Chapter

PDA Closure in ELBW Infants: If, When, and How to Do It

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Abstract

Patent ductus arteriosus (PDA) is the most common cardiovascular condition afflicting premature neonates especially those born extremely low birth weight (ELBW). Despite five decades of scientific inquiry which has produced thousands of publications including over 65 randomized controlled trials, cardiologists, neonatologists, and surgeons still cannot answer simple questions such as if, when and how to close to the PDA in ELBW infants. This chapter will examine current evidence in order to answer these fundamental questions. The chapter will specifically focus on transcatheter PDA closure (TCPC), which albeit a new therapy, has displayed great potential to be the best therapeutic option in the future. It is about time that physicians from all sub-specialties come together and integrate the evidence to develop a management algorithm for ELBW infants with hemodynamically significant PDA.

Keywords: PDA, ELBW, hemodynamics, devicer, ligation

1. Introduction

The ductus arteriosus is a fetal vascular structure that connects the descending aorta to the pulmonary artery (PA). It develops from the left sixth aortic arch in the embryo by the sixth week, directing blood flow returning to the heart away from the lungs. Soon after birth, the ductus arteriosus should begin to close spontaneously in response to environmental changes [1]. Patent ductus arteriosus (PDA) can be expected in all infants immediately after birth but may become pathologic if closure fails to occur within the first few days. Non-pathologic PDAs may occur in infants with cyanotic heart disease and increased pulmonary vascular resistance.

2. Role in fetal life

In a normal fetus, blood flows from right-to-left (PA to aorta) as a result of high resistance in the pulmonary arterioles and low systemic vascular resistance in the fetus and placenta. Patency of the ductus in fetal life is further influenced by oxygen content in the blood and prostaglandins. Dissolved oxygen content in the blood (pO_2) leads to constriction of smooth-walled vessels, possibly due to the influx of calcium into the cell, thus ductal exposure to low pO_2 in utero promotes patency of the ductus [2]. Prostaglandins are hormone-like compounds derived from arachidonic acid by cyclooxygenase enzymes (COX-1 and COX-2). Prostaglandin E (PGE) and prostacyclin (PGIE) are produced in the ductus and play a large role in maintaining its patency during fetal life [2–5].

3. Normal closure of the ductus

When a baby takes its first breath, the increased alveolar oxygen content leads to pulmonary vasodilation, resulting in a decreased ratio of pulmonary vascular resistance (R_P) to systemic vascular resistance (R_S). This drop in R_P/R_S can reverse the flow of blood across the ductus arteriosus from right-to-left to left-to-right (aorta to PA). At this point, the ductus is exposed to high systemic arterial pO_2, which results in vasoconstriction of the ductus arteriosus through mechanisms not fully elucidated [3–5]. A sharp decline in circulating PGE and PGIE along with a rapid increase in pO_2 following birth contributes to constriction, and ultimately functional closure of the ductus. Nearly all healthy, term infants achieve functional closure with 24–72 h [2–5]. Eventually, hypoxia and fibrosis cause the inner layers of the ductus to permanently close, leaving only a fibrous remnant called the ligamentum arteriosum.

4. Incidence of PDA in premature infants

Premature birth prolongs closure as gestational age decreases. As many as 50–70% of infants at <28 weeks of gestation have a moderate-to-large PDA that persists for weeks after birth, whereas most infants born >28 weeks of gestation spontaneously close the ductus within the first week. Among infants >1500 g, spontaneous closure of the ductus occurs within 96 h in 95% of neonates [6]. By contrast, only 34% of extremely low birth weight (ELBW) infants (birth weight ≤ 1000 g) are reported to close the ductus by day 10 of life [6].

Little is known about the natural course of PDA in extremely premature infants due to the use of prophylactic and rescue therapy in modern NICUs. Previous studies in the 1960s and 1970s were limited by a lack of modern imaging techniques and likely only captured audible, hemodynamically significant PDAs [7]. The closest approximation is found by examining infants treated with conservative management of the PDA, in which interventions are held until symptoms of distress meet an established threshold. A large retrospective study using conservative management found that 85% of very low birth weight (VLBW) infants (birth weight ≤ 1500 g) closed the ductus spontaneously before discharge, but it should be noted that infants <26 weeks gestational age took a median of 71 days to close. Thirty-three infants, many of whom had a PDA, were excluded from the study due to death from infection, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and pulmonary hemorrhage [8] (Semberova). Another study found spontaneous ductal closure within the first week in 31% of ELBW infants and 67% in infants greater than 1000 g. For ELBW infants, spontaneous closure was achieved in 47% at a median of 56 days at the time of discharge [8, 9]. Thus, PDA in VLBW and ELBW infants can take weeks to close and may cause morbidity and mortality in this population.

