flow • Severe left heart volume loading (eg, LA:Ao >2.1, mitral regurgitant jet >2.0 m/s) • Severe left heart pressure loading (eg, E/A ratio >1.5 or IVRT >60) • Reversal of end-diastolic flow in superior mesenteric, middle cerebral, and/or renal arteries

2D indicates 2 dimensional; DA Vmax, transductal maximal fluid velocity; E/A (ratio), peak velocity blood flow from the left ventricular relaxation in early diastole (E-wave) to peak velocity flow in late diastole caused by atrial contraction (A-wave); HFOV, high-frequency oscillatory ventilation; HSPDA, hemodynamically significant PDA; IVRT, isovolumic relaxation time; LA:Ao, left atrial diameter to aortic root diameter ratio; MAP, mean airway pressure; NCPAP, nasal continuous positive airway pressure; and PDA, patent ductus arteriosus.

In contrast, among term infants, older children, and adults, there is a general consensus that echocardiographic evidence of left atrial or left ventricular enlargement caused by the ductus constitutes an HSPDA **(10)**.

Table 2: Comprehensive Grading Schema for HSPDA Among Older Children and Adults (3).

PDA size	• Physiological symptoms
Silent or trivial	• "Silent" (inaudible) PDAs are asymptomatic* • No hemodynamic or anatomic sequelae • Normal exercise capacity • Normal renal, hepatic, and pulmonary function
Small	• Small left-to-right shunt, not HSPDA • No restrictions of exercise capacity
Mild/moderate	• Mild-moderate left-to-right or bidirectional shunt, HSPDA • Mild-moderate hemodynamic or anatomic sequelae (mild/moderate LAE and/or LVE, mild-moderate left ventricular dysfunction) • Mild or moderate hypoxemia/cyanosis • Mild or moderate PH • Potential for mild renal, hepatic, and pulmonary dysfunction

Large	• Large left-to-right, bidirectional, or right-to-left shunt • Severe hemodynamic or anatomic sequelae (severe LAE and/or LVE, moderate to severe left ventricular dysfunction) • Moderate or severe hypoxemia/cyanosis • Severe PH • Risk of Eisenmenger syndrome with PH and right-to-left shunting

HSPDA indicates hemodynamically significant PDA, defined as left atrial/ventricular enlargement and/or sustained pulmonary blood flow to systemic blood flow ratio (Qp/Qs) ≥1.5; LAE, left atrial enlargement; LVE, left ventricular enlargement; PDA, patent ductus arteriosus; and PH, pulmonary hypertension. *Not all asymptomatic PDAs are silent **(3)**.

Clinical consequences in preterm infants:

Among preterm infants, the presence of PDA is associated with various adverse outcomes, including death, which are not typically seen in older and more mature patients. Despite extensive research, the specific contributions of a persistent ductus and the effectiveness of treatments used to close the ductus in relation to short- and long-term sequelae remain unresolved **(6)**.

Respiratory:

Left-to-right ductal shunting has potential pathological effects and is associated with increased respiratory support, mechanical ventilation, and chronic lung disease, particularly bronchopulmonary dysplasia (BPD). PDA exposure has been linked to pulmonary hemorrhage, with the incidence ranging from 3% to 23% depending on factors such as gestational age, ductal size, and PDA treatments. However, a recent meta-analysis comparing early treatment (initiated by postnatal day 7) to expectant management for hemodynamically significant PDA in infants born before 37 weeks of gestation found no significant differences in rates of pulmonary hemorrhage between the two groups **(11)**.

Neurologic:

Prematurity itself is associated with intraventricular hemorrhage, periventricular leukomalacia, and compromised performance in school-aged children. Most cases of intraventricular hemorrhage occur within the first week after birth, coinciding with the decrease in pulmonary vascular resistance and the emergence of left-to-right ductal shunting in some preterm infants. Prophylactic indomethacin, given in the early postnatal days, has been shown to reduce the incidence of symptomatic PDA and surgical PDA ligation, as well as the occurrence of severe intraventricular and periventricular hemorrhage. However, the neurological benefits observed with prophylactic indomethacin may not be directly related to ductus closure **(12)**.

Intestinal Injury:

Diastolic flow reversal in the abdominal aorta and systemic arteries, such as the renal, celiac, and superior mesenteric arteries, is common in preterm infants with PDA. While data on the subject are mixed, contemporary randomized clinical trials have not found significant differences in rates of necrotizing enterocolitis following ductal closure compared to nonclosure. Of greater concern, simultaneous administration of early systemic hydrocortisone and indomethacin for intraventricular hemorrhage prophylaxis has been found to increase the risk of spontaneous intestinal perforation, and therefore it is contraindicated to use them together **(5)**.

