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# Significance of the Patent Ductus Arteriosus in Neonates

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**Abstract**

*The patent ductus arteriosus (PDA) is the most common abnormal cardiac finding in neonates. Persistent patency of the ductus arteriosus may be encountered in three different situations: Persistent ductus arteriosus in term newborns, persistent ductus arteriosus in preterm newborns and persistent ductus arteriosus in children with congenital heart disease. Problems associated with PDA include feeding intolerance, necrotizing enterocolitis (NEC), metabolic acidosis, renal failure, peri/intraventricular hemorrhage (PVH/IVH), pulmonary hemorrhage (PH), chronic lung disease (CLD) and death. The use of multimodal technologies can provide assessment of the impact of hemodynamically significant PDA (hs-PDA) including: echocardiography, serum biomarker level (BNP, NT pro BNP, cTnT), NIRS (Near infrared spectroscopy). Determining the degree of shunting can be helpful in making a decision about the need for therapeutic intervention. The goal of treatment in congenital heart diseases with ductus dependent systemic and pulmonary circulation is to re-establish the prenatal circulation pattern before final, hybrid or palliative surgical treatment.*

**Keywords:** *hemodynamically significant patent ductus arteriosus, neonate, congenital heart disease*

## Introduction

The ductus arteriosus is a central vascular shunt that connects the pulmonary artery to the aorta, allowing oxygenated blood from the placenta to bypass the uninflated fetal lungs and enter the systemic circulation.

Although patent ductus arteriosus (PDA) represents persistence of a normal fetal structure, it may present in a variety of different anatomical variations, associated either with normal cardiac anatomy or with more or less complex congenital heart disease. In the vast majority of cases however, the ductus arteriosus is left sided in the presence of a left aortic arch (1).

The incidence of patent ductus arteriosus (PDA) increases with decreasing gestational age at delivery from 57 per 100,000 live births to 55 per 100 live births in ELBW (weighing<1000 g) infants (2-4).

The ductus arteriosus is a vascular structure of vital importance for the circulation in the fetus. While 60% of the fetal cardiac output is ejected from the right ventricle to the main pulmonary artery, only 8% pass the lungs. The remainder of the blood is directed from the pulmonary artery via the ductus to the descending aorta. Premature closure of the ductus in utero in the presence of normal cardiac anatomy results in a maximal increase of right ventricular afterload. In this situation the fetus develops signifcant right ventricular dilatation, tricuspid regurgitation, fetal hydrops and frequently fetal death.

The pathophysiology of the PDA is dependent upon the presence of congenital heart disease, gestational age and many hemodynamic and anatomic factors.

Closure of the ductus after birth begins as a result of some important haemodynamic changes. Due to inflation of the lungs immediately after birth, there is a dramatic decrease in pulmonary vascular resistance and a dramatic increase in pulmonary blood flow resulting in an immediate decrease of right to left shunting across the ductus arteriosus. The ductus arteriosus closes shortly after birth in response to increasing oxygen tension, decreasing levels of prostaglandin and prostacyclin and increasing levels of vasoactive substances (5).

Normally complete functional closure of the ductus occurs within the first few days of life, followed by the anatomical obliteration within the following weeks. In

healthy neonates, closure of the ductus arteriosus is observed by the fourth day of life, and ductal patency beyond this is abnormal. Ductal patency depends on factors that stimulate either patency or ductal closure. Factors involved in maintaining ductal patency are vasodilating prostaglandins and nitric oxyde (NO). Ductal closure is stimulated by a significant increase in partial pressure of oxygen (PO2). Oxygen and endothelin are potent vasoconstrictors and prostaglandins E2 and I2 are potent vasodilators of PDA. Low levels of O2 in utero and high levels of circulating prostaglandins helps to keep open PDA.

Histologically, the walls of the PDA are mainly muscular in contrast to the walls of the adjacent aorta and pulmonary artery, which are fibro-elastic . The PDA is comprised of smooth muscle fibers which are arranged in longitudinal and spiral layers and surrounded by concentric layers of elastic tissue. The great arteries are composed primarily of elastic fibers arranged circumferentially. After birth, the medial smooth muscle fibers contract in response to the exposure to oxygen-rich ambient air (6). This leads to constriction of the lumen and shortening of the PDA length which begins at the pulmonary end until there is functional closure between 24 and 48 h. The second step in closure involves proliferation of the medial and intimal connective tissue and smooth muscle atrophy which leads to the conversion of a muscular vessel into the ligamentum arteriosum over the next 3 weeks (7).