5. Consequences of PDA in ELBW infants

While a very tiny ductus may be safely left untreated, a large ductus can cause pulmonary over-circulation and cardiac failure. A moderate ductus can lead to pulmonary hypertension [10, 11] in the long-term. Even a small ductus is at risk for developing endocarditis [12].

Persistent PDA in ELBW infants with respiratory distress syndrome (RDS) has been linked to numerous pulmonary complications, including increased flow

and pressure to the pulmonary vascular bed, increased lung water, decreased lung compliance [13, 14], prolonged ventilation [15], worsening pulmonary disease [16], pulmonary hemorrhage [13–16], severe bronchopulmonary dysplasia (BPD) [17], and death [17].

Over the first few days, pulmonary vascular resistance drops markedly while the PDA remains large, allowing significant shunting of blood to the pulmonary vascular bed. As blood from the PDA returns to the left atrium, left atrial dilation occurs. The increased LA pressure causes pulmonary edema and symptoms of congestive heart failure. While the body may compensate at first, pulmonary hemorrhage may eventually occur [18, 19]. Besides pulmonary hemorrhage the risks of BPD are increased, as ELBW infants require greater ventilatory support as well as increased oxygen [18, 20]. Although the pathogenesis of BPD is complex, associations between prolonged exposure to a moderate-to-large PDA and BPD have been documented [18, 19]. Additional research further established the association of PDA with systemic complications such as NEC, renal impairment, IVH, periventricular leukomalacia (PVL), cerebral palsy, and death [20–22].

While numerous sequelae have been associated with the presence of a moderate-to-large PDA in ELBW infants, it remains unclear whether these are the result of having a PDA or are the natural consequences of prematurity. Previous randomized control trials (RCT) suggest that long-term morbidities are not affected by short-term exposure to a PDA (3–4 days) [13, 23], however these conclusions are confounded by early spontaneous closure of the PDA, failure to account for differing shunt sizes, and the early use of rescue treatments, or a lack of equipoise, on behalf of the physicians [13]. There is no consensus on the exact consequences of a PDA in the premature infant, but most agree that persistent and significant left-to-right shunting of blood in the ELBW infant is not helpful [24].

6. Hemodynamic significance of the PDA

There is no consensus regarding the definition of a hemodynamically significant PDA (hsPDA), yet it is a key indicator for clinicians when determining whether intervention is needed to close the ductus. Historically, clinical signs have been used as indicators of hsPDA, such as the presence of a systolic murmur, wide pulse pressures,

