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Hemodynamically Significant PDA in Preterm Infants

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Background
Heart failure may occur in premature children due to the common disease known as patent ductus arteriosus (PDA). The likelihood of the ductus arteriosus spontaneously closing is much lower in preterm infants**.** Depending on the ductal resistance and the state of the pulmonary vasculature, the amount of shunting determines the hemodynamic repercussions and clinical symptoms of a PDA**.** The total size, shape, and suppleness of the ductus determine its flow resistance. Over sending the pulmonary circulation and the left ventricle due to aortic-pulmonary pressure gradient-induced left-to-right shunting via the ductus. Multiple factors, including a genetic predisposition and an environmental trigger that happens at a vulnerable moment, are thought to contribute to the apparently random nature of most PDA instances. The neuroendocrine system also undergoes changes, leading to a rise in cardiac contractility and catecholamine levels in the blood**.** Increased vascular resistance develops as a consequence of structural changes in the pulmonary vasculature brought about by prolonged exposure to elevated pressure. When the systemic circulation's resistance is higher than the pulmonary vascular resistance, the duct's flow direction changes from left to right. Even in asymptomatic individuals, untreated PDA may lead to serious complications, especially when combined with the accumulated physiological insult caused by chronic pneumonia.

Key Words: PDA, pulmonary, vasculature.

Definition

PDA, or postnatal communication, occurs when the fetal ductus arteriosus remains open and allows blood to flow via the major pulmonary trunk and the descending thoracic aorta. Typically, the ductus arteriosus (DA) contracts its smooth muscle to shut the ductus 24 hours after birth, and it closes physically within 72 hours. ***(1)*** found that among preterm newborns, patent ductus arteriosus (PDA) is among the most frequent diseases. ***(2)***

Incidence

Approximately 5–10% of all congenital cardiac diseases are PDAs, which affect 1 out of every 2,000 term newborns. According to ***(3),*** isolated PDA ranks third among congenital cardiac anomalies. According to ***(4),*** the prevalence of preeclampsia is higher in babies whose birth weight is less than 1,200 g than in those whose birth weight is less than 2,000 g. Specifically, 80% of newborns with a birth weight of less than 1,200 g had preeclampsia. Forty percent of babies weighing less than 1,000 grams and twenty percent of newborns weighing between one thousand and one,500 grams have a hemodynamically significant shunt because of the PDA ***(5).***

Etiology

Multiple factors, including a genetic predisposition and an environmental trigger that happens at a vulnerable moment, are thought to contribute to the apparently random nature of most PDA instances ***(6).***

Physiology

The endothelium secretes vasoactive chemicals that play a crucial role in regulating the DA tone, and oxygen sensing takes place at the ductus arteriosus smooth muscle cell (DASMC) ***(7).*** During fetal development, prostanoids—including prostaglandin E2 (PGE2) and prostacyclin -12—are responsible for maintaining patency. Fetal PG12 and PGE2 levels are elevated due to placental synthesis and reduced fetal lung clearance**.** Neonatal functional closure of DA occurs as a result of constriction of DASMCs brought about by a rise in PaO2 and a reduction in circulating vasodilators ***(8).***

Pathophysiology

Depending on the ductal resistance and the state of the pulmonary vasculature, the amount of shunting determines the hemodynamic repercussions and clinical symptoms of a PDA**.** The total size, shape, and suppleness of the ductus determine its flow resistance. Over sending the pulmonary circulation and the left ventricle due to aortic-pulmonary pressure gradient-induced left-to-right shunting via the ductus ***(9).***

The preterm myocardium adjusts by increasing contractility and left ventricular output (LVO) to make up for the reduction in systemic blood flow caused by the left-to-right shunt via the PDA. ***(10)*** found that preterm newborns with a big PDA had reduced systemic perfusion in the lower body, as evidenced by reversed diastolic flow in the descending aorta, even though there was a considerable compensatory increase in LVO .

The neuroendocrine system also undergoes changes, leading to a rise in cardiac contractility and catecholamine levels in the blood**.** Increased vascular resistance develops as a consequence of structural changes in the pulmonary vasculature brought about by prolonged exposure to elevated pressure. When the systemic circulation's resistance is higher than the pulmonary vascular resistance, the duct's flow direction changes from left to right. Even in asymptomatic individuals, untreated PDA may lead to serious complications, especially when combined with the accumulated physiological insult caused by chronic pneumonia ***(11)***.

Classification of PDA

According to ***(12),*** PDA may be categorized into two types: hemodynamically significant PDA (hsPDA) and non-hemodynamically significant PDA (non-hsPDA).

