REVIEW

The ductus arteriosus: Physiology, regulation, and functional and congenital anomalies

Le canal artériel : physiologie, régulation, anomalies fonctionnelles et congénitales

Véronique Gournay*

Pediatric cardiology unit, CHU de Nantes, 38, boulevard Jean-Monnet, 44093 Nantes cedex, France

Summary   Over the last three decades, knowledge about fundamental and clinical aspects of the ductus arteriosus has substantially improved, leading to considerable progress in the management of various cardiac diseases involving the ductus. The identification of the mechanisms regulating ductal patency led to design pharmacological drugs to achieve medical closure of PDA in premature infants, or inversely to maintain patency in neonates with duct-dependent congenital heart diseases. Concurrently, widespread availability of echocardiography has improved the detection of congenital PDA, resulting in earlier treatment. Closure of PDA, by either surgery or transcatheter techniques, can now be achieved safely, resulting in a decrease in the incidence of severe complications of PDA.
© 2010 Elsevier Masson SAS. All rights reserved.

Résumé   Au cours des 30 dernières années, les connaissances des aspects fondamentaux et cliniques du canal artériel ont beaucoup progressé, conduisant à une amélioration de la prise en charge des pathologies cardiaques impliquant le canal artériel. L'identification des mécanismes régulant la perméabilité ductale a permis la mise au point de produits pharmacologiques entraînant une fermeture médicale du canal artériel chez le prématuré, ou au contraire maintenant la perméabilité ductale chez le nouveau-né atteint d'une cardiopathie ductodépendante. Simultanément, le développement de l'échocardiographie a amélioré la détection du canal artériel

persistant congénital, permettant un traitement plus précoce. La fermeture du canal artériel, par chirurgie ou par cathétérisme interventionnel, peut maintenant être pratiquée avec un très faible risque, diminuant ainsi l'incidence des complications sévères du canal artériel persistant.

Anatomy

The ductus arteriosus is a large channel found normally in all mammalian foetuses, connecting the main pulmonary trunk with the left-sided descending aorta, about 5 to 10 mm distal to the origin of the left subclavian artery in a full-term infant. The length of the ductus arteriosus varies and its diameter is similar to that of the descending aorta.

Embryology

In normal cardiovascular development, the proximal portions of the sixth pair of embryonic aortic arches persist as the proximal branch pulmonary arteries and the distal portion of the left sixth arch persists as the ductus arteriosus, connecting the main pulmonary trunk with the left dorsal aorta. Normally, the distal right sixth arch degenerates.

Histology

The microscopic structure of the ductus arteriosus is quite different to that of the adjacent pulmonary trunk or aorta. Although the wall thickness of these vessels are similar, the media of the ductus arteriosus consists largely of smooth muscle cells, instead of the circumferentially arranged layers of elastic fibres composing the media of the aorta and the pulmonary artery. Contraction of these smooth muscle cells results in narrowing of the lumen and shortening of the ductus arteriosus.

Physiology

Function

In the foetus, gas exchange occurs in the placenta, and not in the lungs as after birth. There is thus need for only a small amount of blood in the lungs for nutritional and metabolic requirements, accounting for only 5 to 10% of the combined ventricular output (CVO), whereas the right ventricle ejects about 65% of CVO (Fig. 1). The ductus arteriosus diverts a major proportion of the right ventricular output, i.e. about 55% of the CVO, away from the high-resistance pulmonary vascular bed to the low-resistance umbilical-placental circulation.

Regulation of the ductus

The ductus arteriosus is widely patent in the foetus. The factors considered as agents in maintaining ductal patency in the foetus include exposure to low partial pressure of oxy-

gen (pO$_2$; 18 mmHg in the foetal lamb), circulating or locally produced prostaglandins, and local nitric oxide production.

Oxygen has been shown to constrict the ductus arteriosus in vitro and in vivo [1]. In addition, responsiveness of the ductus arteriosus to oxygen increases with advancing gestation.