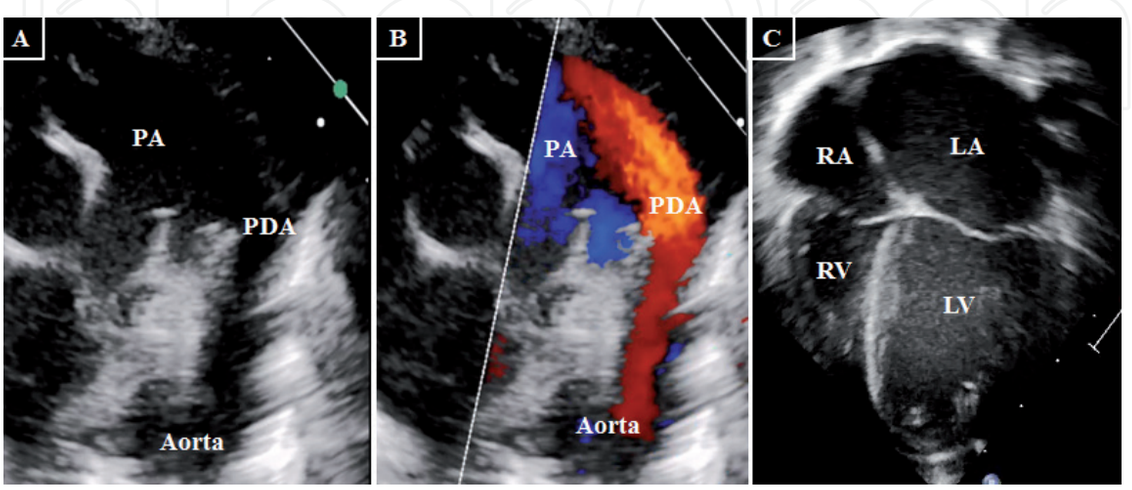

Figure 1.
Transthoracic echocardiogram (TTE) demonstrating a large, hsPDA in a 3 weeks old ex-24 week ELBW infant. (A) 2D-TTE demonstrating a large PDA between the aorta and the pulmonary artery (PA). (B) Color Doppler demonstrating left to right shunt in the PDA from the aorta to the PA. (C) Severe left atrial (LA) and left ventricular (LV) enlargement relative to the right atrium (RA) and the right ventricle (RV).

bounding pulses, pulmonary edema, and increased oxygen requirements. With the advent of echocardiography in the 1970s, more sophisticated measures can be used to determine hemodynamic significance. Approaches to determine hsPDA now include (1) establishing thresholds based on clinical signs and echocardiographic parameters, (2) the need for treatment as determined by the size of the PDA and its likelihood of closing based on age/size of the infant, (3) probable outcomes based on identifying populations most likely to experience complications related to PDA.

Echocardiographic indices to determine hsPDA can be established by PDA shunt size, the extent of volume overload [19–21], the degree of pulmonary overload, and the magnitude of systemic hypoperfusion (**Figure 1**). Moderate to large PDAs may be hemodynamically significant if flow patterns through the duct indicate significant left-to-right shunting. Volume overload is determined by calculating the left atrium diameter (LA) relative to a constant, the aortic root diameter (Ao). An LA:Ao ratio greater than 1.4 is one of the most commonly used indicators of hsPDA, since increased volume through the PDA will return to the left atrium and cause dilation [19–21]. Left ventricular output (LVO), a key indicator of pulmonary overload, may be large due to additional volume from the PDA, or may be small to normal (an ominous sign) if the left ventricle fails to compensate for the additional volume through

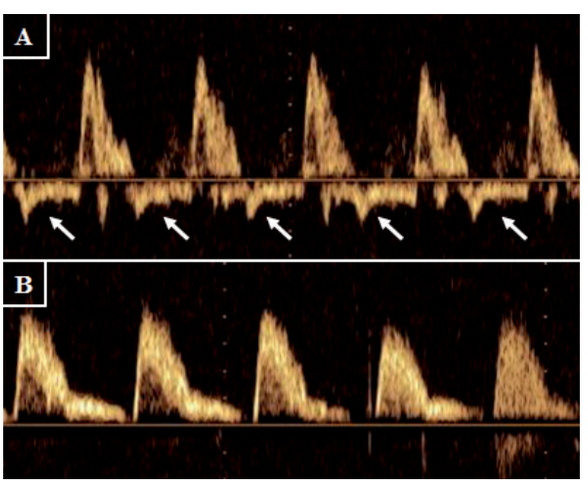

Figure 2.
Pulse wave Doppler assessment in the descending aorta by TTE in the same patient in ***Figure 1****. (A) There is diastolic flow reversal in the descending aorta (arrows) suggesting a large left to right shunt from the aorta to the PA leading to systemic hypoperfusion. (B) Following transcatheter closure, there is normalization in the Doppler pattern.*

Clinical criteria	Echocardiographic criteria
• Oxygenation difficulty (oxygenation index ≥ 10)	• PDA diameter ≥ 2 mm
• High ventilator settings (Mean airway pressure ≥ 10)	• Absent diastolic flow or reversal of end-diastolic flow in descending aorta, superior mesenteric, middle cerebral or renal artery
• Frequent episodes of oxygen desaturations, apnea or bradycardia	• Unrestrictive pulsatile transductal flow
• Inability to feed/abdominal distention	• Left heart enlargement (LA:Ao ratio ≥1.4)
• Systemic hypotension (low mean or diastolic BP)	
• Cardiomegaly ± Pulmonary edema on chest X-ray	
• Metabolic acidosis	

Table 1.
Clinical and echocardiographic criteria for hemodynamic significance.

increased cardiac output. Another indicator of pulmonary overload is the end-diastolic velocity in the PA, where high velocities may indicate pulmonary overload. Retrograde diastolic blood flow through the descending aorta (**Figure 2**) may be the most telling sign of systemic hypoperfusion due to a PDA, although end-organ blood flow may be assessed to further quantify these effects [19–21].