Clinical consequences among older patients (term infant through adulthood)

Pulmonary arterial hypertension and Eisenmenger syndrome

Clinical consequences observed in older patients, ranging from term infants to adulthood, who have PDA, include the development of pulmonary arterial hypertension (PAH) and Eisenmenger syndrome. The exact

mechanisms underlying these conditions are not fully understood, but prolonged left-to-right shunting results in increased pressure and blood flow in the pulmonary arterial system **(13)**.

This leads to progressive changes in the structure of pulmonary blood vessels, such as thickening of the arterial walls, proliferation of inner layers, and eventual narrowing of arterioles and capillaries. These changes contribute to the development of PAH. When the pulmonary vascular resistance exceeds the systemic vascular resistance, the direction of shunting reverses, resulting in Eisenmenger syndrome. A characteristic sign of Eisenmenger syndrome in the presence of a PDA is clubbing of the toenails, while finger clubbing may be milder or absent. Right ventricular systolic failure is a common cause of mortality in individuals with Eisenmenger syndrome **(10)**.

Infective endocarditis

In terms of associated complications, there is a low incidence of infective endocarditis (IE) in patients with PDA. Diagnostic criteria for IE are met in a small percentage of individuals with PDA, although the risk is generally low. Antibiotic prophylaxis is no longer recommended for the prevention of IE in patients with PDA, except during the first six months after definitive closure of the ductus, according to current American Heart Association guidelines **(14)**.

Diagnostic assessment of PDA

Unique Considerations in the Diagnosis of PDA Among Preterm Infants

The diagnostic assessment of PDA varies depending on the significance of the ductus. In the case of preterm infants, transthoracic echocardiography is the preferred noninvasive method for evaluating the importance of the ductus. This imaging technique utilizes 2-dimensional and color flow Doppler to assess the size, direction, and volume of the shunt **(15)**.

Ascertaining hemodynamic importance

To identify preterm infants who are most likely to benefit from treatment for PDA, healthcare providers have made efforts to categorize subgroups of infants with high-risk significant PDAs based on clinical or sonographic criteria. However, the absence of a standardized or validated definition of high-risk significant PDA has led to uncertainty regarding which infants should receive treatment. This uncertainty is partly due to the lack of consistency in the definitions used in previous randomized clinical trials. A previous review of these definitions revealed significant variation, with the use of arbitrary echocardiographic thresholds that were not validated against relevant clinical outcomes **(3)**.

A Comprehensive Approach to Defining HSPDAs

Contemporary definitions of high-risk significant PDAs take a comprehensive approach, integrating multiple echocardiographic assessments. The goal is to identify preterm infants where ductal shunt volumes are the primary pathological contributors to current physiological instability, taking into account other concurrent pathologies such as lung immaturity or ventilator-associated injury. The process of determining hemodynamic significance should consider clinical and echocardiographic parameters, emphasizing the hierarchy of shunt volume rather than solely evaluating ductal patency **(16)**.

Specific considerations in PDA diagnosis among older patients (from term infants to adulthood)

Transthoracic echocardiography is a suitable imaging technique for term infants, but its effectiveness may be limited in older patient populations due to poor acoustic windows. In such cases, transesophageal echocardiography can be employed by obtaining views in the upper esophagus with a clockwise rotation from the aortic views **(17)**.

However, the assessment of color flow Doppler can be misleading, especially when there is elevated pulmonary vascular resistance. Distinguishing right-to-left shunting at the ductus from adjacent structures, like the left pulmonary artery, can be challenging. These challenges have prompted healthcare professionals to explore alternative diagnostic methods for PDA in older patients, including magnetic resonance imaging or computed tomography **(18)**.

In adolescent and adult patients with PAH, cardiac magnetic resonance imaging or computed tomographic imaging can reveal a PDA that was not initially detected by echocardiography. Cardiac magnetic resonance

imaging has been widely regarded as the preferred noninvasive technique for assessing flow, quantifying function, and evaluating anatomical features. It provides valuable information about ductal morphology and characteristics without the need for ionizing radiation. On the other hand, computed tomography offers faster imaging and allows for breath-holding, which is beneficial for detecting in situ thromboembolic disease that is common in older patients with long-standing PDA and associated PAH. Additionally, cardiac-gated multidetector computed tomography scans can identify and track the extent of calcifications present in certain adults with PDA. This is particularly relevant when considering definitive closure of the ductus **(7)**.

