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Patent Ductus Arteriosus: Update Review

Lucilla do Espírito Santo Brandão[1*], Rose Mary Ferreira Lisboa da Silva[2], Roberto Max Lopes[1] and Cristiane Nunes Martins[1]

[1]Biocor Instituto, Brazil.
[2]Department of Internal Medicine, Faculty of Medicine, Federal University of Minas Gerais, Brazil.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The Ductus Arteriosus (DA) is a vascular structure of the fetal heart that communicates the isthmus of the aorta (at the junction of the aortic root with the descending aorta) to the roof of the bifurcation of the pulmonary trunk. It is an essential structure of the fetal heart that connects the pulmonary circulation to de systemic circulation bypassing the lungs. The DA is usually patent at birth. It undergoes through muscle contraction between 10 and 15 hours of life and closes due to fibrous proliferation of the intimal layer by the third week of life. The change in the natural history of DA, with consequent permeability beyond the predicted period, promotes the Patent Ductus Arteriosus (PDA) a congenital acyanotic heart disease. The most important risk factor for PDA is prematurity. Other risk factors are the congenital rubella, chromosomal abnormalities, genetic factors, low birth weight, perinatal asphyxia and birth in high altitude places. The clinical manifestations of a PDA are determined by the degree of left-to-right shunting, which is dependent upon age, the size and length of the PDA and the difference between pulmonary and systemic vascular resistances. The diagnosis of PDA is usually based on its characteristic clinical findings and confirmation by echocardiography. The proper management of PDA depend on age, hemodynamic impact and resource available and may include conservative management, pharmacologic treatment, surgical approach and percutaneous closure. The complication rates for percutaneous and surgical closure are rare.

Keywords: Patent ductus arteriosus; congenital heart defects; therapy; treatment outcome.

**Corresponding author: E-mail: lucillabrandao@yahoo.com.br;*

1. INTRODUCTION

1.1 Definition and Epidemiology

The Ductus Arteriosus (DA) is a vascular structure of the fetal heart that communicates the isthmus of the aorta (at the junction of the aortic root with the descending aorta) to the roof of the bifurcation of the pulmonary trunk (PT). It is an essential structure of the fetal heart that connects the pulmonary circulation to de systemic circulation bypassing the lungs. Once the blood exits the right ventricle through the PT, it finds a high pulmonary resistance due to immature lungs, which are still a liquid-filled organ. On the other hand, the systemic circulation is connected to the placenta, a low blood resistance organ. This difference of pressures between the pulmonary and systemic circulations leads to a shunt from the pulmonary artery to the descending aorta. This deviation of pulmonary blood to the systemic circulation does not harm the fetus, since the oxygenated blood is delivered by the placenta and not the lungs [1].

The DA is usually patent at birth. It undergoes through muscle contraction between 10 and 15 hours of life and closes due to fibrous proliferation of the intimal layer by the third week of life. Higher oxygen concentration at the blood on the DA associated with a drop in the prostaglandin E2 production of the placenta and a decrease in blood pressure within the DA lumen are the main factors that lead to DA closure through muscular contraction. Thus, the functional closure of the DA occurs within the first 24 to 48 hours and the anatomical closure occurs in 2 to 3 weeks [1,2]. The change in the natural history of DA, with consequent permeability beyond the predicted period, promotes the Patent Ductus Arteriosus (PDA) a congenital acyanotic heart disease.

In term infants, the reported incidence of isolated PDA ranges from 2 to 6 per 1000 live births. Isolated PDA accounts for 5 to 10% of congenital heart defects. For unknown reasons, there is a female predominance for PDA with a 2:1 female to male ratio [1]. In premature infants, its incidence is approximately 0.008%. Up to 30% of newborns weighing less than 2500 g develop PDA [3]. Its prevalence is estimated at 14.2% in the total population (12.4% in children and 16.3% in adults). It is among the five most common diagnoses of congenital heart surgery [4].

2. CAUSES AND RISK FACTORS

The most important risk factor for PDA is prematurity. Premature infants have a lower blood oxygen concentration and therefore are more susceptible to PDA, since one of the prime mechanisms of ductal contraction is not effective [1,3].