Echocardiographic evidence alone cannot determine hsPDA, but should be used in conjunction with clinical factors (**Table 1**), vulnerability of the infant due to gestational and chronological age, and risk of organ overflow (lungs) or hypoperfusion (brain, kidneys, intestines). Clinical findings that may help identify hsPDA include the need for vasopressors/inotropes, ventilator support and pulmonary edema, feeding intolerance, and rising creatinine levels.

7. Established techniques for closure

Treatment options are continuously evolving [25], and have included routine pharmacological treatment, conservative management, surgical ligation and transcatheter closure (**Table 2**). While indications for closure are not fully agreed upon, certain contraindications are noted below:

- Severe pulmonary vascular disease.
- Pulmonary artery hypoplasia.
- Duct dependent congenital heart disease

7.1 Medical therapy

Pharmacological treatment with COX inhibitors is usually the initial treatment for PDA. Currently, pharmacological therapy consists of intravenous or oral

Pharmacologic therapy	Surgical ligation	Transcatheter closure
Advantages:	**Advantages:**	**Advantages:**
• Non-Invasive • Efficacy 50–70% • May take a few days to be effective	• Invasive • Efficacy 100% • Immediate and definitive closure	• Minimally-Invasive • Efficacy 100% • Immediate and definitive closure
Disadvantages:	**Disadvantages:**	**Disadvantages:**
• Impairment in renal function, oliguria, proteinuria, hyperkalemia • Cerebral white-matter damage • Impairment in cerebral perfusion • NEC, Gastrointestinal perforation • Platelet dysfunction	• Post-Ligation Syndrome (30%) • Vocal cord dysfunction (30%) • Impaired neurodevelopmental outcomes • Risk of worsening of BPD • Chylothorax • Diaphragmatic paralysis • Bleeding • Pneumothorax • Cardiorespiratory failure	• Vascular access complications (1%) • LPA stenosis (1%) • Aortic arch stenosis (1%) • Device embolization (1%) • Tricuspid valve regurgitation (2%) • Exposure to X-Rays and contrast medium • Hypothermia

Table 2.
Advantages and disadvantages of therapies.

indomethacin, ibuprofen, or acetaminophen in varying dosages. The two most common options are intravenous standard doses of indomethacin and ibuprofen. In 2018, a meta-analysis of 68 RCT of 4802 infants found that among all preterm infants <37 weeks gestation, the overall PDA closure rate with one of the above treatment modalities was 67%. Oral ibuprofen was the most effective treatment, and none of the treatments increased the risk of mortality, NEC, or IVH compared to placebo or no treatment controls [25]. Slower absorption rates and a longer half-life of oral ibuprofen may increase the time of contact with the PDA, possibly explaining its improved effectiveness over intravenous routes [25]. The effectiveness of medical therapy is at best 50–70% and lower for those <32 weeks gestation [24–26].

Conservative management without the use of pharmacotherapeutics has become a recent trend in management of the PDA [16, 22]. Because many preterm infants will spontaneously close the ductus within the first week, early routine treatment with pharmacological therapy may not offer any benefit. Targeted therapy towards hsPDA based on clinical and echocardiographic thresholds is becoming the standard of care.

7.2 Surgical ligation

Surgical ligation through a limited left thoracotomy, although invasive, offers definitive, immediate closure of the PDA. Robert Gross performed the first successful PDA surgical ligation at Children's Hospital of Boston in 1939 while his chief was out of town. While surgical ligation carries minimal risk of mortality, other risks include pneumothorax, recurrent laryngeal nerve paralysis, chylous effusions, and post-ligation syndrome [12, 24, 26, 27]. Post-ligation syndrome occurs in the first 6–24 h in approximately 30% of neonates who undergo surgical ligation; neonates experience hypotension, which in some cases may be resistant to catecholamines, as a result of changes in myocardial function and impaired vascular tone [20, 21]. Long term complications such as thoracic scoliosis and neurosensory impairment have been reported in some cases following surgical ligation [24, 26, 27]. Only one trial has compared surgical ligation to nonintervention and found that infants undergoing ligation required longer ventilation, oxygen therapy, and hospitalization than control subjects, although differences did not reach statistical significance [28]. Even so, surgical ligation may still be desirable in infants for whom medical therapy has failed and transcatheter closure is not possible [12].