Treatment for PDA in preterm infants:

Indomethacin

Indomethacin, a cyclooxygenase inhibitor that targets prostaglandin synthesis, is the primary NSAID extensively studied for closing the ductus among preterm infants. Numerous randomized trials (23 for prophylaxis, 4 for early asymptomatic PDA treatment, and 12 for symptomatic PDA treatment) consistently demonstrate its efficacy in achieving ductal closure. The trials reveal reduced persistent patency risk (RR: 0.39 [95% CI, 0.35-0.44], 0.41 [95% CI, 0.26-0.65], and 0.40 [95% CI, 0.32-0.50]) at mean treatment ages below 1 day, 2.5 days, and 6 days, respectively **(10)**.

However, apart from ductal closure, no significant benefits are observed in terms of mortality, BPD, necrotizing enterocolitis, and neurodevelopment. Indomethacin treatment often leads to oliguria and elevated serum creatinine levels, which may increase the risk of spontaneous intestinal perforation, especially in infants exposed to postnatal corticosteroids **(19)**.

Ibuprofen

Ibuprofen has been compared to placebo or non-treatment in 15 randomized controlled trials (6 for prophylaxis and 9 for treatment). Collectively, these trials demonstrate efficacy in PDA closure comparable to indomethacin. Oral dosing appears to be more effective than intravenous dosing. Direct comparisons with indomethacin also suggest comparable efficacy and a lower likelihood of oliguria and necrotizing enterocolitis with ibuprofen treatment **(3)**.

Apart from ductal patency, ibuprofen prophylaxis or treatment does not significantly affect other outcomes. Due to its comparable efficacy in ductal closure and lower risk of adverse effects, some reviewers consider ibuprofen as the preferred NSAID for medical PDA closure **(20)**.

Acetaminophen

Limited reports suggest that acetaminophen (paracetamol) could be a less toxic yet equally effective alternative to indomethacin or ibuprofen for inducing ductal closure. Most reports are anecdotal without proper controls, and there are few randomized trials **(21)**.

Two randomized trials comparing acetaminophen with placebo or no treatment, involving a total of 80 subjects, found that treatment reduced the risk of ductal patency after 4 to 5 days by 51% **(22)**.

No differences were observed in mortality, oxygen use at 36 weeks' postmenstrual age, or other outcomes. Several small trials comparing acetaminophen with ibuprofen or indomethacin found no significant differences in ductal closure rates, suggesting therapeutic equivalence. However, prospective nonrandomized data from the PDA-TOLERATE trial indicate that acetaminophen is not more effective than conservative treatment and is less effective than indomethacin in inducing ductal closure **(23)**.

Pharmacogenetics of Drug Treatment for PDA

Recent evidence suggests that varied responses to pharmacological PDA treatments, such as indomethacin and ibuprofen, may be influenced by differences in developmental trajectory, genetic variability of drug-metabolizing enzymes, and drug targets. For instance, current weight-based dosing of indomethacin results in variable drug exposures, with up to 14-fold variation in drug concentrations 24 hours after identical intravenous dosing **(24)**.

Surgical Closure

Surgical ligation of the ductus, performed through the application of a surgical clip via a left posterolateral thoracotomy, offers nearly universal achievement of ductal closure. However, rare cases of ligation of the left pulmonary artery or mainstem bronchus have been reported. Only four procedural trials have been conducted in preterm infants for PDA closure, all of which evaluated open surgical ligation before the 1980s when modern neonatal care advancements were not available **(25)**.

Prophylactic ligation of the ductus on the day of birth for infants weighing less than 1000g was associated with lower rates of necrotizing enterocolitis. However, it resulted in more frequent use of oxygen and mechanical ventilation at 36 weeks, with no difference in mortality. For symptomatic PDA, ligation did not show a clear decrease in adverse outcomes related to ductal patency. A landmark study comparing ligation with indomethacin for the treatment of persistent PDA found that ligation was more likely to achieve ductal closure but was associated with higher rates of pneumothorax and retinopathy of prematurity. However, it did not affect mortality, chronic lung disease, or other outcomes. Postligation syndrome, characterized by cardiorespiratory deterioration, often occurs within hours after ductal ligation. This complication appears to be related to altered afterload, leading to impaired left ventricular systolic performance. Infants who undergo ligation at less than 30 postnatal days are more susceptible to this complication. Surgical ligation has also been associated with increased risks of BPD and neurodevelopmental impairment. Over the past decade, rates of surgical ligation in US hospitals have significantly decreased **(26)**.

Transcatheter Closure

Transcatheter closure has become the preferred procedure for definitive PDA occlusion in adults, children, and infants weighing 6 kg or more. In smaller preterm infants, this approach has emerged more recently. The availability of devices designed specifically for preterm infants' unique ductal morphology, including those with type F (fetal) PDA, has led to increased interest and utilization of transcatheter closure. A multicenter trial evaluated the safety and effectiveness of the Amplatzer Piccolo Occluder device in 200 patients, including those weighing 2 kg or less. The trial demonstrated high success rates in implantation (95.5% and 99% for patients weighing 2 kg or less) and low rates of major complications (2.1% of cases) ***(27)***.