Diagnosis of PDA (clinical)

The size, length, and disparity between pulmonary and systemic vascular resistance are among the several variables that influence the degree of left-to-right shunt and, by extension, the clinical symptoms of PDA**.**

Most small PDAs don't cause any symptoms, but if you listen closely enough at the left sternal border, second intercostal space, and left infraclavicular area—where the murmur becomes louder with breathing—you might hear the classic crescendo-decrescendo murmur, which is typically a grade III–IV continuous machinery murmur ***(13)***.

A continuous murmur, tachycardia, hyperactive precordium, signs of systemic hypoperfusion (systolic/diastolic hypotension, wide pulse pressure, bounding pulses, metabolic acidosis and oliguria), and signs of pulmonary over circulation (tachypnea, increased need for oxygen and ventilatory support, increased pulmonary vascular signs, and apnea) are clinically defined as hemodynamically significant PDA (hsPDA) ***(14)***.

The clinical significance of PDA was evaluated using a variety of scoring systems. One of these was the SIMPLE scoring system, which relies on risk factors and clinical findings of ELBW infants to predict hsPDA early on; it is easy to administer, straightforward, and objective; and it does not necessitate additional testing or echocardiographic evaluation .

To reduce the frequency of unneeded pediatric cardiology visits, SIMPLE was proposed as a screening tool to determine whether ELBW babies need echocardiographic assessment ***(15)***.

Using a severity scale ranging from 1 to 4, fourteen characteristics were developed for the SIMPLE score based on findings from a literature research. Maternal chorioamnionitis, antenatal steroids, birth weight, cord blood gas, necessary inotropic support for hypotension, heart rate, need for invasive mechanical ventilation (MV), metabolic acidosis, respiratory acidosis, maximum inspiratory pressure (PIP), reduction of PIP, fraction of inspired oxygen (FiO2) upon admission, decrease of FiO2 over evaluation time points, and surfactant requirement are all items that are known to be risk factors for PDA ***(16)***.

Echocardiographic evaluation of PDA

Because it displays the shunt, the extent of the aperture, and permits assessment of pulmonary arterial pressure, echocardiography is still the gold standard for diagnosis. Also, to evaluate its effect on the left and right cardiac hemodynamics as well as the pulmonary circulation. For a correct diagnosis, the data given by the echocardiogram is vital ***(17)***.

To determine how serious hsPDA shunting is in premature babies, many echocardiographic grading systems have been created. Both the Shaare Zedek and El-Khuffash PDA severity ratings have been used to assess PDAs in premature neonates, however they use distinct parameter value**s** ***(18)***.

Other investigations

Section A. Standard laboratory tests:

CBC administered within the first three days of life:

In order to assess the child's general health, a CBC with differential is taken. Nevertheless, results with this condition are often within the reference range. If a kid has other congenital cardiac abnormalities, polycythemia may be present.

Serum creatinine and blood urea nitrogen (BUN) tests for kidney function :

Extremely preterm babies (EPT) with conservatively treated hsPDA do not have any poor outcomes related to changes in kidney function. ***(19)*** speculate that renal immaturity, rather than pathologic circumstances, may explain the high frequency of stage acute kidney injury (AKI) without unfavorable outcomes in EPT with conservatively treated hsPDA.

Blood Gases: Research into this is crucial since arterial Pao2 increased significantly (even with tiny left-to-right shunts) and Paco2 decreased (with big shunts) when the ductus was patent. Significant changes in the blood flows to specific organs occurred as a consequence of reduced

perfusion pressure and localized vasoconstriction, even though the heart was able to manage the elevated volume burden of a PDA. Even with little PDA shunts, the blood supply to the abdominal organs was significantly reduced. One possible explanation for the pathophysiologic symptoms of PDA in premature babies is the reduction in blood flow to the organs ***(20).***

C Reactive Protein (CRP): A notable disparity in CRP levels was seen between neonates with and without PDA, suggesting a possible link between the two. Studies conducted by ***(21)*** found that C-reactive protein levels were greater in newborns with PDA compared to infants without PDA. Accordingly, oxidative stress-induced systemic inflammation was postulated as a potential contributor to PDA pathophysiology. According to ***(22),*** when there is inflammation, the expression of cyclooxygenase 1 and 2 may rise. This, in turn, can lead to an increase in prostaglandin E2 and prostacyclin, which ultimately serve to maintain the duct open. An inflammatory index or potential involvement in inflammatory responses and pathways may be indicated by a high blood CRP measurement. A study conducted by Hung et al. in 2018 established this. Closing the duct may be possible with prenatal interventions that address inflammation. ***(23)*** discovered that neonatal sepsis is a risk factor associated with PDA occurrences in preterm newborns.