Another risk factor is the Congenital Rubella Syndrome that can present with congenital heart disease in 60% of the patients and PDA is the most frequent. The incidence of PDA is also increased in high altitude locations compared with those born at sea level, for the same lower oxygen concentration typical of such places [5].

Mutations in the TFAP2B gene cause Char syndrome, a rare condition that presents with distinctive face appearance, PDA and hand abnormalities. The TFAP2B gene appears to play a role in the normal formation of structures in the face, heart and limbs. Other genetic syndromes associated with PDA are CHARGE syndrome, Holt-Oram syndrome, Noonan syndrome and DiGeorge syndrome [6]. There is a higher frequency in siblings, even without any genetic disorder, with a recurrence rate of 5%. In addition to prematurity, chromosomal abnormalities, genetic factors and infections, other etiological factors are low birth weight, perinatal asphyxia and birth in high altitude places [3].

3. MORPHOLOGY

In 1989, Krichenko developed an angiography-based classification in 5 categories: conical (type A), window (type B), tubular (type C), complex (type D) and elongated (type E) [7].

The right definition of the morphology is important to define the proper treatment, considering that some categories are more challenging to be treated with percutaneous closure and should be consider closure with the surgical approach.

Type A is the most frequent and it is characterized by a conical shape with the narrowing point at the pulmonary end. On Type B PDAs there is no constrictive point and is resembles aortopulmonary window. This morphology makes percutaneous closure difficult, due to the lack of narrow point to hold the closure device. Type C is tubular shaped and is also related with higher complications when

percutaneously closed. Type D is rare and has multiple constrictive points. At last, type E resembles type A but is more elongated and also has a narrow point at the pulmonary end (Fig. 1). Frequently PDA is associated with other congenital heart diseases (CHD), sometimes being the responsible for the maintenance of the infant's life. In the group of the CHD that course with low pulmonary flow, the PDA compensates the deficiency of pulmonary circulation. The most common CHD in this group are Tetralogy of Fallot, tricuspid atresia, pulmonary stenosis, pulmonary atresia with intact ventricular septum and single ventricle with pulmonary stenosis and transposition of great arteries. In the cases of hypoplasic left heart disease, the PDA represents the only path for systemic circulation. In the presence of other CHC with left to right shunt, PDA can worsen left chambers overflow and therefore result in more precocious hemodynamic consequences [8].

4. PHATOPHYSIOLOGY

The clinical features of the PDA depend on the amount of blood that deviates from the systemic to pulmonary circulation. The intrinsic resistance of the PDA and the pulmonary resistance regulate the flow that reach the lungs.

Large, tubular PDAs offer low resistance and makes aortic end pressure similar to the pulmonary end pressure. It is known by the Ohm Law that pressure = flow x resistance, therefore pulmonary extremity pressure of the PDA = flow through the ductus x pulmonary resistance. By similarity, aortic extremity pressure = flow through the ductus x systemic resistance. If no narrowing points are present, pressure in both extremities are similar and the proportion of pulmonary and aortic flow (Qp/Qs) will be defined by the relation between systemic resistance (Rs) and pulmonary resistance (Rp). At birth, the Rp is 25% the Rs and therefore, pulmonary flow can be 4 times the systemic (Table 1) [9].

5. SYMPTOMS AND PHYSICAL EXAM

The PDA has great clinical variability and may remain asymptomatic or be associated with symptoms of heart failure and pulmonary vascular remodeling, leading to inversion of the shunt and characterization of Eisenmenger Syndrome. The clinical manifestations of a PDA are determined by the degree of left-to-right shunting, which is dependent upon age, the size and length of the PDA and the difference between pulmonary and systemic vascular resistances. In term infants, the most typical presentation of PDA in the absence of other congenital heart defects is murmur [10].