Vasodilator prostaglandins, especially prostaglandin E2 (PGE2), play a part in maintaining the patency of the ductus during foetal and neonatal life [2]. Inhibition of prostaglandin synthesis, through inhibition of the enzyme cyclo-oxygenase, results in constriction of the foetal ductus. After birth, PGE2 is metabolized in the lungs and its concentration falls rapidly within 3 hours. Furthermore, prostaglandin-induced ductal dilation is developmentally regulated. The immature ductus produces more prostaglandin and is also more sensitive to the relaxant effect of PGE2 [3].

Finally, endothelial cells of the ductus produce nitric oxide, contributing to ductal patency.
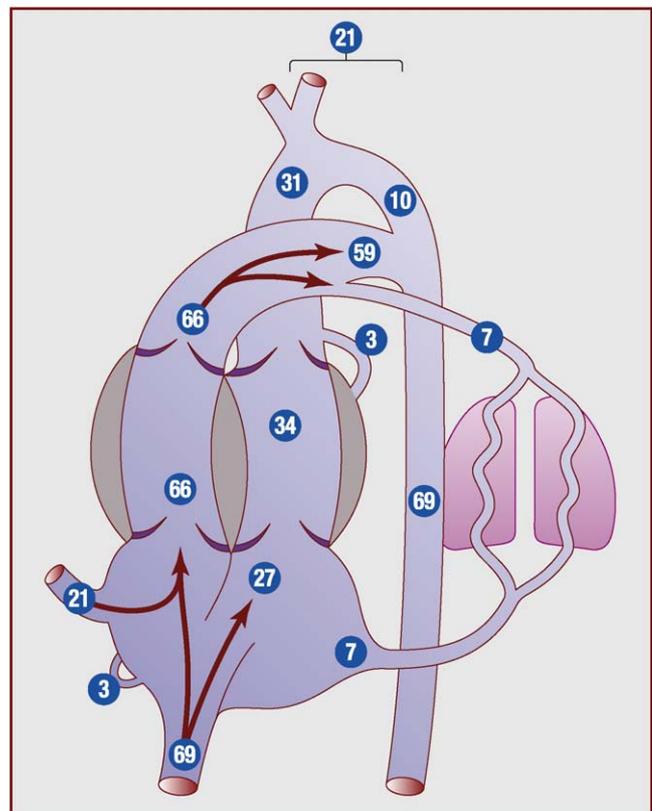

Figure 1. Percentages of combined ventricular output that return to the foetal heart, that are ejected by each ventricle and flow through the main vascular channels in a late gestation lamb. [32].

Mechanisms of normal closure

In full-term infants, postnatal closure of the ductus is effected in two phases: smooth muscle constriction produces ''functional'' closure of the lumen of the ductus within 18 to 24 hours after birth; and ''anatomical'' occlusion of the lumen occurs over the next few days or weeks.

After delivery, there is an increase in arterial pO_2, a drop in circulating PGE2 and a drop in blood pressure within the lumen of the ductus (caused by the drop in pulmonary vascular resistance). All these events promote constriction of the ductus. This initial functional constriction of the ductus arteriosus is responsible for its ultimate anatomical closure; the loss of luminal blood flow produces a zone of hypoxia in the muscle media of the ductus necessary for irreversible anatomical closure [4]. This hypoxic zone is associated with local induction of smooth muscle cell death in the media and local production of hypoxia-inducible growth factors. These growth factors stimulate endothelial proliferation, leading to extensive neointimal thickening. In addition, the profound vessel wall hypoxia inhibits endogenous prostaglandin and nitric oxide production and prevents subsequent reopening. The endothelium proliferation results in fibrosis and permanent seal, producing a fibrous band known as the ligamentum arteriosum in 2 to 3 weeks.

Patent ductus arteriosus

Epidemiology — risk factors

The incidence of PDA in term infants is about 1 in 2000 births, accounting for 5 to 10% of all congenital heart disease. The female to male ratio is ~2:1.