7.3 Transcatheter therapy

Transcatheter PDA closure (TCPC) is a minimally invasive therapy associated with low rate of adverse events that has become the procedure of choice for children >5 kg [29]. Historically, transcatheter closure of PDA has not been performed in premature neonates for a variety of reasons including: fear of patient fragility, concerns regarding vascular access and arterial injury, unknown effects of intravenous contrast media, concerns regarding catheter manipulation, and most importantly, absence of a suitable PDA closure device. Recently, a growing body of clinical evidence has emerged suggesting that transcatheter closure of PDA can be performed safely and effectively in premature infants [24, 30]. Risks of transcatheter therapy include embolization requiring surgery, cardiac perforation, aortic coarctation, and LPA obstruction, however these risks are very low even among ELBW infants.

8. Highlights of transcatheter PDA closure

- No arterial access is needed for the procedure.
- The procedure time is minimal.
- Therapy is definitive and minimally-invasive.
- Risks of pharmacotherapeutics and surgery can be avoided.
- The procedure can be safely performed in infants as small as 700 g using an FDA-approved device.

9. Controversy and practice variation

Controversy regarding if, when, and how to close the PDA abounds. Survey results of neonatologists and cardiologists in 2018 describe the practice variations in management of the PDA [31]. Some neonatologists responded that even a large, hemodynamically significant PDA in a premature baby never requires treatment including medical management as the majority are likely to close, while no cardiologists agree with this option. Nearly half the neonatologists believe that closing the PDA does not alter outcomes in children born <28 weeks' gestation, while most of the cardiologists disagree with this opinion. When institutions do believe that closure is needed after failed medical therapy, the majority of neonatologists and cardiologists currently still prefer surgical ligation to TCPC, while watchful waiting was still preferred by some neonatologists. There are immense variations in the practice of managing PDAs in ELBW infants in the United States. Neonatologists and cardiologists have differing opinions of the consequence of a hsPDA on the eventual outcomes. Certain landmark papers questioning the utility of PDA closure in premature infants may have influenced these opinions [16, 22].

In 2010, William Benitz performed a meta-analysis of 49 RCTs involving nearly 5000 preterm infants who underwent pharmacological or surgical treatment to close the PDA [16]. Evidence showed that while treatment was effective in achieving ductal closure, only a single study showed improvement in other outcomes such as pulmonary hemorrhage, BPD, NEC, or death. Correlations between PDA and IVH were and did not support the hypothesis that closure of the ductus improves neurological outcomes [16–22]. It was concluded that the association of comorbidities with PDA might arise from prematurity itself rather than through prolonged patency of the ductus. Benitz recommended prolonging treatment of the PDA in infants ≤1000 g until the second week after birth to increase the odds of spontaneous closure, and refraining from all treatment specifically intended to close the ductus in infants >1000 g. Fluid restriction, diuretics, supplemental oxygen, and other treatments were recommended in lieu of COX inhibitors and surgical ligation [16]. Certain patients at special risk for complications related to PDA would still require ductal closure and should be identified via a scoring system, such as the one proposed by McNamara and Sehgal [21]. Benitz's study provided impetus for the trend against early routine treatment of the PDA in premature infants and towards a more selective approach wherein only certain infants at increased risk received intervention to close the ductus.

In 2018, Ronald Clyman designed the PDA Tolerate Trial [13] to further examine early routine therapy versus conservative management by controlling for variables that had confounded many of the previous RCTs. Inclusion criteria was limited to

infants with a moderate-to-large PDA that did not close spontaneously within the first week. In so doing, the number of infants who spontaneously closed the ductus was reduced, though not eliminated. Early routine therapy (ERT) with pharmacological treatment was then compared to conservative management. As in previous trials, ERT did not always result in constriction of the ductus. Results indicated that ERT did not improve the incidence of NEC, IVH, BPD or death but instead delayed full feeding and may have increased the rate of sepsis and death in infants between 26 and 28 weeks gestation. Again, evidence did not support broad, routine ductal closure by pharmacotherapeutics in preterm infants.