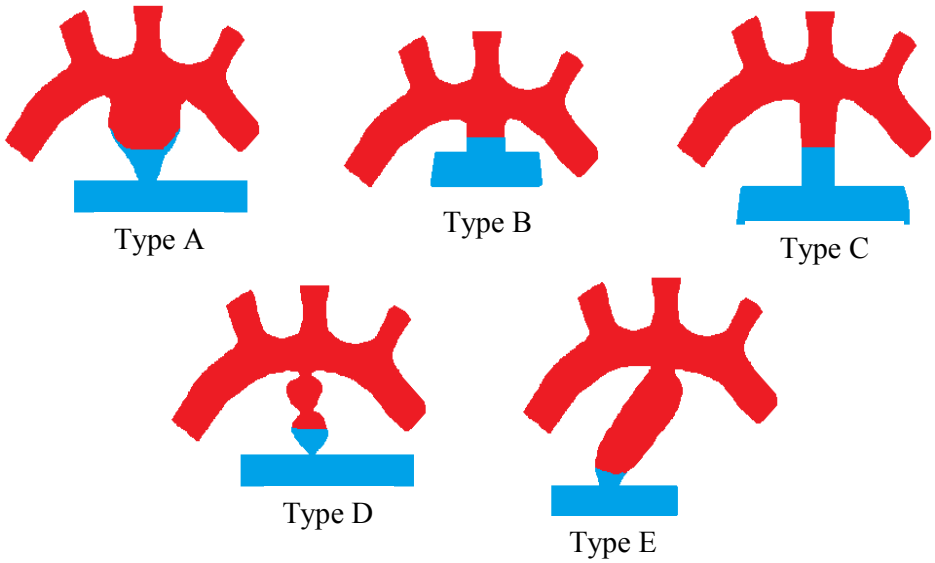

Fig. 1. Krichenko PDA classification. Type A: Conical shape with the narrowing point at the pulmonary end. Type B: No constrictive point and resembles aortopulmonary window. Type C: Tubular shaped. Type D: Multiple constrictive points. Type E: Resembles type A but is more elongated and also has a narrow point at the pulmonary end. Red vessel: Proximal aorta; blue vessel: Pulmonary artery

Table 1. Relationship between volume, pressure and resistance

Pp = Qp x Rp and Ps = Qs x Rs
If Pp = Ps (present at tubular and window shaped PDA), then Qp x Rp = Qs x Rs
Qp/Qs (proportion of pulmonary flow and systemic flow) = Rs/Rp
Rp/Rs = ¼ at birth or Rs/Rp = 4
So Qp/Qs = 4 (4 times the amount of blood reaches pulmonary circulation compared to systemic flow)

Pp: pulmonary pressure / Qp: pulmonary flow / Rp: pulmonary resistance / Ps: systemic pressure / Qs: systemic flow / Rs: systemic resistance

In preterm infants, typical signs are absent in the first hours of life, due to the transition of the pulmonary vascular resistance that take several hours or days to be complete. The increased shunt velocity coinciding with declining pulmonary vascular resistance produces a typical murmur described by Gibson in 1898 (a louder continuous or machinery murmur in the first or second left intercostal space). As the myocardium performance improves, there can be seen hyperactive precordium, increased pulse volume and wide pulse pressure [3,9].

Large PDA with considerable pulmonary flow can have hemodynamic consequences such as enlargement of left chambers and congestive heart failure resistant to clinical treatment. If not treated, the child can have failure to thrive, feeding disorders, swelling, shortness of breath and fatigue.

Term infants, children and adults show clinical manifestation according to pulmonary-to-systemic-flow ratio (Qp:Qs). A small PDA (Qp:Qs < 1,5 to 1) that restricts excessive blood flow into the lungs may go undetected with no symptoms. The diagnosis is usually incidental after murmur identification at routine primary care visit or by a diagnostic study performed for other medical conditions. Patients will have normal precordial activity, heart sounds and pulses. The PDA murmur is characteristically continuous best heard in the left infraclavicular region. Murmur does not change according to patient's position. Patients with moderate PDA (Qp:Qs between 1,5 and 2 to 1) can show exercise intolerance. The physical exam shows the typical murmur, a wide systemic pulse pressure and signs of left ventricular volume overload, such as displaced left ventricular apex. Infants with large PDA (Qp:Qs > 2,2 to 1) may present with heart failure, failure to thrive, poor feeding and respiratory distress. The older child may present with shortness of breath or easy fatigability, dynamic left ventricular impulse and wide pulse pressure. Adults with large PDA that still with left-to-right shunting have clinical manifestations similar than older children. The diastolic component of the murmur disappears when there is moderate pulmonary hypertension. Once Eisenmenger syndrome is established, there is an inversion on shunting and the adult may present with cyanosis and clubbing [10]. Both cyanosis and clubbing can be more pronounced in the lower extremities (differential cyanosis) because the ductus typically delivers unoxygenated blood distal to the left subclavian artery.