In contrast to premature infants, in whom PDA is due to developmental immaturity, PDA in term infants results from a significant structural abnormality. It occurs with increased frequency in several genetic syndromes, including chromosomal aberrations and single gene mutations. Although most cases of PDA are seemingly sporadic, many are believed to be due to multifactorial inheritance, with the requirement of genetic predisposition and an environmental trigger that occurs at a vulnerable time [5]. The genetic mechanisms of PDA in some patients may be autosomal recessive inheritance with incomplete penetrance [6]. The precise mechanisms of how these genetic abnormalities result in PDA are not clear. Genetic studies suggest that the abnormalities in Char syndrome (an inherited disorder with PDA) result from derangement of neural crest derivatives [7].

In addition to these genetic factors, infection and environmental factors, such as congenital rubella, may play a role.

Aetiology

In a breed of dogs with hereditary PDA, the media of the ductus has an abnormal structure, with smooth muscle cells partly replaced by collagen and elastic fibres [8]. In this animal model, the endothelial cells fail to separate normally from the internal elastic lamina. These histological features resemble those of the PDA in humans, suggesting a similar pathogenesis.

Pathophysiology

The haemodynamic impact of PDA depends on the magnitude of the left-to-right shunting, determined by the size of the ductus and the relationship between systemic and pulmonary vascular resistance (PVR), and on left ventricular performance. After birth, the rise in systemic vascular resistance and the fall in PVR results in left-to-right shunting, increasing over the first weeks of life. Left-to-right shunting through the ductus results in pulmonary overcirculation and left ventricular overload. Increased pulmonary blood flow leads to increased pulmonary fluid volume, decreased lung compliance and increased work of breathing. Although uncommon, pulmonary oedema may occur.

Increased flow returning to the left heart results in left ventricular overload. The left ventricle is able to handle the increased volume load up to a shunting of 50% of its output. Above that limit, left ventricular failure may occur.

In the long term, pulmonary hypertension resulting from pulmonary overcirculation may induce progressive morphological changes in the pulmonary vasculature. These changes, including arteriolar medial hypertrophy, intimal proliferation and eventual obliteration of pulmonary arterioles and capillaries, lead to increased PVR. This form of pulmonary hypertension as a consequence of left-to-right shunt is called Eisenmenger's syndrome. When PVR exceeds systemic vascular resistance, ductal shunting is reversed and becomes right-to-left.

Clinical manifestations

The clinical picture varies depending on the magnitude of the shunting. In the most severe forms, infants with a moderate or large PDA will present with progressive congestive heart failure, often within 8 to 10 weeks after birth. Most patients with small to moderate left-to-right shunt compensate well throughout childhood, but may finally develop congestive heart failure secondary to chronic volume overload in adulthood, starting in the third decade. Some patients with a small ductus may remain completely asymptomatic. In those patients, PDA is usually diagnosed during evaluation of a heart murmur. Since the introduction of echocardiography, very small ductus, referred to as ''silent'' ductus, may be detected incidentally by an echocardiogram performed for another purpose.

Physical examination findings also vary. Typically, a continuous murmur is heard, located at the upper left sternal border, referred to as a ''machinery'' murmur. It radiates down the left side of the sternum and into the back, and a thrill may be present. If the shunt is moderate or large, the pulse is rapid and bounding and pulse pressure is increased. Hepatomegaly is usually noted.

In the severe forms presenting during infancy, the symptoms of cardiac failure will gradually subside after 3 to 6 months, as pulmonary vascular resistance increases. The time course of subsequent changes varies between 2 to 3 years and late adolescence or even early adult life. In the late stages of Eisenmenger's syndrome, the patients are cyanotic and may have differential cyanosis, more marked with exertion. There is no murmur during systole or diastole because shunting is minimal. Auscultation may reveal a diastolic murmur of pulmonary regurgitation and/or a

holosystolic murmur from tricuspid regurgitation. The intensity of the pulmonic component of the second heart sound is increased.