With evidence mounting against the use of COX inhibitors and surgical ligation, the trend towards permissive conservative observation of this lesion has developed, reserving surgery for only the most severe cases [13–17, 32]. Unfortunately, recent data suggests that this approach is associated with an increased risk for the development of chronic lung disease and death, especially in infants born ≤26 weeks' gestation [8–17]. More recently in the United States, survival of infants born as early as 22 weeks' gestation is now possible [33], making the need for effective PDA therapy in this high risk, ELBW population more important than ever.

10. Role of transcatheter PDA closure in the future

Transcatheter therapy has evolved significantly in the last decade. Emerging technology has paved the way for the use of this therapy in smaller and smaller infants [34, 35]. The Amplatzer Piccolo Occluder (Abbott Structural Heart, Plymouth, MN, USA) is a self-expandable, Nitinol mesh device with a central cylindrical waist and low-profile retention discs that are marginally larger than the waist, resulting in a nearly isodiametric device. The device comes pre-loaded on a delivery wire, which has a soft floppy distal end with a microscrew attachment at the tip. It is delivered through a catheter using a loading device. The APO has ideal characteristics (size, shape, delivery system) for closure of PDAs in premature neonates including ELBW infants. With an increasing need for a less invasive therapy for PDA closure in this population, a clinical study evaluating the safety and efficacy of the APO was conducted that led to the approval of this device by the U.S. Food and Drug Administration (FDA) for children ≥700 g [36].

While transcatheter closure of the PDA is common among larger children and adults, several modifications specific for ELBW patients are necessary to ensure success and minimize complications.

- Transportation of ELBW infants to the catheterization lab poses challenges for these fragile patients, but with proper coordination of team members, can be accomplished without complication [37]. Special accommodations for temperature control and ventilator support are essential. One operator has thus far reported success with procedures performed at the bedside. While this procedure may eventually become common at the bedside, transport to the catheterization lab will likely be necessary in most institutions.

- Arterial access in these small patients is very likely to cause damage leading to limb ischemia and should be avoided [34, 38]. Instead, antegrade access through the femoral vein is the method of choice.

- The lack of arterial access and resulting inability to perform aortography post-deployment necessitates the use of TTE [39] to assess aortic flow, residual PDA shunting, and left PA (LPA) flow (**Figure 3**).

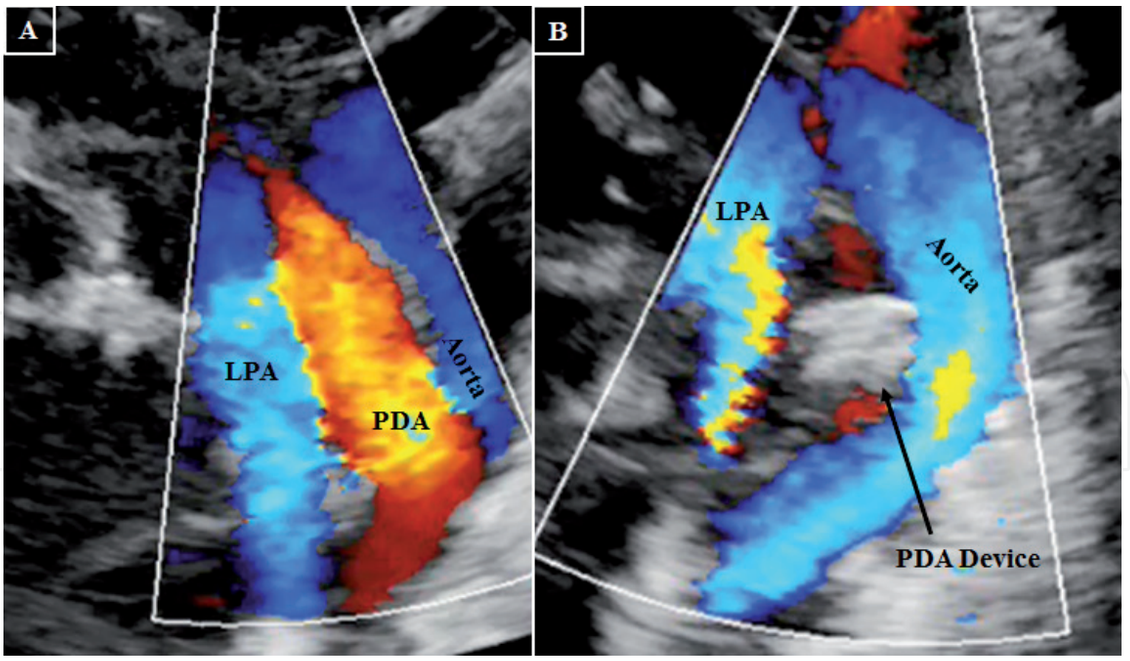

Figure 3.
TTE with color Doppler interrogation of the PDA of patient described in ***Figures 1*** *and* ***2*** *before (A) and after transcatheter device closure (B). The PDA is completely closed following intraductal implantation of the occlusion device. There is no stenosis of the left pulmonary artery (LPA) or the aorta caused by the device (B).*