Persistent patency of the ductus arteriosus may be encountered in three different situations:
1.Persistent ductus arteriosus in term newborns
2.Persistent ductus arteriosus in preterm newborns
3.Persistent ductus arteriosus in children with congenital heart disease:

a)Right-sided obstructive lesions

b)Left-sided obstructive lesions

## Persistent Ductus Arteriosus in Term Newborns

Closure of the PDA is expected in healthy, term neonatal for 48-72 hours after birth. The haemodynamic repercussionss of PDA in term newborns hang on its width and on systemic and pulmonary vascular resistance. With a widely patent ductus, the pulmonary vascular bed continues to be exposed to systemic blood pressure and is confronted with a significantly increased pulmonary blood flow. A large ductus arteriosus allows equalization of pressures in the aorta and pulmonary artery. Elevated pulmonary artery pressure in combination with increased blood flow exposes the pulmonary vascular bed to increased shear stress, resulting in progressive pulmonary vascular damage. In term newborns, this refers to ductus with a minimal diameter of>3 mm. Medium-size ductus with a diameter of 2–3 mm does not allow equalization of pressures in the aorta and pulmonary artery, while they still allow signifcant LR-shunting. Left to right shunt through a patent ductus arteriosus ends in notable volume overload of the pulmonary arteries as well as the left heart cavities. Small ducts with a diameter of<2 mm neither expose the pulmonary arteries to elevated pressure nor do they allow signifcant LR-shunting.

## Persistent Ductus Arteriosus In Preterm Newborns

PDA occurs in up to 33% of very low birth-weight infants and up to 65% of all extremely low birth-weight (ELBW) infants (8,9,10). The ductal steal phenomenon in preterm infants leads to complex circulatory consequences in pulmonary and systemic circulation.

In these children, patency of the ductus contributes signifcantly to respiratory complications, aggravates respiratory distress syndrome by impairment of lung function and promotes development of chronic lung disease. In addition signifcant LR-shunting and diastolic run-off from the systemic circulation in the presence of a large ductus result in reduced perfusion of the postductal organs including the gastrointestinal tract and the kidneys. Ischaemia due to hypoperfusion of the gastrointestinal tract is a significant risk factor of necrotizing enterocolitis. Changes in blood flow of the brain as well as the intraventricular haemorrhage also seem to be connected with PDA in premature children. There is still debate however about the details of their causal relationship (11-13).

Prematures have higher sensitivity to the effect of prostaglandins in relation to term neonates, prolonged course, higher incidence of hypoxia and acidosis, defect of smooth muscle cell migration. Prematures with birth weight > 1000 g: spontaneous closure of DAP in 67% of cases by day 7 and in 94% of cases by discharge. Only 3% of prematures birth weight > 1000 g require PDA closure intervention.

57-69% extremly low birth weight (ELBW) group of premature baby (birth weight <1,000 g) will have open PDA at 7-10 days of age. In 30% ELBW is expected to reopen the duct, which may close or become hemodynamically significant, requiring pharmacological or surgical closure. Hemodynamically significant PDA **(hsDAP)** is defined as PDA resulting in reduced organic blood flow and reduced tissue oxygenation

Problems associated with PDA include feeding intolerance, necrotizing enterocolitis (NEC), metabolic acidosis, renal failure, peri/intraventricular hemorrhage (PVH/IVH), pulmonary hemorrhage (PH), chronic lung disease (CLD) and death (14-25).

Clinical signs of open PDA are continuous or systolic murmur, but also "silent" DAP if the ductal shunt is large enough, but without non-turbulent flow and noise, low diastolic pressure (due to diastolic "escape" in DAP-mainly in prematurity), wide pulse pressure (over 25mmHg) (due to ductal "escape or steal"), hypotension (especially in prematurity), bounding pulses, increased serum creatinine or oliguria, hepatomegaly.

Signs of pulmonary edema (tachypnea, decreased satO2, increased respiratory effort) could be present and heart rate increases by 25% to overcome ductal " steal". Metabolic acidosis, unrelated to sepsis and hypoperfusion, deterioration of respiratory status after 3-4 days of relative stability, increased ventilatory needs, unexplained CO2 retention, fluctuations in FiO2 needs and recurrent apnea are very important signs to recognise open, hemodynamically significant duct in these patients.