Section B. Heart-Related Tests:

The results of a chest x-ray (CXR) will vary according on the severity of the shunting. Radiographs of the chest might show no abnormalities at all or show signs of cardiomegaly, such as enlarged bronchovascular markings. It is common to see an enlarged main pulmonary artery and possible ductal calcification in elderly individuals with pulmonary hypertension ***(24).***

Second, an electrocardiogram (ECG) may show how much shunting is occurring and how big it is**.** Hemodynamic load is often accompanied by symptoms of left ventricle and left atrial enlargement, while the electrocardiogram (ECG) may be normal in tiny shunts, suggesting normal pulmonary blood flow and pulmonary vascular resistance. A leftward and posterior shift occurs along the mean QRS axis. If the QRS axis is moved to the left in V5 and V6, the R wave will be larger and the S wave will be smaller; if the QRS axis is moved to the back in V1, the R wave will be smaller and the S wave will be larger ***(25).***

B-type natriuretic peptide (BNP): BNP levels may indicate the effectiveness of therapy and if there is hemodynamically significant PDA (hsPDA). One research indicated that at a cut-off value of 70pg/mL for the identification of a hsPDA, BNP had a sensitivity of 92.9% and a specificity of 73.3%. Measurement of BNP, albeit a straightforward and easily performed at-the-bedside test, does not replace echocardiography in the diagnostic process but rather adds to it ***(26) .***

When BNP levels return to normal after therapy, it means the treatment was effective. In order to establish that the PDA has been successfully closed, a repeat echocardiogram should be performed if the BNP level remains elevated following therapy ***(27).***

Perfusion Index and Near-Infrared Spectroscopy: NIRS is a non-invasive technique that continually evaluates the oxygenation of specific regions of the body. Continuous monitoring of changing oxygen dynamics in the presence of hsPDA, as well as early identification of decreased renal, cerebral, and mesenteric circulation, may be achieved using near-infrared spectroscopy monitoring. When integrated with existing biomarkers, clinical data, and echocardiographic results, near-infrared spectroscopy data might be valuable. The use of near-infrared spectroscopy allows for the continuous measurement of regional tissue oxygenation without intrusive procedures ***(28).***

5. Doppler ultrasonography:

To confirm the phasic properties of the ductal shunt on spectral and audio outputs, waveform spectral doppler sampling might be done in certain spots guided by the doppler flow map. Doppler flow mapping confirmed right-to-left ductal shunts in this cohort of newborns, and shunts via a tiny patent ductus arteriosus were often seen ***(29).***

6. Catheterization:

Catheterization is often necessary for both the diagnosis and percutaneous treatment of PDA. Pressure gradients may be obtained by inserting a catheter either into the pulmonary artery and then into the aorta, or, more often, into the pulmonary artery and then into the aorta ***(30).***

Complications

A. Immediate problems:

1 .Congestive heart failure: This condition often affects all newborns with a big PDA. Pulmonary congestion and left-sided failure are the first symptoms**.** When the atrial size and pressure grow, causing left ventricular (LV) failure in infants, a stretched and incompetent foramen ovale, which is responsible for a left-to-right shunt, may be present ***(31).***

Hypotension and systemic hypoperfusion are caused by low diastolic pressure, which changes the blood flow to organs that rely on blood pressure, including the skin, muscles, kidneys, brain, and intestines. Hypoperfusion may cause renal failure or necrotizing enterocolitis (NEC), depending on which organ is impacted ***(32).***

Third, changes in cerebral blood flow may cause intraventricular hemorrhage ***(33).***

B. Consequences in the long run:

Pulmonary hypertension and pulmonary vascular disease: Major consequences of an untreated big PDA include pulmonary hypertension and pulmonary vascular disease ***(34).*** Damage to the basement membrane and extracellular matrix occurs as a result of endothelial dysfunction brought on by excessive blood flow via the pulmonary artery**.** Second, pulmonary hypertension and pulmonary vascular disease are caused by these alterations, which also raise the risk of vaso-reactivity and intrinsic vascular resistance**.** Third, chronic lung illness is more common in people with PDA. According to a prior research, there is a significant risk of bronchopulmonary dysplasia (arrested alveolar development) in preterm infants exposed to a PDA for 14 days ***(35).***

Thirdly, bacterial endocarditis: Infective endocarditis has been shown to occur in 1% of PDA patients annually, a significant decrease likely brought about by advances in healthcare and the broad use of antibiotics ***(36).***