6. DIAGNOSIS - COMPLEMETARY EXAMS

The diagnosis of PDA is usually based on its characteristic clinical findings and confirmation by echocardiography. Before echocardiogram, angiography was the only diagnostic method for PDA. Currently, catheterization is only necessary in the context of treatment, not diagnosis [10].

ECG has a low sensitivity and specificity for PDA, and when alterations are present, it is due left chambers enlargements such as wide P wave (for left atrium) and signs of ventricular hypertrophy (R wave seen at derivations I, II, aVL, V5 and V6, S wave at V1 and V2) [11].

Chest radiography is usually normal. When altered it can present cardiomegaly, left atrium (LA), left ventricle (LV) and aorta dilatation if significant shunt happens. If so, prominent main pulmonary artery blending with a prominent aortic knob along the upper left heart border can be seen. Pulmonary vascular marking can be found if significant pulmonary overflow [3,10].

Echocardiogram is the current main diagnostic tool for PDA. PDA can be well identified between the origin of the left pulmonary artery and descending aorta, distal the left subclavian artery at the parasternal and suprasternal views. Chamber enlargements measures and shunt velocity are important to define the hemodynamic

consequences of the PDA. Typically, there is no need to magnetic resonance or tomography to diagnose PDA. Sometimes, however, it is an additional finding when examining different structure [10].

7. NATURAL HISTORY AND OUTCOME

In 1968 Mitchell first described the natural history of PDA as it was at the time. He concluded that even if the DA does not close shortly after birth, it still has the potential to close during the first year of life [12], with an estimated spontaneous closure rate of 0.6% per year [3].

As any left to right shunt congenital heart disease, long term pulmonary overflow can lead to vascular remodeling of the lungs and pulmonary hypertension (PH). It is rare for PDA to develop PH comparing with ventricular left to right shunt situations such as ventricular septal defect and total atrioventricular septal defect. The PDA usually offers pulmonary overflow resistance and the inversion of shunt is rare. If it happens, eventually pulmonary pressure turns higher then systemic pressure and the shunt at the PDA instead of from left to right turns to right to left. This is called Eisenmenger Syndrome [8]. Once that endpoint is reached, there is no benefit in PDA closure, since vascular remodeling will continue despite closure [12].

Other possible complications are endarteritis and formation of aneurysms of the DA. Endarteritis is the endocarditis inside the DA which can be difficult to diagnose for general physicians if the patient does not have the PDA diagnosis [13]. The risks of aneurysm are rupture and bleeding.

Premature neonates with low body weight may present with respiratory distress and heart failure, with indication of DA closure for a favorable impact on morbidity and mortality. The mortality rate of untreated patients is 20% at 20 years of age, reaching 60% at 60 years of age [3].

8. MANAGEMENT: PHARMACOLOGIC TREATMENT, SURGICAL INTERVENTION, CATHETER-BASED TREATMENTS

The proper management of PDA depend on age, hemodynamic impact and resource available. They can be better summarized according patients age:

8.1 Preterm Infants

Infants born before proper gestational age are more likely to persist with a fetal structure after birth. This occur due to the comparative hypoxemia preterm children have comparing to term infants.

Some important questions remain difficult to answer regarding the most advantageous way and the impact of PDA closure in preterm infants. First, does the PDA need to be closed? It is well known that a significant portion of symptomatic PDA can close spontaneously; therefore, which ones should be treated before? And if so, how to perform the closure? There is still a lack of studies supporting any answers to those questions yet [14]. The 2020 Indian Guidelines for Management of Congenital Heart disease recommend treating the preterm infants with heart failure with 2 courses of drug therapy or surgical ligation when pharmacological approach is unsuccessful [15].