The use of multimodal technologies can provide a superior and more robust assessment of the impact of hs-DAP including: echocardiography, serum biomarker level (BNP, NT pro BNP, cTnT), NIRS (Near infrared spectroscopy) (23).

### *ECHO evaluation*

- Gold standard for PDA diagnosis, assessment of hemodynamic impact on premature circulation and monitoring of therapeutic response
- Thorough echocardiographic assessment must include markers of pulmonary overcirculation, systemic hypoperfusion, and ductus characteristics, including diameter and Doppler flow pattern.

Echocardiographic surrogates for ***pulmonary hypercirculation*** include:

ratio of left atrium to aortic root (LA: Ao), LVOT and LVOT / VCS ratio, end-diastolic diameter LV, mitral velocities: E wave, A wave and IVRT

Echocardiographic indices assessing ***systemic hypoperfusion*** include examination peak systolic velocity and diastolic flow direction in the descending aorta and renal, celiac, and middle cerebral arteries. Color Doppler shows that PDA reduces the blood flow velocity of the middle cerebral artery in ELBW in the first 5 days of age. It was previously thought that PDAs would only have negative effects on blood flow postductally; a 2017 study reported that DAP at 5-7 days of age was also associated with reverse diastolic flow in the brachiocephalic artery (24).

A vital but often forgotten component of the ECHO examination is the assessment of myocardial performance, diastolic function and coronary perfusion. L-D shunt through PDA compromises coronary perfusion with subclinical signs of myocardial ischemia and additional systolic and diastolic dysfunction.

| ECHO indicators | HS PDA |
|---|---|
| **Diameter PDA (mm)** | ≥1,5 ( ≤ 26 WG)<br>≥2,0 ( ≤30 WG)<br>>1,4mm/kg |
| **Shunt pattern** | Growing, pulsating (non HS PDA – closing, bidirektional)<br>- Flow direction (left to right, bidirectional with right to left ≤ or >30% of the cardiac cycle, right to left)<br>- velocity in systole and diastole (m/s) and gradient |
| **Level of pulmonary hypercirculation**<br>LA/Ao ratio, LVEDD (mm)<br>LVO/SVC ratio<br>LVO (ml/kg/min)<br>LPA EDV (m/sec)<br>Transductal velocity ratio<br>Pulmonary vein d wave velocity (m/sec)<br>Mitral valve E:A<br>IVRT (ms) | <br>LA/Ao ≥ 1,4<br>>4<br>LVO > 300<br>LPA EDV > 0,2<br><1,8<br><br><br>(<40 ms) |

| | |
|---|---|
| **Magnitude of systemic hypoperfusion**<br>Desc.aorta flow<br><br>Organic perfusion<br>(MCA, RA, SMA, CA) | <br>Retrograde( non HS PDA-antegrade)<br><br>Low antegrade flow in systole or diastole, absent / reverse diastolic flow |
| Clinical factors | |
| Cardiovascular<br>Respiratory<br>Gastrointestinal<br>Renal | Vazopresors/inotrops<br>Ventilation support + pulmonary edema<br>Feeding intolerance<br>Increased kreatinin |

**Fig1.** *ECHO characteristics of hemodynamically significant PDA (hs-PDA).WG-weeks of gestation, LA-left arium, AO-aorta, LVO-left ventricular outflow, LVEDD- left ventricle end diastolic diameter , LPA EDV-left pulmonary artery end-diastolic velocity*

**Near-Infrared Spectroscopy (NIRS)-** non-invasive technology that continuously measures regional tissue oxygenation. Studies have established the usefulness of this technique in determining the significance of DAP and assessing response to treatment. NIRS has the ability to detect systemic hypoperfusion associated with hS PDA: renal NIRS <66% identifies hS PDA with a sensitivity of 81% and a specificity of 77% in prematures below 29 gestation weeks. Significant correlations between reverse diastolic flow in the descending aorta secondary to hS PDA and low mesenteric regional oxygenation. Research is underway with NIRS to assess the long-term effects of HS PDA on cerebral perfusion and brain growth (25-27).