Electrocardiogram

The electrocardiogram shows left ventricular hypertrophy and left atrial enlargement in patients with moderate or large PDA. In patients with smaller shunts, the electrocardiogram is usually normal. In advanced stages (Eisenmenger's syndrome), the electrocardiogram shows nonspecific signs of pulmonary hypertension.

Echocardiogram

The echocardiogram is the procedure of choice to confirm the diagnosis, evaluate the impact of a PDA, and assess the presence of associated lesions (Fig. 2A). The ductus can be imaged throughout its length using a high left parasternal view, allowing evaluation of ductal size and geometry. M-mode studies provide an assessment of left atrial and ventricular size, which gives some idea of the magnitude of the shunt. In patients with moderate or large PDA, the left atrium and left ventricle are enlarged, whereas they are normal in patients with smaller PDA. A left atrium/aorta ratio > 2 is considered to be a reliable marker of a haemodynamically significant ductal shunt.

Colour Doppler is a very sensitive technique to detect even tiny ductus, showing retrograde high-velocity flow entering the pulmonary artery trunk near the origin of the left pulmonary artery (Fig. 2B). On the other hand, when colour Doppler shows the presence of bidirectional or pure right-to-left shunting, it indicates elevated pulmonary vascular resistance. However, in these patients, the PDA may be difficult to visualize, even if it is large. The most prominent echocardiographic features in this setting may be enlargement of the right cardiac chambers, septal flattening, right ventricular hypertrophy or high-velocity tricuspid and/or pulmonary regurgitation. These findings should prompt to look for a patent ductus. Contrast echocardiography performed with saline and microbubbles may be helpful in this setting.

Except when the ductus is very long and tortuous, pulmonary artery systolic and diastolic pressures can be estimated approximately by measurement of the pressure gradient between the aorta and the pulmonary artery, derived from the application of the modified Bernouilli equation to the Doppler velocity of the ductal flow (Fig. 2C) [9].

Natural history and complications

Spontaneous closure of the ductus may occur even beyond infancy, at a rate of 0.6% per year, varying with the ductal size.

Congestive heart failure in adulthood, starting around the third decade, may result from chronic left ventricular overload, even in patients with moderate left-to-right shunt.

Eisenmenger's disease, when it occurs, usually results from a moderate to large shunt causing chronic pulmonary overload [10], although in some cases pulmonary vascular changes appear to be a primary disease coinciding with the presence of a small ductus [11].

The incidence of infective endarteritis, which was reported to be 1% per year, has fallen dramatically over the last two decades, secondary to improved dental care, widespread use of antibiotics and a general reduction in the occurrence of infections in the population [12]. In developing countries, the incidence of endarteritis remains significantly high [13].

Principles of management

Techniques for PDA closure are either surgery or transcatheter closure. Surgical ligation is performed by
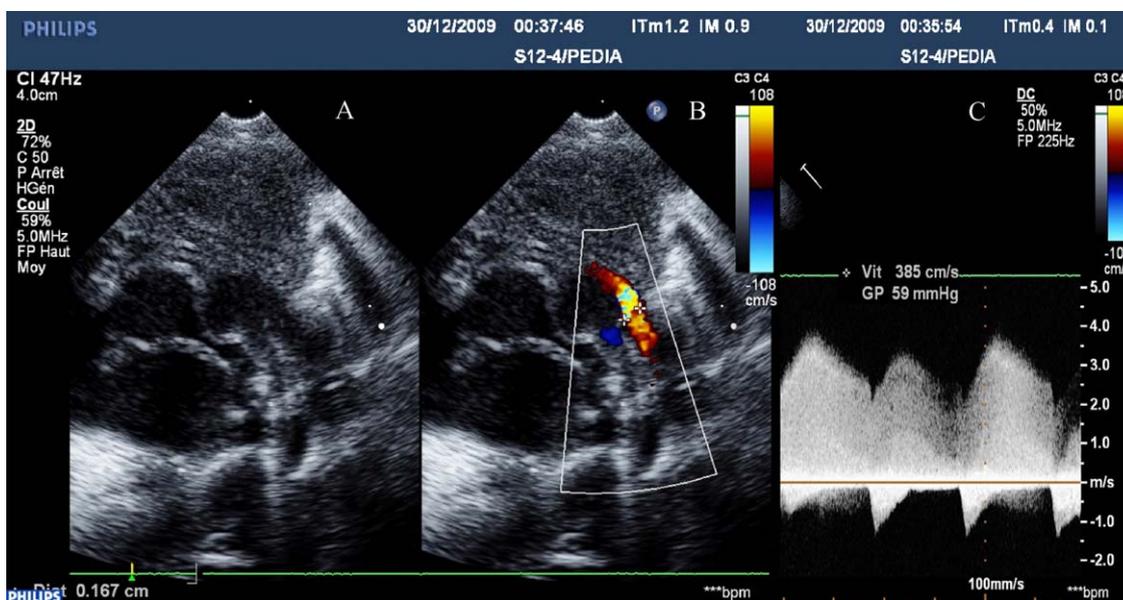