The first line of treatment is the conservative management in which general supportive measures are applied with no drugs or procedures. If those measures do not work, and the child remains on mechanical ventilation when other factors have been excluded, such as infection or bronchopulmonary dysplasia, pharmacologic closure can be performed. In a very low number of cases, and when the less invasive treatments were ineffective, surgical or percutaneous closure may be the final option [5].

8.1.1 Conservative management

For infants with a hemodynamically significant PDA, an initial conservative approach can include fluid restriction, maintenance of a higher hematocrit, use of diuretic and minimal respiratory support. Excessive fluid administration is associated with an increased incidence of PDA and, therefore, a moderate daily intake of 120-130ml/kg is suggested. When diuretic therapy is considered, it is wise not choosing furosemide, as it stimulates renal synthesis of prostaglandin E2, a potent vasodilator that maintains ductus arteriosus patency. Hematocrit at 35 to 40 percent can increase pulmonary vascular resistance and reduce left to right shunting, and minimal mechanical ventilation minimize further pulmonary injury [14].

8.1.2 Pharmacologic treatment

When the conservative approach fails and there is still hemodynamic impact of the PDA, pharmacologic intervention may be needed. The drugs that show effectiveness on PDA closure are those who target inhibiting prostaglandin synthetase, as prostaglandin promotes ductal patency. The best choices are non-selective cyclooxygenase (COX) inhibitors such as ibuprofen and indomethacin and acetaminophen, which interferes the peroxidase segment [16].

The choice of drug is center-bases. It is known that between the two COX inhibitors, ibuprofen has lower risk of necrotizing enterocolitis and transient renal insufficiency then indomethacin, but shows no difference on mortality, intraventricular hemorrhage, pulmonary hemorrhage, bowel hemorrhage, sepsis or retinopathy rates.

The standard dose for ibuprofen is an initial dose of 10 mg/kg followed by two additional doses of 5 mg/kg given at 24 hours interval. This dosing is the same for both oral and intravenous administration. IV ibuprofen is typically used in developed countries because of availability and because it is more expensive then the oral form. However, studies have shown the same effectiveness and developing countries continue to use the oral form with same results [16]. Some studies suggest high dose ibuprofen as an alternative and point higher likelihood of success. In these cases, an initially dose of 15-20mg/kg followed by two additional doses of 7,5-10mg/kg administered every 12 to 24 hours can be used.

Indomethacin is given intravenously with great dosing variety between neonatal centers. Typically, it is chosen 0,1-0,2mg/kg per dose administered every 12 to 24 hours in three doses. Four or more doses show no additional increase in success rates.

COX inhibitors are contraindicated in infants with proven or suspected infections, active bleeding (especially intracranial hemorrhage or gastrointestinal bleeding), thrombocytopenia or coagulation defects, necrotizing enterocolitis suspected or confirmed and renal function impairment. In those cases, oral or IV acetaminophen (when available) are used. The administered dose of acetaminophen is 60mg/kg per day over a two to seven days program. This dosage is significantly higher than the pain and fever dose used, so attention to hepatotoxicity should be considered and liver blood test performed [5].

There is still a lack of trials to determine the best treatment choice. Recent Cochrane meta-analysis, however, states that prophylactic treatment exposes a large proportion of infants unnecessarily to a drug that has important side effects without conferring any important short-term benefits. Current evidence does not support the use of ibuprofen for prevention of patent ductus arteriosus. Until long-term follow-up results of the trials included in this review have been published, no further trials of prophylactic ibuprofen are recommended [17].

8.1.3 Percutaneous approach

Percutaneous transcatheter occlusion in preterm infants should be performed in specialized centers with expertise in this particular population. In 2019, the FDA approved the Amplatzer Piccolo Occluder, used in infants > 700g and 3 days of life. This device in not largely available yet [14].

8.1.4 Surgical approach

Surgical ligation is the last option when conservative approach and two courses of pharmacologic therapy fail and the patient remain with hemodynamic impact and need for maximum mechanical ventilation. It is associated with risk of infection, chylothorax, recurrent laryngeal nerve paralysis, bronchopulmonary dysplasia, pressure fluctuations, intraventricular hemorrhage and death. It still remains uncertain, however if the surgical ligation is the major contributor to morbidity and mortality or if patients who undergo surgical ligation are more severely compromised to begin with [18].

