A patient with a diagnosed patent ductus arteriosus – what next?

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ABSTRACT

Among congenital heart defects of the cardiovascular system, patent ductus arteriosus (PDA) comprises about 10% in the general population. Prematurity significantly raises the likelihood of PDA: in preemies of very low birth weight this defect appears with a frequency up to 65%, and in extremely low birth weight preemies up to 80%. Over a span of many years of research many different methods for treating PDA have been discovered, modified, and improved. Invasive treatment (thoracotomy, thoracoscopy, and percutaneous closure) as well as therapeutic strategies (symptomatic treatment, pharmacological treatment) allow for complete closure of PDA in every patient. The limitations of particular methods in regard to age and body mass of the child, their clinical state, as well as the morphology of the PDA itself, require careful analysis when choosing the appropriate treatment method based on the effectiveness and permanency of closing the duct as well as minimal invasiveness. Among preemies and newborns it is possible to close the PDA using symptomatic and pharmacological treatment as well as through thoracotomy and thoracoscopy, while in older children and adults the method of choice is the percutaneous closure of PDA. Matching the correct treatment strategy with the clinical situation is key to the successful closure of the duct. Presented in the text below is an overview of available methods and their usefulness in treating PDA.

KEY WORDS:
patent ductus arteriosus, pharmacological therapy, percutaneous closure, video-assisted thoracoscopy.

CHARACTERISTICS OF THE DUCTUS ARTERIOSUS, METHODS AND POSSIBILITIES OF TREATMENT

The ductus arteriosus (DA) is a vessel connecting the pulmonary trunk with the proximal section of the descending aorta, which allows blood to circumvent pulmonary circulation during foetal life. In normal circumstances after birth, with the newborn’s first inspiration there is a sudden and significant drop in pulmonary resistance and a reversal of pressure gradient between the pulmonary trunk and the aorta, which in turn changes the flow of blood from the right-left direction present during in utero life to left-right. The increase in oxygen concentration in the newborn’s blood initiates the secretion of endothelin from the vascular endothelium as well as the outflow of potassium ions from potassium channels, which results in the contraction of the smooth muscles of the vessel. The lungs of the newborn start to produce bradykinin, a natural vaso-constrictor [1]. A very important stage in the functional patent ductus arteriosus (PDA) closure is the decrease in PGE1 and PGE2 levels, which are called endogenous prostaglandins. PGE1 and PGE2 are produced by the lumen of the ductus to main-
PDA most commonly occurs sinistrally (from the left pulmonary artery); however, in very rare cases it can also occur dextrally (from the right pulmonary artery) as well as bilaterally. Sinistral DA is a physiological structure that functions during proper foetal development. The presence of dextral DA is commonly connected with congenital defects of the aortic arch and/or pulmonary trunk [13]. The morphology of PDA is characterised by significant diversity; most commonly, however, it has a conical or funnel shape. The aortic end, called the ductal ampulla, is wide and narrows incrementally as it proceeds towards the pulmonary end, achieving its smallest diameter at the pulmonary end. The common descriptors of the duct, i.e. conical, tubular, short, or long, have been supplanted by a classification system introduced by Krichenko and used during angiographic examination of the duct [13].

Depending on the size of the PDA and diagnosed clinical symptoms, we can classify several types of PDA [14, 15]:

- silent PDA, with a diameter of 1.5 mm or less, characterised by absence of audible murmur or clinical symptoms; may be left open; some authors report an increased risk of endocarditis as an indication to close the PDA,
- very small PDA, diameter less than or equal to 1.5 mm, characterised by an audible murmur but often without clinical symptoms. Closure of PDA is recommended because the benefits of closure outweigh the risks of the procedure,
- small PDA, diameter 1.5 to 3.0 mm, with a present audible murmur and clinical symptoms of PDA also present. Closure of PDA is recommended,
• medium PDA, diameter of 3.0 to 5.0 mm as well as large PDA, diameter of over 5.0 mm both with loud audible murmur and exacerbated symptoms of PDA.

Closure of PDA recommended.