Effective ductal closure was observed in 99.4% of patients at 6 months. Some infants showed evidence of moderate tricuspid regurgitation on echocardiography following transcatheter closure, likely due to catheter manipulation across the tricuspid valve ***(27)***.

Based on these results, the device received approval from the US Food and Drug Administration for transcatheter PDA closure ininfants weighing 700 g or more and who were at least 3 postnatal days old. This approval marked a significant advancement in the field, providing a less invasive option for PDA closure in eligible preterm infants ***(27)***.

It is worth noting that transcatheter closure, while effective, requires expertise and experience from interventional teams due to the delicate nature of the procedure. The development of specialized devices tailored to the unique anatomy of preterm infants has facilitated the success and safety of transcatheter closure **(28)**.

The correlation between the risk of complications following transcatheter PDA closure and postnatal age or procedural weight is uncertain. However, variations in how complications are defined, timing of event reporting (intraprocedural or postprocedural), and assessment of procedural-related adverse events across studies limit the interpretation of available data. Recent procedural modifications, such as using femoral venous access instead of femoral arterial access, have significantly reduced the incidence of postprocedure limb ischemia. Additionally, consensus-based guidelines outlining strategies to prevent and manage complications associated with transcatheter closure are expected to enhance safety **(29)**.

The optimal treatment approach to achieve definitive ductal closure in preterm infants remains unknown, as there are no direct comparisons available. Although short-term data show promise for transcatheter PDA closure, the long-term outcomes are lacking. Whether the higher certainty of achieving ductal closure with this

approach translates into increased benefits compared to NSAID treatment or conservative management is yet to be determined **(28)**.