8.2 Term Infants and Children

In term infants and children with moderate to large PDA or in whom there is a prior episode of endocarditis, the closure decision is straightforward, whereas in small or silent PDA without significant left-to-right shunt the decision for closure is less clear. In case of small audible PDA (i.e, those presenting with murmur), the closure is recommended because it prevent occurrence of bacterial endocarditis, a rare but recognized complication of small PDA. Some physicians, however, believe that the chances of endocarditis in patients with small PDA is similar

then general population, and therefore should be left untreated [18].

Small silent PDA usually are incidentally detected by imaging studies performed for other indications. Silent PDA do not have hemodynamic consequences, and thus, the only impetus for closure is the theoretical risk of bacterial endocarditis or family/personal preference.

Once the patients are not newborns anymore, they do not respond to pharmacologic closure. If they are asymptomatic, it is recommended to delay closure until proper weight for percutaneous closure is achieved. If symptomatic, medical management as digoxin and diuretics can help waiting to suitable weight for percutaneous closure. In symptomatic non-responders to medical treatment, surgical closure is preferable. Although there have been many devices used for smaller children with a huge success rate, the smaller the child less than 6kg is, the higher chance for procedure complication. In children over 6kg, percutaneous occlusion is generally preferred over surgical ligation because it is less invasive and less expensive or at least as cost-effective [18].

Therefore, the timing of PDA closure depends on the PDA's size and hemodynamic consequences. Large to moderate PDA with significant left heart volume overload, congestive heart failure or pulmonary hypertension must have early closure (by 3 months). When there is some degree of left heart overload, mild or no congestive heart failure and/or mild pulmonary arterial hypertension, it is considered moderate. In this case, it can be closed when the child is between 6 and 12 months old. Small PDA should be closed by the age of 12-18 months and if silent PDA, the closure is not recommended [15].

8.3 Adults

In older patients, percutaneous occlusion is always preferred than surgical [19]. Coils can be used for small PDA and, for moderate to large PDA, other devices such as ductal occluder or general vascular plugs are available.

It is important to point out that once there is irreversible pulmonary hypertension, there will be no benefit in performing the procedure and progressive pulmonary vascular disease will continue despite PDA closure. If Eisenmenger Syndrome is present (severe pulmonary hypertension that results in right to left shunt), closing the PDA may worsen clinical symptoms because they depend on the shunt to avoid heart failure and maintain cardiac output [20].

8.4 Interventional Options

8.4.1 Catheter-based treatment

Percutaneous closure of the ductus arteriosus began in 1966 when Portsmann was successful in percutaneous prosthesis implantation in a 17-year-old patient [21]. In the last 5 decades, there have been great advances in the development of prostheses and sheaths, making it possible to reduce the duration of the procedure and include less weight children.

Its execution is particularly challenging if we consider the great morphological variability of this vascular structure, as seen in the morphology description above. In view of the increased number of possible configurations, no device has been shown to be efficient for contemplating all anatomical variants of the ductus arteriosus.

Ideally, the occlusion should be total so that there is no residual shunt, no part of the device should remain exposed, and there should be no protrusion of the device into the pulmonary artery and/or aorta (Fig. 2). Calibrated tubular channels, with small aortic ampulla and angled channels, especially in low weight patients, are at higher risk of complications.

Currently, the proper devices for percutaneous closure of the DA are prostheses specifically designed for DA closure. Coils used to be particularly useful in closing small DA with reduced performance for large ductus. In those cases, sometimes it was necessary to use more than one coil to fill a single DA, increasing the procedure time and the risk of embolization. Specific designed prostheses, on the other hand, come in different sizes and brands; however, their use is limited due to cost, both at public and private levels [22].

In patients with an DA diameter of less than 8 mm, there is ductal closure in more than 85% of cases during the 1-year follow-up and with less than 1% mortality [23].