Patients with haemodynamically irrelevant PDA, so-called “small PDA” typically present asymptptomatically or with only a quiet heart murmur. In these cases the PDA is often discovered incidentally in the process of echocardiographic examination for unrelated causes. The psychomotor development of children with “small PDA” proceeds properly; however, they may be predisposed to achieving slightly smaller gains in body mass in comparison to their contemporaries without PDA [16]. The main argument for closing silent and small PDAs is prophylaxis of later complications of PDA such as increased risk of endocarditis and aneurysm and risk of its dissection [16, 17]. Routine closure of PDA is controversial and should only be considered in children of preschool or school age [16, 17].

Patients with haemodynamically significant PDA (hsPDA) can present various clinical symptoms. Because symptoms are not homogeneous and remain in strict correlation to the age of the child, we can only definitively diagnose hsPDA when we can observe at least two of the following symptoms: systolic or systolic-diastolic heart murmur, tachycardia, pulsus celer, systolic-diastolic amplitude in blood pressure measurements > 25 mm Hg, hepatomegaly, pulmonary haemorrhage, marked respiratory exertion, crackles in the lung fields, bloody expectoration in the respiratory tract, oliguria, failure to thrive, and intolerance or reduced tolerance to physical exertion [8, 9, 16, 18, 19].

On chest X-ray we may observe an enlarged cardiac shadow with obliteration, enlargement of the left atrium, features of increased vascular visibility, and in extreme cases pulmonary oedema and emphysema.

EKG may be unremarkable during the newborn period and early infancy. In older infants and children we can diagnose left axis deviation, traits of left ventricular enlargement, as well as repolarisation disturbances over the left ventricle. According to source data, a partial block of the left branch of the bundle of Hiss was described in a portion of patients [16]. Echocardiography is the primary examination as well as the gold standard allowing for the closure of PDA; 33% mortality in newborns born after the 29th week of gestation, mortality is eight times higher in newborns with a birth weight under 1000 g. In newborns with PDA born before 1500 g and almost half of newborns with a birth weight under 1500 g in comparison to their contemporaries without PDA, has never been proven [4, 23]. Numerous studies show a strict relationship between the degree of immaturity of the newborn and the increase in mortality risk as a result of PDA; 33% mortality in newborns with a birth weight under 1500 g and almost half of newborns with a birth weight under 1000 g. In newborns with PDA born before the 29th week of gestation, mortality is eight times higher than in children born at the same gestational age without PDA [24]. The possibility of spontaneous closure of the PDA is different in selected groups of newborns and differs significantly in the cited studies. Some authors underline that in 70% of newborns born after the 28th week of gestation, PDA closes spontaneously up to the 10th day of life, and in newborns born before the 28th week of gestation it closes spontaneously in 75% up to the 12th month of life [21]. Koch claims that the PDA closes spontaneously...
ously up to the 7th day of life in 34% of newborns with low birth weight and born before the 28th week of gestation [25], other researchers report a spontaneous closure of the PDA up to the 7th day of life in 31% of preemies with a birth weight below 1000 g and in 67% with birth weight above 1000 g [20, 26].

The optimal time of symptomatic treatment is from two to seven days after diagnosis of PDA with a USG examination [11]. The primary advantage of this method is the lack of exposure of the newborn to the side effects of drugs or interventional treatment [27, 28]; however, we should be mindful of the fact that a delay in implementation of pharmacological treatment decreases the chances of the expected closure of the PDA. Additionally, preemies born before the 25th week of gestation react less well to symptomatic therapy [28]. Symptomatic treatment in preemies with a birth weight over 1000 g with mild symptoms of PDA, and in whom there are no respiratory disturbances [12], usually gives satisfactory results [4]. In cases of symptoms of circulatory-respiratory insufficiency we should proceed to advanced pharmacological therapy [5].

PHARMACOLOGICAL THERAPY

Pharmacological therapy is an alternative in cases where symptomatic therapy has failed to yield the desired results [28]. Cyclooxygenase inhibitors such as indomethacin and ibuprofen, which have been approved for this purpose by the FDA (US Food and Drug Administration) are used as primary drugs to close the PDA [11, 27]. Paracetamol has been proposed as an alternative to indomethacin and ibuprofen due to its accessibility and low cost of treatment [28]. Numerous cases of successful closure of PDA in extreme preemies with the help of paracetamol have been documented; however, further studies are needed to assess the safety and efficacy of this option [12, 28–32].