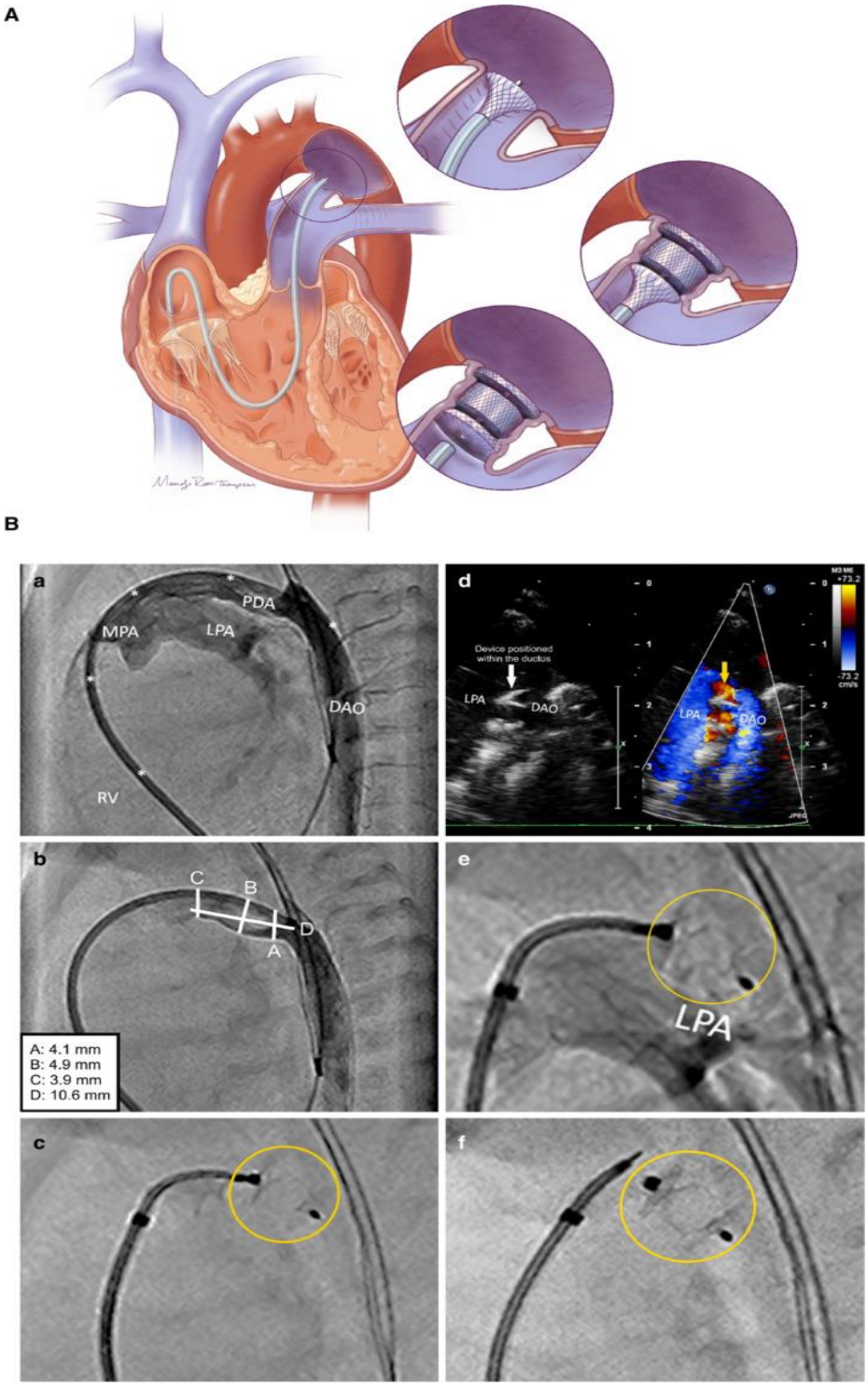

Figure 1: Percutaneous closure of a patent ductus arteriosus (PDA) (A) and the use of intraprocedural imaging during the closure (B) are depicted in the following description.

In illustration A, the procedure begins with the insertion of an end hole catheter through the tricuspid valve into the right ventricle (RV). Then, a soft, floppy-tipped wire is carefully guided across the PDA and into the

descending aorta (DAO) (not shown in the illustration). Subsequently, the catheter in the right ventricle is removed while keeping the wire in place. A delivery catheter is then advanced over the wire, through the venous sheath, and into the PDA and descending aorta (not shown in the illustration). The device, designed for closure, is gradually advanced to the tip of the catheter (a). Under the guidance of fluoroscopy and transthoracic echocardiography, the device is deployed within the PDA, ensuring it doesn't protrude into the aorta or pulmonary artery (b). Once the position is deemed satisfactory, the device is released from the delivery cable (c). Moving on to illustration B, a series of radiographs are presented to illustrate the steps involved in the percutaneous PDA closure procedure. Firstly, a 4F catheter is introduced through femoral vein access and guided to the right ventricle under fluoroscopic guidance. Through this catheter, a floppy-tipped wire is directed across the PDA and into the descending aorta. Subsequently, a 4F delivery catheter is exchanged for the wire (a). An angiogram is obtained to gather configuration and dimensional data of the PDA, aiding in the selection of the most appropriate device for closure (b). The device is then carefully advanced through the delivery catheter and deployed, but not completely released (c). Additional echocardiographic imaging is performed to confirm the correct placement of the device (d). Further angiographic imaging is conducted to evaluate any potential obstruction in the aorta or left pulmonary artery caused by the device (e). Once the positioning, stability, residual shunting, and other clinical parameters are assessed, the device is released (f). Additional imaging may be necessary to evaluate post-release positioning and stability, residual shunting, and other clinical parameters, such as the presence of new or increased tricuspid valve regurgitation **(29)**.

Conservative treatment

Conservative management, which involves avoiding definitive closure and waiting for spontaneous closure, has gained popularity due to the lack of long-term benefits demonstrated by randomized trials of pharmacological and surgical ligation treatments. Various strategies are employed in conservative management to manage the consequences of the ductus, such as fluid restriction, diuretics, systemic afterload reduction, and adjustments in airway pressures or hematocrit levels **(10)**.

However, these approaches have not been evaluated through systematic randomized trials. While the adoption of conservative management has not shown significant differences in outcomes overall, there are unanswered questions regarding its safety and effectiveness compared to definitive closure in high-risk subgroups **(30)**.

Timing of therapy

The timing of therapy for PDA closure has been influenced by concerns about delaying treatment and potentially missing opportunities for effective NSAID treatment. However, data from randomized clinical trials do not support a decline in efficacy with advancing postnatal age. Trials including subjects with a mean postnatal age above 7 days have demonstrated comparable PDA closure efficacy to trials conducted at earlier ages. The effectiveness of medical therapy beyond the fourth postnatal week is uncertain, but delaying treatment into this period does not seem to compromise its ability to achieve ductal closure **(31)**.

Postdischarge Treatment

Limited data are available on the post-hospital outcomes of preterm infants discharged with a persistent PDA. In a recent prospective study conducted across multiple centers, researchers examined 201 preterm babies who were sent home with a patent ductus arteriosus (PDA). These infants were monitored at six-month intervals until they reached 18 months of age. The findings revealed that spontaneous closure of the ductus occurred in approximately 47% of the infants at the 12-month mark and increased to around 58% by the time they reached 18 months of age. Some studies suggest a significant rate of spontaneous closure after discharge, but optimal outpatient surveillance for these infants remains unknown **(32)**.