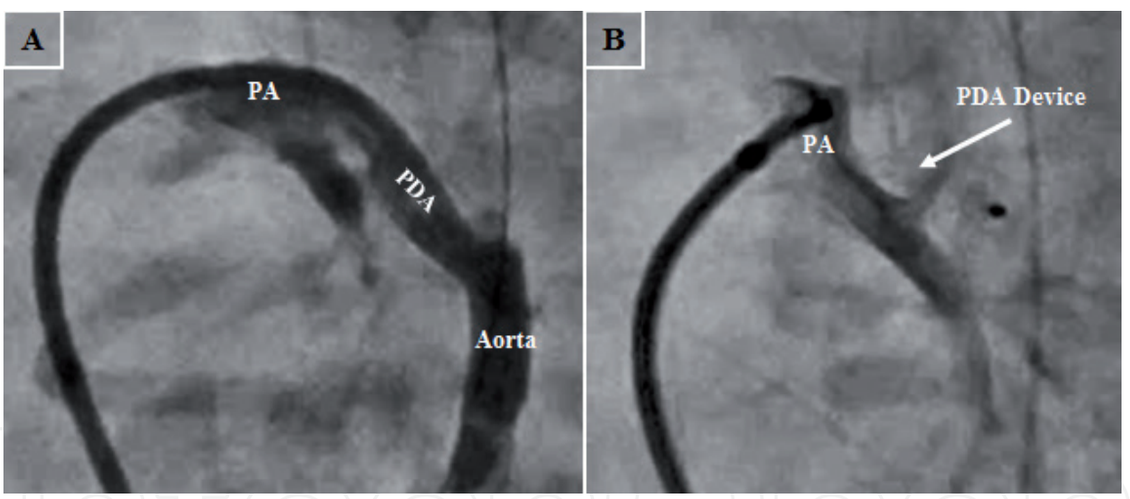

Figure 4.
Angiograms performed during transcatheter device closure of the PDA of patient described in ***Figures 1*** *and* ***2****. Prior to closure (A), a large PDA is demonstrated shunting left to right between the aorta and the pulmonary artery (PA). Following device implantation within the PDA (B), there is no residual PDA, and no stenosis of the PA or the aorta caused by the device.*

- The central waist of the APO is designed to fill the ductal lumen, and the retention discs are designed to deploy in the pulmonary and the aortic ends of the PDA. However, when treating small infants, especially those ≤2 kg, implantation of both retention discs completely within the duct (intraductal placement) to avoid protrusion into the aorta or the LPA (**Figure 4**) is essential to avoid inadvertent stenosis of these vessels by the device discs [24, 34, 40].

- Minimization of contrast dosing, intracardiac catheter manipulation, and unnecessary hemodynamic measurements that prolong procedure time are recommended to achieve optimal outcomes [24, 34, 40].

- Following deployment, but prior to device release, in addition to echocardiographic assessment as noted above, angiography should be performed to check for stenosis of the proximal LPA caused by the device [39].

By observing these precautions, transcatheter therapy in ELBW infants can be safely performed. This new therapy could shift the paradigm of treatment. Future randomized trials using TCPC are necessary to determine whether PDA closure would impact the short term and long term outcomes of children born prematurely. The benefit of this therapy over other therapies must be demonstrated before it can become standard of care for premature infants [41, 42], but this new option may offer a solution to the substantial unmet need in this population for a minimally invasive, definitive closure of the ductus.

11. Conclusions

The role of TCPC in ELBW infants will likely grow steadily, given the potential benefits of TCPC over other therapies. However, the most important question of "whether" the PDA needs to be closed at all still has to be answered. It is also prudent to determine "which" patients will benefit from closure, and in whom it is likely to close spontaneously. An RCT comparing TCPC vs. observation/conservative approach may be important to answer these questions. Hopefully, in the near future we will establish a treatment algorithm for ELBW with hsPDA.

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