Ibuprofen and indomethacin have identical efficacy in closure of PDA [11]. No significant difference has been found in the incidence of necrotising enterocolitis or development of neurological abnormalities in comparative analysis of both drugs [11]. It has been proven, however, that indomethacin is completely ineffective at closing PDA in term newborns and older children, and in preemies with extremely low birth weight the efficacy may be decreased as well [20].

Analysis comparing indomethacin and ibuprofen has indicated a comparable pharmacological efficacy for both drugs; the PDA very often closes after the second dose of the drug. Meta-analysis stresses the lower nephrotoxicity of ibuprofen, rarer episodes of oliguria, and its weaker peripheral vasoconstrictive properties when compared to indomethacin [4, 12, 21, 27, 31]. Consequently, the first-line drug in pharmacological therapy of PDA is ibuprofen [12]. Echocardiographic monitoring of pharmacological therapy is recommended in order to limit the exposure of the newborn to possible side effects of the drug [25, 26].

There are currently three main strategies of pharmacological therapy, which differ in time of induction of treatment, and the appropriate moment to begin pharmacological therapy is still a matter of some controversy [4, 10, 21, 26].

1) Prophylactic administration of COX inhibitors within 24 hours.

This method is significantly more effective in inducing vasoconstriction of the arterial duct when compared to delayed administration of drugs [10]. Indomethacin introduced 6-15 hours after birth in newborns born before 28th week of gestation decreases the incidence of haemodynamically significant PDA and reduces the risk of potential later surgical intervention as well as reducing the risk of intraventricular haemorrhages [4, 10, 21]. According to some sources, ibuprofen does not significantly reduce mortality or the potential need for later surgical intervention.

2) Introduction of pharmacological therapy before the appearance of clinical symptoms.

Sensitivity to NSAIDs decreases with age. Postponement of pharmacological therapy may reduce the effectiveness of the therapy in this strategy [10, 26, 27]. In cases of recurrence of PDA, pharmacological treatment may be reintroduced safely [22].

In preemies with PDA and hypotension, dopamine is used in the dosage below 10 micrograms/kg/min, causing a rise in pulmonary pressure resulting in reduction in left-right shunting, which promotes spontaneous closure of the duct [32].

Among the disadvantages of pharmacological therapy are side-effects of the drugs as well as frequent recurrence of the PDA, which occurs in approximately 33% of newborns with a birth weight below 1000 g and in 8% of newborns with a birth weight over 1500 g [5]. However, the benefits of pharmacological therapy in newborns have been confirmed in many respected studies showing a four-fold decrease in mortality rates in newborns born before the 28th week of gestation [16]. Additionally, the majority of meta-analyses regarding pharmacological therapy highlight its role in reducing the necessity for later surgical intervention [4].

CARDIOSURGICAL INTERVENTION

The historical date of the first successful cardiosurgical operation closing a patent ductus arteriosus is 28 August 1938 when doctor Robert E. Gross successfully closed a PDA in a seven-year-old patient with heart failure at the Children’s Hospital in Boston [33]. An indication for surgical intervention is a lack of technical possibilities to close the duct using minimally invasive percutaneous pro-
cures, which is an indication for classical thoracotomy in preemies and newborns [5], as well as the method of choice in cases with a very large diameter duct [2].

Surgical closure of the arterial duct is an extracardiac procedure and is carried out under general anaesthesia, most commonly using a left sided thoracotomy approach. Another possible approach is through a median sternotomy, especially in cases with complex heart defects, or a right sided thoracotomy in cases of right-sided aortic arch as well as in situations where other surgical procedures need to be carried out on the right side of the thorax simultaneously, i.e. Blalock-Hanlon procedure [18].

Closing the lumen of the duct is achieved through ligation and excision of the duct or through utilisation of vascular clips [12, 27]. The efficacy of complete closure of the duct is high and reaches 94-100% with a perioperative mortality rate of 0-2% [2, 34].

Over a span of decades, the surgical procedures used to close PDA have been modified and improved in order to minimise damage to the adjacent tissues. Mehmet et al. [35], introducing a lateral thoracotomy conserving the posterior zone of skeletal muscle, suggest clipping the duct rather than ligation as well as abandoning drainage of the thoracic cavity. The authors of the work report that this procedure leads to reduced postoperative in-hospital care duration, reduces the risk of perioperative complications, and at the same time reduces costs.