PDA treatment in older patients (term infant through adulthood)

Moving beyond the first few months of life, pharmacological therapy for ductal closure becomes ineffective in term infants. Diuretics may be used to address pulmonary overcirculation during this period, but decisions regarding the need for ductal closure in term infants are primarily based on the presence of HSPDA and factors

related to ductal shunting and pulmonary artery systemic pressure. The frequency and timing of outpatient follow-up depend on the classification of the PDA **(4)**.

Management of HSPDA

For older patients, transcatheter PDA closure remains the primary approach for achieving definitive ductal closure. In patients weighing more than 6 kg, most PDAs can be effectively closed using transcatheter occlusion, except for type B ductus. According to the 2011 guidelines from the American Heart Association, transcatheter PDA occlusion is recommended for older patients with HSPDA and left-to-right shunt that leads to congestive heart failure, failure to thrive, pulmonary overcirculation, or enlargement of the left atrium or left ventricle, provided that the patient's anatomy and size are suitable **(3)**.

Management of PDA With Associated PAH in Term Infants and Older Children

In term infants and older children, elevated pulmonary artery pressure associated with unrestrictive ductal shunting may be due to excessive flow rather than pulmonary vascular resistance indicative of pulmonary vascular disease. In such cases, health care providers may consider transcatheter closure after conducting short-term pulmonary vasodilator testing. This testing involves assessing the decrease in mean pulmonary artery pressure by at least 20% following administration of 100% oxygen and/or inhaled nitric oxide at a concentration of 80 parts per million. If a favorable hemodynamic response is observed during test occlusion, transcatheter closure can be performed **(33)**.

Management of PDA With Associated PAH in Older Patients and Adults

Recent guidelines from the American Heart Association and the American College of Cardiology emphasize the evaluation of left-to-right shunting and hemodynamic assessment for pulmonary arterial hypertension (PAH) when considering ductal closure in older patients. Similarly, European guidelines suggest that pulmonary/systemic shunt ratios less than 1.5 and pulmonary vascular resistances greater than 5 Wood units are not favorable for ductal closure in adults. Pharmacological treatments, such as endothelin receptor antagonists and phosphodiesterase-5 inhibitors, have shown to improve functional capacities in adult patients with Eisenmenger syndrome. Patients on PAH therapies have demonstrated significant increases in survival compared to those not on PAH therapies. Before transcatheter closure, balloon test occlusion can provide valuable insights into the risk-benefit profiles, particularly for patients with evidence of PAH **(34)**.

Definitive Closure (Transcatheter or Surgical Ligation)

Transcatheter PDA closure remains the preferred method for achieving definitive ductal closure in older patients. After hemodynamic assessment, if the ductal morphology is unfavorable for transcatheter closure, surgical intervention can be performed using video-assisted thoracoscopic or open thoracotomy approaches, which have high success rates and low complication rates **(35)**.

Management of "Silent" or Small PDAs

Thresholds for intervention based on the risk of infective endocarditis have been adjusted over time with advancements in antibiotic treatment and the availability of transcatheter PDA occlusion. The previous indication for closing PDAs was to prevent endarteritis, which eliminated the need for long-term antibiotic prophylaxis. However, since "silent" or small PDAs are not considered HSPDA, current guidelines no longer recommend antibiotic prophylaxis, and there is no longer a rationale for closing such PDAs **(36).**

References:

1. Xiong, J., Sun, Q., Qian, Y., Hu, L., Tong, Z., Liu, J., & Liu, J. (2021). Effects of Patent Ductus Arteriosus on the Hemodynamics of Modified Blalock–Taussig Shunt Based on Patient-Specific Simulation [Original Research]. Frontiers in Physiology, 12.
2. Bannan, B., Aly, S., Yoo, S.-J., Seed, M., & Lam, C. Z. (2021). The Many Faces of Neonatal Ductus Arteriosus Aneurysms: Multimodality Imaging with an Emphasis on CT and MRI Appearance. Radiology: Cardiothoracic Imaging, 3(3), e210017.
3. Backes, C. H., Hill, K. D., Shelton, E. L., Slaughter, J. L., Lewis, T. R., Weisz, D. E., Garg, V. (2022). Patent Ductus Arteriosus: A Contemporary Perspective for the Pediatric and Adult Cardiac Care Provider. J Am Heart Assoc, 11(17), e025784.
4. Ovalı, F. (2020). Molecular and Mechanical Mechanisms Regulating Ductus Arteriosus Closure in Preterm Infants [Review]. Frontiers in Pediatrics, 8.
5. Hamrick, S. E. G., Sallmon, H., Rose, A. T., Porras, D., Shelton, E. L., Reese, J., & Hansmann, G. (2020). Patent Ductus Arteriosus of the Preterm Infant. Pediatrics, 146(5).
6. Parkerson, S., Philip, R., Talati, A., & Sathanandam, S. (2021). Management of Patent Ductus Arteriosus in Premature Infants in 2020 [Review]. Frontiers in Pediatrics, 8.
7. Villamor, E., Borges-Luján, M., & González-Luis, G. (2023). Association of patent ductus arteriosus with fetal factors and endotypes of prematurity. Seminars in Perinatology, 47(2), 151717.
8. Vaidya, R., Knee, A., Paris, Y., & Singh, R. (2021). Predictors of successful patent ductus arteriosus closure with acetaminophen in preterm infants. Journal of Perinatology, 41(5), 998-1006.
9. Erdeve, Ö., Okulu, E., Singh, Y., Sindelar, R., Oncel, M. Y., Terrin, G., Clyman, R. I. (2022). An Update on Patent Ductus Arteriosus and What is Coming Next. Turk Arch Pediatr, 57(2), 118-131.
10. Hundscheid, T., El-Khuffash, A., McNamara, P. J., & de Boode, W. P. (2022). Survey highlighting the lack of consensus on diagnosis and treatment of patent ductus arteriosus in prematurity. Eur J Pediatr, 181(6), 2459-2468.
11. Terrin, G., Di Chiara, M., Boscarino, G., Metrangolo, V., Faccioli, F., Onestà, E., De Curtis, M. (2021). Morbidity associated with patent ductus arteriosus in preterm newborns: a retrospective case-control study. Ital J Pediatr, 47(1), 9.
12. Routier, L., Querne, L., Ghostine-Ramadan, G., Boulesteix, J., Graïc, S., Mony, S., Bourel-Ponchel, E. (2023). Predicting the Neurodevelopmental Outcome in Extremely Preterm Newborns Using a Multimodal Prognostic Model Including Brain Function Information. JAMA Network Open, 6(3), e231590-e231590.
13. Stącel, T., Sybila, P., Mędrala, A., Ochman, M., Latos, M., Zawadzki, F., Urlik, M. (2022). Novel Hybrid Treatment for Pulmonary Arterial Hypertension with or without Eisenmenger Syndrome: Double Lung Transplantation with Simultaneous Endovascular or Classic Surgical Closure of the Patent Ductus Arteriosus (PDA). J Cardiovasc Dev Dis, 9(12), 457.
14. Mahajan, O. A., Agrawal, G., Acharya, S., & Kumar, S. (2022). Infective Endocarditis in Patient With Uncorrected Patent Ductus Arteriosus: A Case Report From Rural India. Cureus, 14(11), e32004.
15. Wu, W., Chen, H., & Chen, T. (2022). Evaluation of Cardiac Function Characteristics after Patent Ductus Arteriosus Closure in Children and Adults by Echocardiographic Data. Comput Math Methods Med, 2022, 1310841.
16. Zhou, Z., Gu, Y., Zheng, H., Li, S., Xu, L., Liu, Q., Jin, J. (2022). Transcatheter Closure of Patent Ductus Arteriosus via Different Approaches [Original Research]. Frontiers in Cardiovascular Medicine, 8.
17. Wang, C., Zhang, F., Ouyang, W., Zhao, G., Lu, W., Zou, M., & Pan, X. (2020). Transcatheter Closure of Patent Ductus Arteriosus under Echocardiography Guidance: A Randomized Controlled Noninferiority Trial. Journal of Interventional Cardiology, 2020, 4357017.