Figure 2. Echocardiogram showing patent ductus arteriosus. A: two-dimensional image of patent ductus arteriosus. B: colour Doppler flow showing retrograde flow in the pulmonary trunk. C: spectral Doppler of continuous ductal flow, enabling measurement of a systolic pressure gradient of 59 mmHg.

a left thoracotomy without cardiopulmonary bypass. Complications are rare and include bleeding, pneumothorax, recurrent laryngeal nerve palsy and chylothorax. Transcatheter closure of the PDA is more recent. The first experience was reported by Portsmann et al. in 1967, followed by Rashkind et al. with the use of a double-umbrella device [14]. These devices required the use of large introducer sheaths and left a significant number of residual shunts. Subsequently, the closure by coils that reduced the required catheter size became the technique of choice for small to moderate ductus [15]. More recently, the use of the Amplatzer duct occluder made possible the transcatheter closure of large shunts [16].

Currently, most patients with PDA can have safe, successful transcatheter closure above 5 kg. Rare complications are embolization of device (usually retrievable), device protrusion causing obstruction of the descending aorta or of the left pulmonary artery, and haemolysis resulting from high-velocity residual shunting.

Indications for closure

Symptomatic infants who do not respond rapidly to medical anticongestive treatment should undergo PDA closure, by surgery if under 5 kg and by transcatheter technique otherwise.

In asymptomatic patients with significant left-to-right shunt, PDA closure is indicated to prevent complications, but can be delayed beyond infancy if pulmonary artery pressure is less than half of systemic arterial pressure.

In patients with markedly increased PVR and those with fixed pulmonary hypertension emphasized by right-to-left shunt (Eisenmenger's syndrome), PDA closure is contraindicated. Pulmonary hypertension in this form progresses independently from the shunt and once pulmonary vascular resistance overtakes systemic vascular resistance (SVR), the existence of a right-to-left shunt delays fall of systemic outflow and right ventricle failure. In patients with moderately increased PVR (> 6 Wood units/m^2, ratio PVR/SVR > 0.35), the decision is difficult and is based on the pulmonary response to vasoreactivity testing (inhaled nitric oxide or oxygen) and sometimes on lung biopsy.

The indications for closure in patients with silent ductus remain controversial. In these patients, the main argument to close the ductus is the prevention of endarteritis. However, the risk is considered so low that antibiotic prophylaxis is no longer recommended by the most recent guidelines for patients with PDA. Because closure can be achieved with minimal morbidity and mortality, some authors advocate routine closure of any PDA [17], whereas such an approach appears unreasonable to others [18].