### *Biomarkers*

*Plasma NT-proBNP* on second day of life was found as a sensitive marker for predicting HsPDA in preterm infants. Termination of PDA was found to be related with the decrease in NT-proBNP. The increased pressure, volume, and ventricular wall stress that occurs during hsPDA causes ventricular myocytes to synthesize and release brain natriuretic peptide (BNP) and aminoterminal pro-B-type natriuretic peptide (NT-proBNP) (28).

*NT-proBNP* is the inactive fragment of BNP formation within the myocytes. Both are markers for heart failure in adults and children. In neonates, however, levels of BNP and NT-proBNP vary with both gestational and chronological ages and are highest during the first few days of life and in the most premature infants (29).

*Cardiac troponin T (cTnT)* levels significantly correlated with DAP diameter, LA / Ao ratio, and flow rates in the descending aorta and diastolic velocities (30-32).

### *PDA Scoring systems*

Scoring the degree of shunting should help place it along this continuum and facilitate improved decision making vis-a-vis the need for therapeutic intervention. Several PDA severity risk scores, predominantly based on echocardiographic parameters, have been proposed (33-37). Both the El-Khuffash and Shaare Zedek scores are predictive of PDA-associated morbidities.

Echocardiographic Scoring System for the Patent Ductus Arteriosus (38)

| Parameter | 0 | 1 | 2 |
|---|---|---|---|
| LA/Ao ratio | <1 | 1-1,3 | >1,3 |
| Retrogarde artic flow (reverse:forward flow) | none | 0-0,4 | >0,4 |
| PISA | No duct | some | None when DAP is present |
| DAP:LPA ratio | <0,25 | 0,25-0,5 | >0,5 |
| DAP Doppler | Continuous flow | L-R and stops at baseline | bidirectional |

**Fig2.** *PDA Severity Scoring Systems : Hamodynamically significant if score >5*

Functional ductal closure occurs in nearly all term infants within the first 72 hours of life, by the fourth day in 90% to 98% of healthy preterm infants born at 30 weeks' gestation or more. In two-thirds of infants born at 28 to 30 weeks' gestation, this closure occurs by the seventh day, and 94% of these close spontaneously by discharge (39).

Treatment depends of: patient's age, ductal size and morphology and degree of shunting and symptomatology

Therapeutical options:

a) Medication (prostaglandin synthesis inhibitors)

b) Percutaneous catheter occlusion

c) Surgical ligation

d) Spontaneous closure

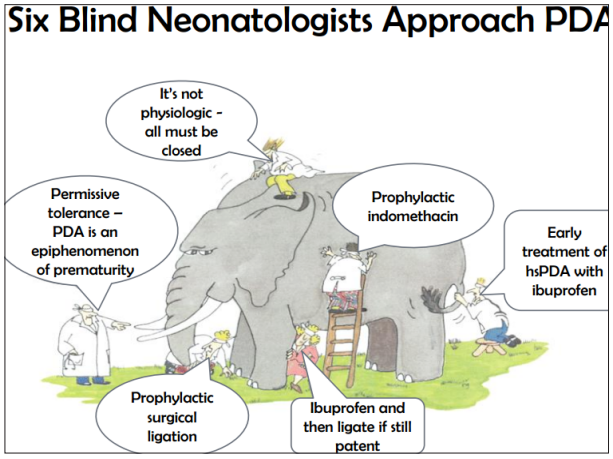



**Fig3.** *PDA: As Pendulum Swings, Cathy Hammerman*

## Basic and Pharmaceutical Measurements

- Fluid restriction: 60% of basal needs (avoid excess fluid administration while also avoiding extreme fluid restriction)
- Avoid acidosis and hypoxia
- High PEEP and low Tinsp.
- Frusemide NO (because it increases prostaglandin levels), except in certain cardiac insufficiency
- Digoxin NO

Furosemide encourages production of prostaglandin. and is thus disadvantageous in the setting of PDA closure.

Therapeutic strategy has three options: prophylaxis, early target and symptomatic Cyclooxygenase inhibitors, indomethacin and ibuprofen, are the most studied pharmacologic agents for the treatment of PDA. Both drugs block prostaglandin synthesis, inducing ductal closure (40).

A 2015 Cochrane review examined 2 trials comprising 250 infants that compared oral paracetamol with oral ibuprofen and found similar PDA closure rates and fewer adverse effects in the paracetamol groups but noted that animal studies have indicated adverse neurodevelopmental effects of paracetamol exposure; so, longterm outcome studies are needed before this therapy can be recommended (41).