18. Siagian, S. N., Prakoso, R., Putra, B. E., Kurniawati, Y., Lelya, O., Sembiring, A. A.,Lilyasari, O. (2022). Echocardiography-Guided Percutaneous Patent Ductus Arteriosus Closure: 1-Year Single Center Experience in Indonesia. Front Cardiovasc Med, 9, 885140.
19. Atasay, B., Erdeve, Ö., Sallmon, H., & Singh, Y. (2021). Editorial: Management of Patent Ductus Arteriosus in Preterm Infants [Editorial]. Frontiers in Pediatrics, 9.
20. Ohlsson, A., Walia, R., & Shah, S. S. (2020). Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. Cochrane Database Syst Rev, 2(2), Cd003481.
21. Bouazza, N., Treluyer, J.-M., Foissac, F., Urien, S., Aikio, O., Roze, J.-C., & Hallman, M. (2021). Pharmacokinetics of Intravenous Paracetamol (Acetaminophen) and Ductus Arteriosus Closure After Premature Birth. Clinical Pharmacology & Therapeutics, 110(4), 1087-1095.
22. Asbagh, P. A., Zarkesh, M. R., Nili, F., Nayeri, F. S., & Naeem, A. T. (2015). Prophylactic teatment with oral paracetamol for patent ductus arteriosus in preterm infants: a randomized clinical trial. Tehran University Medical Journal, 73(2).
23. Liebowitz, M., Kaempf, J., Erdeve, O., Bulbul, A., Håkansson, S., Lindqvist, J., Clyman, R. I. (2019). Comparative effectiveness of drugs used to constrict the patent ductus arteriosus: a secondary analysis of the PDA-TOLERATE trial (NCT01958320). J Perinatol, 39(5), 599-607.
24. Shelton, E. L., Singh, G. K., & Nichols, C. G. (2018). Novel drug targets for ductus arteriosus manipulation: Looking beyond prostaglandins. Seminars in Perinatology, 42(4), 221-227.
25. Suciu, H., Harpa, M. M., Moraru, L., Raicea, A. D., & Raicea, V. C. (2022). Surgical treatment for patent ductus arteriosus in adult patients: a single center experience. Rom J Morphol Embryol, 63(4), 633-638.
26. Giesinger, R. E., Bischoff, A. R., & McNamara, P. J. (2019). Anticipatory perioperative management for patent ductus arteriosus surgery: Understanding postligation cardiac syndrome. Congenit Heart Dis, 14(2), 311-316.
27. Sathanandam, S. K., Gutfinger, D., O'Brien, L., Forbes, T. J., Gillespie, M. J., Berman, D. P., Zahn, E. M. (2020). Amplatzer Piccolo Occluder clinical trial for percutaneous closure of the patent ductus arteriosus in patients ≥700 grams. Catheter Cardiovasc Interv, 96(6), 1266-1276.
28. Shibbani, K., Mohammad Nijres, B., McLennan, D., Bischoff, A. R., Giesinger, R., McNamara, P. J., Aldoss, O. (2022). Feasibility, Safety, and Short-Term Outcomes of Transcatheter Patent Ductus Arteriosus Closure in Premature Infants on High-Frequency Jet Ventilation. J Am Heart Assoc, 11(10), e025343.
29. Barcroft, M., McKee, C., Berman, D. P., Taylor, R. A., Rivera, B. K., Smith, C. V., Backes, C. H. (2022). Percutaneous Closure of Patent Ductus Arteriosus. Clin Perinatol, 49(1), 149-166.
30. Shin, J., Lee, J. A., Oh, S., Lee, E. H., & Choi, B. M. (2021). Conservative Treatment Without Any Intervention Compared With Other Therapeutic Strategies for Symptomatic Patent Ductus Arteriosus in Extremely Preterm Infants: A Nationwide Cohort Study in Korea [Original Research]. Frontiers in Pediatrics, 9.
31. Mitra, S., Scrivens, A., von Kursell, A. M., & Disher, T. (2020). Early treatment versus expectant management of hemodynamically significant patent ductus arteriosus for preterm infants. Cochrane Database Syst Rev, 12(12), Cd013278.
32. Tolia, V. N., Powers, G. C., Kelleher, A. S., Walker, M. W., Herrman, K. K., Ahmad, K. A., Clark, R. H. (2022). Low Rate of Spontaneous Closure in Premature Infants Discharged with a Patent Ductus Arteriosus: A Multicenter Prospective Study. J Pediatr, 240, 31-36.e32.
33. Philip, R., Lamba, V., Talati, A., & Sathanandam, S. (2020). Pulmonary Hypertension with Prolonged Patency of the Ductus Arteriosus in Preterm Infants. Children (Basel), 7(9).
34. Assenza, G. E., Krieger, E. V., Baumgartner, H., Cupido, B., Dimopoulos, K., Louis, C., Opotowsky, A. R. (2021). AHA/ACC vs ESC Guidelines for Management of Adults With Congenital Heart Disease. Journal of the American College of Cardiology, 78(19), 1904-1918.

35. Galeczka, M., Szkutnik, M., Bialkowski, J., Smerdzinski, S., Knop, M., Sukiennik, A., & Fiszer, R. (2020). Transcatheter Closure of Patent Ductus Arteriosus in Elderly Patients: Initial and One-Year Follow-Up Results-Do We Have the Proper Device? J Interv Cardiol, 2020, 4585124.
36. Fortescue, E. B., Lock, J. E., Galvin, T., & McElhinney, D. B. (2010). To Close or Not to Close: The Very Small Patent Ductus Arteriosus. Congenit Heart Dis, 5(4), 354-365.