PDA in the premature infant

Mechanisms for patency

In preterm infants, the ductus frequently remains open for many days after birth. Several factors may explain this delayed closure. First, as stated above, the immature ductus has a high threshold of response to oxygen. In addition, the immature ductus is more sensitive to the vasodilating effects

of PGE2 and nitric oxide. Furthermore, the circulating levels of PGE2 are particularly high in the premature infant because they fail to be metabolized completely by immature lungs. Even when the ductus does constrict, this constriction is not sufficient to produce the profound media hypoxia necessary for anatomical closure. Subsequent reopening of the ductus may ensue. All these elements account for the fact that 70 to 80% of the infants with a birth weight below 1000 g have a PDA [19].

Pathophysiology

In premature infants, the rapid postnatal fall in vascular pulmonary resistance results in a left-to-right shunt through the unconstricted ductus. The consequences of this shunt are twofold: pulmonary overcirculation and low systemic output.

Respiratory distress syndrome due to lung immaturity is a common occurrence in premature infants. It usually improves after 2 to 3 days, but ductal shunting may alter pulmonary compliance, causing a secondary increase in ventilatory requirements. Increased permeability of the immature capillaries results in pulmonary oedema and sometimes leads to pulmonary haemorrhage, a rare but life-threatening event, usually occurring within 72 hours of life [20]. Epidemiologic studies have also found an association between PDA and a higher incidence of chronic lung disease, the long-term pulmonary complication of prematurity [21].

In contrast to full-term patients, systemic output may be compromised in premature patients with a PDA. In experimental studies in lambs, Clyman et al. demonstrated that normal systemic blood flow is maintained in full-term animals with left-to-right shunts of as much as 75% of left ventricular output, whereas systemic flow is inadequate in immature lambs with shunts exceeding 50% of left ventricular output [22]. This leads to low diastolic aortic pressure and decreased organ perfusion. Decreased renal perfusion results in renal failure, aggravating volume retention associated with congestive heart failure. Similarly, impaired intestinal blood flow and intestinal ischaemia causes feeding intolerance and possibly necrotizing enterocolitis.

Diagnosis

Typical clinical findings, including a continuous or systolic murmur, hyperactive precordium and bounding pulses, are specific but not sensitive enough for PDA. Their appearance is delayed compared with other ''symptoms'' of PDA that reflect its haemodynamic consequences before cardiac failure develops. These symptoms are increased ventilatory requirements 2 to 3 days after birth, which can sometimes be difficult to distinguish from the initial respiratory distress syndrome. Therefore, early presymptomatic reliable diagnosis of PDA in the first 4 days of life depends on ultrasound examination. Among the several potential markers, colour Doppler measurement of the ductal diameter seems to be most accurate in predicting a ''haemodynamically significant'' PDA requiring subsequent medical and/or surgical intervention. In ventilated newborns within the first 30 hours of life, a ductus with left-to-right shunt and

a diameter greater than 1.5 mm predicts a significant PDA with a sensitivity of 81% and a specificity of 85% [23]. A left atrial to aortic ratio > 1.5, left ventricular dilation, diastolic pulsed Doppler flow velocity in the left pulmonary artery > 0.2 m/sec and a retrograde diastolic flow in the descending aorta are very specific but occur later. However, when present, they clearly indicate a haemodynamically significant PDA.

Therapeutic strategies

Ductal patency may be prevented antenatally by the maternal administration of steroids and postnatally by avoidance of excessive parenteral fluid.

Medical treatment relies on cyclo-oxygenase inhibitors, which were shown in the mid 1970s to close the ductus successfully in about 80% of premature infants [24]. Indomethacin is the cyclo-oxygenase inhibitor that was first and most widely used. Adverse effects, mainly related to the vasoconstrictor effect from inhibition of prostaglandin synthesis, include transient renal failure [25] and gastrointestinal bleeding and perforation [26]. In contrast to indomethacin, ibuprofen, a more recent cyclo-oxygenase inhibitor, does not reduce cerebral, renal and intestinal blood flow. A meta-analysis of comparative trials has shown that ibuprofen is as effective as indomethacin in closing the ductus. Regarding side effects, there is no difference in the incidence of necrotizing enterocolitis, but fewer renal side effects with ibuprofen [27]. However, the clinical significance of this theoretical advantage is still debated. There are no data available concerning long-term outcome.