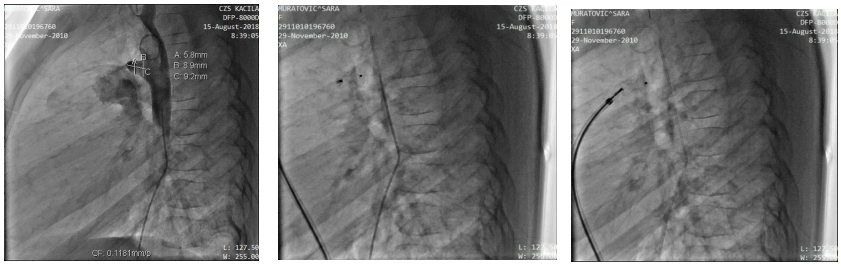
| Medicament | Doses | Contraindications | Drug monitoring |
|---|---|---|---|
| Acetaminophen | IV or PO: 7,5-15mg/kg/doses every 6-8 hours for 3-7 days | Hepatic insufficiency | AST, ALT, GGT, drug level before the ninth dose |
| Ibuprofen | IV: 20mg/kg→10mg/kg after 24 hours, a total of 3 doses<br>PO: 10mg/kg→5mg/kg after 24 sata, a total of 3 doses | Significant renal failure, NEC, intestinal perforation, thrombocytopenia | Urine output |
| Indomethacin | IV: 0,2mg/kg/ every 12 hours a total of 3 doses | Significant renal failure, NEC, testinal perforation, thrombocytopenia | Urine output |

**Fig4.** *Medicament treatment of PDA*

## Transcatheter Closure of the PDA

Transcatheter closure of the ductus arteriosus has been described since the late 1960s and has mostly been used in adults, children, and infants older than 6 months or weighing more than 6 kg who demonstrate left ventricular volume overload and pulmonary arterial hypertension. The width and rigidity of the sheath can limit this approach in infants with low body mass. As experience, devices, and delivery systems improve, this method may supersede other types of ductal closure if success rates remain high and complication rates remain low. Transcatheter closure is preferable to surgical closure if infant size allows and experts are available to perform the procedure (42).

Measurement must include: the narrowest diameter, aortic ampoule diameter, duct length and central diameter of the ampoule.



Keep in mind:

- vasoreactivity in young children
- mechanical stimulation effect
- anesthesia

Amplatzer Piccolo™ Occlude

Amplatzer Piccolo™ Occluder is one of the first trans-catheter treatments to be approved for the treatment of patent ductus arteriosus (PDA), a common congenital disorder that results in a life-threatening opening in the heart of premature infants and newborns.

The success rate with this new device was 95.5% (191/200) in all patients and 99% (99/100) in patients ≤ 2 kilograms. Of implanted patients, 99.4% reached the primary effectiveness endpoint (43).

The device received 510(k) certification from the US Food and Drug (FDA) for clinical use in January 2019. Amplatzer Piccolo Occluder is a pea-sized, minimally invasive, self-expanding, percutaneous trans-catheter occlusion device used for non-surgical closure of PDA in patients weight > 700 grams at time of the procedure. It is a wire-mesh structure made from nitinol and interwoven polyester for future stimulation of tissue growth.

The device is deployed via an anterograde (venous) or a retrograde (arterial) approach. It contains a 3 mm - 5 mm diameter central waist and two retention discs with a diameter of 4 mm -6.5mm. The length between the two retention discs ranges from 2mm to 6mm.

## PDA Ligation

Surgical ligation has been associated with pneumothorax, chylothorax, vocal cord palsy, postligation left ventricular dysfunction, CLD, ROP, and NDI. Traditionally, ligation is reserved for infants whose ductus is both symptomatic and refractory to conservative and pharmacologic therapies (44). A sudden increase in afterload and a decrease in left ventricular (LV) preload occurs following ligation, putting the neonate at high risk for decreased cardiac output. Studies have found a significantly lower incidence of post-ligation syndrome in ELBW infants who underwent transcatheter PDA closure compared to surgical ligation (45-52).