Complications of thoracotomy are rare, but when they occur they include: residual leakage, injury of the laryngeal nerve, injury of the phrenic nerve, pneumothorax, chylothorax, and accidental closure of another vessel [37, 38]. In comparative meta-analyses many authors note that VATS is usually carried out in an operating room if an emergency thoracotomy arises; however, there is also the possibility of carrying out the procedure in smaller treatment rooms, or in the case of newborns in the neonatal intensive care unit [38].

Thoracoscopic closure of PDA is conducted under general anaesthesia in the prone position with the left side of the chest slightly elevated. Three ports are introduced using three or four 5-mm incisions, depending on the selected method (single or double handed). Small incisions are located in the posterior axillary line as well as posterolaterally in the neighbourhood of the left scapula. Carbon dioxide is introduced into the pleural cavity through the ports in order to visualise the operative field, and a video-scope as well as surgical tools (forceps and retractor) are then inserted through the ports [38, 41–43]. The camera allows the visualisation of the operative field and in doing so reduces the risk of damage to surrounding tissues.

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Thoracoscopic closure of another vessel [37, 38]. VATS was introduced and described initially by Jean Laborde in 1993 [39] and two years later by Redmond Burke [40]. The technique was implemented for the first time in Poland by Prof. Dariusz Patkowski from Wroclaw Medical University in 2012 operating on a child with Down's syndrome and oesophageal atresia.

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Contraindications for VATS are: large diameter of the duct (above 8 or 9 mm), short, wide, or windowed PDA, calcification of the duct, severely scarred pleura, earlier thoracotomy, persistent infection, or coexisting aneurysm of the PDA [37, 38, 41, 42]. Complications arising from thoracotomy are rare but may include: injury to the recurrent laryngeal nerve, injury to the phrenic nerve, pneumothorax, residual leakage, chylothorax, and accidental closure of another vessel [37, 38].

In comparative meta-analyses many authors note frequent injury to the laryngeal nerve when compared to thoracotomy; however, the injuries are also more frequently transient in nature [44]. Mortality due to VATS is nearly zero, which confirms its safety for use in all age groups.

In cases of duct closure in older children and adults, VATS is an alternative treatment method to percutaneous closure of the duct [42, 47]. The necessity for cardio-
logical follow-up in uncomplicated cases of thoracoscopic closure of PDA is short term. In most cases the patient requires no further follow-up a year after the procedure.

PERCUTANEOUS CLOSURE OF PDA – CARDIOLOGICAL TREATMENT

Significant technological advances in medicine have allowed development of percutaneous operative methods. The technique of percutaneous closing of patent ductus arteriosus has its roots in East Germany in 1967 when doctor Werner Portsmann with his surgical team closed a PDA in a 17-year-old patient with the help of a plug made from polyvinyl sponge [34, 48]. Several years later in 1976, William Rashkind introduced a new technique for PDA closure using a so-called “double umbrella” [49]. In Poland, this method was used until 1999 because procedures carried out using Rashkind’s double umbrella method were burdened with residual leakage [50].

Currently the method in everyday use utilises coils, first implemented in PDA closure in 1992 by the team of Cambiera and Moore [51], as well as clasps, called Amplatz implant (ADO) [34]. The main limiting factor in percutaneous closure of the patent ductus arteriosus is the minimal body mass of the patient. According to various sources, body mass should be above five kilograms, which is why this method is used in older infants, children, and adults [2, 14, 24, 52, 53]. The choice of device is based not only on body mass and age of the patient but also on the diameter of the ampulla and the morphology of the duct [14, 54]. An indication to closing the arterial duct with a coil is diameter below 2–2.5 mm in the narrowest place [34, 55, 56]. In cases of closing PDA with diameter below 1.5 mm a single coil is usually enough. Arterial ducts with a diameter of over 1.5 mm require multiple coils according to certain authors, which raises the need to take into account the increased risk of residual leakage. Researchers in many available studies underline the significant risk of implant shifting as well as other complications arising from the usage of multiple coils. As a result, placement of multiple coils should no longer be practiced, and due to the gathered experience and development of technology Amplatz implant should now be used for closure of PDAs with a diameter over 1.5 mm in their narrowest part.