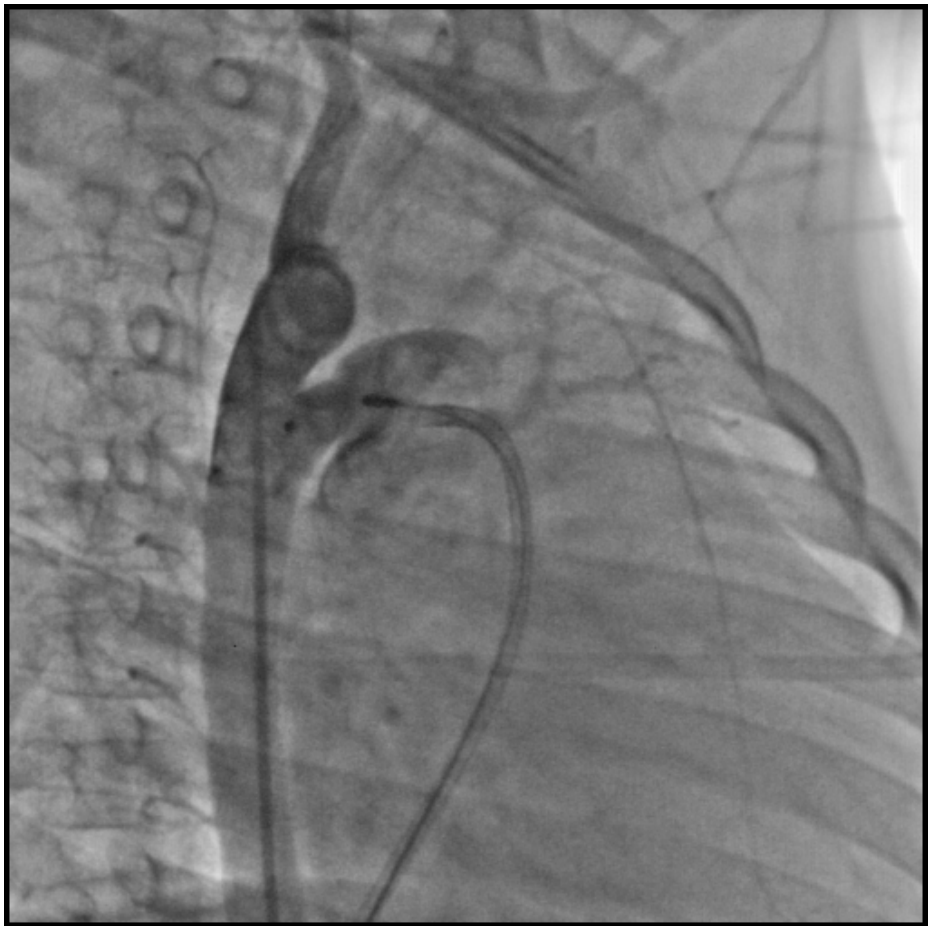

Fig. 2. Right anterior oblique (RAO) aortogram showing the device placed into the PDA ampulla by retrograde approach

8.4.2 Surgical treatment

Since the first successful surgical PDA ligation in 1939, the technique has been improved and now it can be performed safely inclusive in extremely low birth weight infants (<1000 g) [20].

The surgical approach is the third left intercostal space in infants and fourth left intercostal space in infants and fourth left intercostal space in older patients. Many surgeons prefer multiple ligations or division to minimize the risk of recurrent shunt. Video-assisted thorascopic surgery is a safe and effective procedure for PDA closure and is less invasive than standard thoracotomy surgical closure. It is contraindicated if the PDA is greater than 9 mm, in patients with prior thoracotomy, ductal calcifications, active infections or ductal aneurysm [20]. In more than 95% of patients, the murmur disappears on physical examination. However, the mortality rate can reach 3.5%, especially in adults with PH [23].

The complications reported after surgical ligation include: recurrent laryngeal nerve paralysis, respiratory compromise, infection, pleural effusion or chylothorax, pneumothorax, bleeding, scoliosis or residual duct patency [20].

9. CONCLUSIONS

Persistent ductus arteriosus is an acyanotic congenital heart condition originated by main patency of a fetal structure. It can have hemodynamic pulmonary vascular consequences and treatment should be performed. The complication rates for percutaneous and surgical closure are rare. Complications include pulmonary device protrusion, aortic protrusion, embolization and residual shunt in the percutaneous approach,

and chylothorax, pneumothorax, vocal cord paralysis in the surgical approach.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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