## Persistent Ductus Arteriosus in Children with Congenital Heart Disease

In the context of congenital heart disease ***associated with right-sided obstructive lesions*** and diminished pulmonary blood flow, the ductus arteriosus may function as a source of collateral pulmonary perfusion. These are children with pulmonary atresia and intact ventricular septum, critical pulmonary stenosis, tetralogy of Fallot and pulmonary atresia with VSD, tricuspid atresia with pulmonary stenosis and other forms of complex congenital heart disease with critical reduction of antegrade pulmonary blood flow. If the malformation is associated with signifcant reduction of pulmonary blood flow during fetal life, the ductus is usually long and tortuous and originates with an acute angle from the aortic arch, indicating preferential LR-shunting already in fetal life. Following spontaneous closure of the ductus in the neonatal period, patients experience critical reduction of collateral pulmonary blood flow, associated with life-threatening hypoxaemia. This can be reverted by reopening of the ductus arteriosus through administration of prostaglandin E1, a medical treatment that has revolutionarized treatment of patients with duct-dependent congenital heart disease.

In ***critical left heart obstructions***, the ductus arteriosus bypasses the left heart in fetal life: in these patients, the right ventricle takes care of the entire cardiac output via the main pulmonary artery and the ductus, thereby supporting the systemic circulation (53).

Progressive constriction of the ductus arteriosus following birth deprives the systemic circulation of its source of perfusion. In synchrony with the progressive constriction of the ductus, there is a gradual decrease of systemic output with incipient shock and acidosis. In patients with critical coarctation, ductal constriction results in reduced perfusion of the lower half of the body. In this situation again administration of prostaglandin E1 has been established as a very effective emergency treatment. For patients requiring ductal patency for a longer time period, ductal stenting by interventional cardiac catheterization has been introduced both in the setting of ductal dependency of the pulmonary and the systemic circulation (54,55).

Patent ductus arteriosus may be associated with a variety of other congenital cardiac malformations. In the context of septal defects like VSD and AVSD, additional shunting via the patent ductus arteriosus may aggravate the deleterious haemodynamic effects of the intracardiac defects.

## Ductus Dependent Systemic Circulation

The goal of treatment is to reestablish the prenatal pattern of circulation, with a systemic supply circulation via PDA from the pulmonary system. Optimal saturation O2 75-85% and saturation O2> 85% indicates excessive pulmonary flow. The treatment principles of ductal dependent systemic circulation are as follows:

Prostaglandins (PGE1): 20-50ng/kg/min

SVR reduction: - afterload reduction (Na nitroprusside)

- Catecholamines: Milrinone and / or Dobutamine (vasodilating effect)

Avoid the vasoconstrictor effects of catecholamines (Dopamine, Noradrenaline)

PVR elevation, increase PA pressure: avoid intubation, extubate as soon as possible, avoid additional oxygen, mild metallic acidosis (pH 7.35), mild hypoventilation (pCO2 about 60 mmHg)

Oxygen administration with the goal of increasing saturation above 85% and can cause hyperventilation with ACUTE DECOMPENSATION

## Ductus Dependent Pulmonary Circulation

The goal of treatment is to re-establish the prenatal circulation pattern

- optimal sat.O2 75-85%

- satO2> 85% indicates excessive pulmonary flow

The treatment principles of ductal dependent pulmonary circulation are as follows:

Prostaglandins (PGE1): 20-50ng /kg /min (maintain high doses)

Reduction of PVR: - mild metal alkalosis (pH 7.45-7.5)

- mild hyperventilation (pCO2 about 35mmHg)

- increase FiO2

Elevation of SVR and support of systemic pressure:
- Noradrenaline

- Adrenaline

- Volume

- NO Dopamine

## Conclusions

- PDA is an important condition in prematurity ≤28 gestation weeks
- neonatuses> 28WG and > 1000 g usually do not require medical and surgical treatment DAP
- it is important to recognize hemodynamically significant PDA: the size of PDA itself is not decisive and standardization of ECHO criteria, gestational age, postnatal age, markers of HS PDA, degree of respiratory support, oliguria
- optimal time of treatment, choice of treatment method, development of endovascular occlusive devices suitable for prematurity
- Risk-benefit ratio of treatment
- surgical ligation after a failed second drug cycle
- Congenital heart diseases with ductus dependent systemic and pulmonary circulation

(therapeutic goals of elevation and reduction of PVR and SVR)

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