Duct calcification: Non-infective endocarditis or thrombosis in the ductus might complicate what is first identified as a mediastinal mass ***(37).***

Fifthly, pulmonary artery or ductal atherosclerosis may cause a ballooning of the Aneurysm. Unilateral wheezes, stridor, or a raspy voice are symptoms that might develop when nearby nerves or pulmonary structures are compressed ***(38).***

Management of PDA

Presently, there are three methods for treating PDA: conservative treatment, pharmacological closure, and surgical ligation**.**

Part A: Conservative Leadership

It doesn't matter what method is used to treat PDA in newborns; what is important is that they get enough oxygen and keep their hemocrit between 35% and 40%, which may raise pulmonary vascular resistance and decrease the left-to-right shunt ***(39).***

It is essential to keep fluid levels balanced since preliminary randomized studies shown that high fluid intake might cause pulmonary edema, increased left-to-right shunt via PDA, increased left ventricular preload, and an increased need for oxygen and ventilatory support, among other complications ***(40).*** Hence, a hsPDA necessitates a decrease in fluid consumption of 110-130 ml/kg/day.

A. Pharmacological Closure

Infants shown to have reversible pulmonary artery hypertension, left volume overload, or a large left-to-right shunt should have their PDAs closed ***(41).***

• Medications used for medical closure: often prescribed medications including ibuprofen and indomethacin, which are inhibitors of the cyclo-oxygenase (COX) component of prostaglandin-H2 synthetase. Additionally, parcetamol's potential therapeutic function has been suggested ***(42),*** which is an inhibitor of prostaglandin H2 synthetase's peroxidase component.

• How it works: cyclooxygenase (COX) inhibitors prevent the production of prostaglandins, which are essential for fetal DA patency and ductal closure ***(43).***

• Current practice recommends treating presymptomatic PDA between 2 and 7 days of birth, after confirmation of the condition by echocardiograph**.**

• Serious adverse effects, such as bleeding, renal impairment, gastrointestinal ulcers and perforation, and other complications, are linked to these medicines ***(44).***

B. Interventional management of the PDA

There is less of a need for pharmaceutical intervention to close the ductus as the postnatal age increases ***(45).*** You may do it in two ways:

• Closure of the PDA by a transcatheter, sometimes using coils or devices, is the preferred method in the majority of instances. Even for newborns, it has become the gold standard due to its safety ***(46).*** Reducing blood transfusion, alleviating pain, and minimizing hospital stay are some of the advantages of transcatheter closure of PDA compared to surgical methods**.**

• Surgical ligation: The procedure is carried out under general anesthesia by a left lateral posterior thoracotomy. According to ***(47),*** the PDA is located, cut open, and then ligated twice. In contrast, ***(48)*** found that it raises the chances of neurosensory impairment, bronchopulmonary dysplasia (BPD), and severe retinopathy of prematurity (ROP). Pneumothorax, infection, paralysis of the laryngeal nerve, respiratory compromise, and phrenic nerve or major blood artery damage ***(49)*** are among the additional potential consequences.

Fate of PDA

No evidence has been found in either individual clinical trials or meta-analyses to suggest that closing the ductus improves long-term outcomes, despite the fact that both surgical closure and non-steroidal anti-inflammatory drug medical treatment of PDA are effective in closing the ductus in a large proportion of infants**.**

According to ***(50),*** the most important outcomes, including BPD, necrotizing enterocolitis, neurosensory impairment, death, and the combined outcomes of death or BPD and death or neurosensory impairment, have odds ratios that suggest early, routine treatment does not work. The confidence intervals are also narrow, so it's unlikely that serious differences have gone unnoticed.

Conventional PDA management involves cyclooxygenase inhibitors and/or surgical ligation; however, there is insufficient proof that these PDA therapies are beneficial compared to supportive care and watchful waiting; furthermore, they may cause side effects on various organ systems.

New worries about surgical ligation-related morbidity have been raised, particularly in the youngest infants and during the first week of life. ***(51)*** could not find an answer to the issue of whether cautious nonintervention allowing spontaneous closure is more favorable than obligatory PDA closure treatment.

Conclusion

Combining echocardiographic markers with clinical signs may enhance the clinical identification of hsPDA. The hsPDA has to be evaluated in a more thorough and significant way.

For any newborn clinically suspected of having PDA, an echocardiographic assessment should be conducted. We should restrict medical closure of PDA to hsPDA so that these premature newborns, who are already at a higher risk of adverse drug reactions, are not put at unnecessary risk. Optimal timing and therapy options should be the focal points of future clinical studies using hsPDA, in addition to universal and practical diagnosis .

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