The Amplatz implant is a self-expanding construction in the shape of a mushroom, made from a Nitinil wire mesh with polyester elements that are capable of free movement and correct placement during the procedure [2, 14]. Indications for use of ADO and its derivatives are medium sized and larger arterial ducts, whose diameter in the narrowest segment is larger than 2.5 mm (≥ 2 mm) [2, 34, 55, 56]. Currently these are the most widespread devices used in surgical treatment of PDA [34], however, due to the significantly higher costs of Amplatz implant, treatment with multiple coils in cases of larger PDAs still occurs sporadically.

The complications of percutaneous closure of PDA are residual leakage, haemorrhage and trauma of large vessels, exposure to X-ray radiation, and risk associate with the toxicity of contrast medium. Additionally, due to mechanical irritation of the area with the tools, contraction of the tunica media of the arterial duct may occur [34], leading to misinterpretation of the actual size of the duct and improper clasp selection, which may in turn lead to persistent leakage or displacement of the coil or clasp. Late complications may also occur, such as coarctation of the aorta and stenosis of the left pulmonary artery [57]. The risk of complications increases with the diameter of the patent duct. Percutaneous closure of PDA is characterised by a mortality of close to zero, quick convalescence, and short hospital stay. The lower invasiveness, fewer complications, and comparable efficacy indicate the superiority of percutaneous closure of PDA over traditional surgical therapeutic techniques. Small patients, after successful, uncomplicated closure of a PDA require sporadic cardiological monitoring. The first echocardiographic exam takes place directly after the placement of percutaneous closure, and additional consultations are indicated for one month after the procedure as well as for six months and one year thereafter. Further cardiological care is sporadic. In order for percutaneous PDA closure methods to become the method of choice for the youngest children, it is necessary to miniaturise the equipment, which will facilitate manipulation of the catheter and prevent perioperative trauma, arrhythmias, and haemodynamic instability [58].

SUMMARY

Based on analysis of the presented methods of PDA closure, currently available and performed, it is impossible to pick a single, best method. Each of the described methods has its advantages as well as drawbacks. Choosing the method should be based on many diverse qualifying criteria: the haemodynamic significance of the PDA, the overall health of the patient, their age and body mass, minimal invasiveness, and the minimisation of peri- and post-operative trauma. Symptomatic treatment is limited to newborns in stable condition with a haemodynamically significant PDA; it is not available to older children due to the ineffectiveness of this method in that cohort. The primary advantage of this method is the exclusion of the possibility of side effects from pharmacological or invasive treatment. Meanwhile, in cases where symptoms of cardiorespiratory insufficiency are present, advanced pharmacological treatment should be implemented using COX inhibitors. In available meta-analyses the side effects of ibuprofen are described as significantly lower when compared to indomethacin as well as the lower risk of spontaneous reopening of the PDA at a later date [26]. The time of start of treatment with these drugs varies significantly in the data sources, from prophylactically to
24 hours after birth, based on whether the source says to start treatment before clinical symptoms appear or after.

In the past, the method of choice for closing haemodynamically significant PDA was cardiac surgery. Presently, thanks to the development of techniques, less traumatic methods of PDA closure exist, such as minimally invasive surgical thoracoscopic closure VATS as well as percutaneous closure using coils or Amplatzer implant. The main drawbacks of percutaneous closure of the PDA are the body mass of the patient (which, according to various sources, should be over five kilograms) as well as availability of access to a haemodynamic procedure room and use of X-ray technology for visualisation of the field. The smaller the body mass of the child and the larger the diameter of the PDA, the greater the risk of complications.

The latest method of those presented is thoracoscopic closure of the PDA, which currently appears to be the most universal method, without limitations regarding the body mass, age, or general condition of the patient and can be performed in an operating theatre as well as in a procedure room. Complications arising from thoracoscopy are rare and few.

The limitations of this treatment method as well as the percutaneous technique are: large diameter of the duct, calcification of the duct, structural defects of the pleura, earlier thoracotomy, persistent infection, or simultaneous aneurysm of the PDA. Perioperative mortality in the presented methods is close to zero. The highest procedural effectiveness in closing PDA belongs to surgical closure, but with percutaneous and thoracoscopic methods of PDA closure very close behind.

The decision regarding the method of closure of PDA should be based on the best current medical knowledge, the experience and expertise of the cardiac surgeon, and the procedural capabilities of the hospital in which the procedure takes place.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES


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