The best timing of medical treatment to prevent morbidity remains highly controversial. Based on the assumption that it might be wiser to treat the PDA before it has clinical consequences, indomethacin has been given earlier over the years. The most recently described strategy is prophylactic treatment, consisting of indomethacin administration within the first 24 hours of life to all extremely premature infants. Although this approach reduces the incidence of severe intraventricular haemorrhage and the need for surgical ligation, it does not improve long-term neurodevelopmental outcome [28]. Therefore, a prophylactic strategy is not recommended because no clear benefit outweighs the unnecessary exposure to potential side effects of infants that could have closed their ductus spontaneously. Currently, the most widely used strategy is early curative ''presymptomatic'' treatment, i.e. treatment administration 2 to 3 days after birth to infants in whom echocardiographic markers of a significant PDA are detected. However, some authors disagree strongly with such an attitude and favour conservative management [29].

Surgical ligation can now be performed safely in the neonatal unit in most centres when medical treatment has failed or is contraindicated. In addition to the complications of thoracotomy mentioned above, recent epidemiologic studies have suggested that surgical ligation might increase the likelihood of impaired neurodevelopmental outcome, chronic lung disease and retinopathy of prematurity [30,31]. Therefore the benefit/risk ratio of surgery should be weighed carefully on an individual basis.

Ductus arteriosus and congenital heart diseases

Haemodynamics

In many congenital heart diseases, volume and oxygen content of blood carried by the ductus during foetal life are altered markedly, resulting in modifications of its size, shape and ability to constrict [32].

Normally, the ductus arteriosus in the foetal lamb carries about 55% of the CVO from the pulmonary artery to the aorta. It joins the aorta at an obtuse inferior angle, presumably because flow is directed down to the descending aorta (Fig. 3A).

In case of left-sided obstruction, a much larger proportion of the output has to flow through the ductus to maintain a normal CVO, resulting in a wider ductus (Fig. 3B). However, due to a mixture of systemic venous and umbilical venous blood in the right atrium, the blood crossing the ductus arteriosus has a higher-than-normal oxygen saturation, inducing ductal constriction.

In case of right-sided obstruction, the ductal shunt is markedly different from normal. First, the direction of the shunt is reverted as blood flows from the aorta to the pulmonary artery to maintain pulmonary blood flow. Second, pulmonary blood flow being only 5 to 10% of the CVO in the foetus, the volume of blood crossing the ductus is lower than normal. The ductus arteriosus may thus be narrower and its connection with the aorta has an acute inferior angle (Fig. 3C). Third, the blood crossing the ductus arteriosus has higher oxygen saturation because all systemic venous, umbilical venous and pulmonary venous blood mixes in the left atrium. This higher oxygen saturation induces ductal constriction.

In case of transposition of the great arteries, the pulmonary artery, and thus the ductus arteriosus, receive blood with high oxygen saturation ejected from the left ventricle. This could induce ductal constriction and increase pulmonary blood flow. In addition, the saturation of the blood flowing through the foetal pulmonary circulation is increased, initially lowering pulmonary vascular resistance and further increasing pulmonary blood flow. Secondarily, pulmonary blood flow decreases by a myogenic reflex-mediated mechanism, and remodelling of pulmonary arterioles occurs. These mechanisms could partly explain the increased incidence of persistent pulmonary hypertension in newborns with transposition of the great arteries.

After birth, ductal closure is frequently delayed in congenital heart defects. In cyanotic infants, the arterial pO_2 may not be sufficient to stimulate ductal constriction. In infants with left-sided obstructive lesions, pO_2 increases significantly after birth. However, due to right-to-left shunting, the ductus is exposed to mixed venous saturation and therefore to less oxygen stimulus to constrict. In addition, in these infants, high pulmonary arterial pressure and high ductal flow may contribute to maintain its patency. However, the ductus does tend to constrict after a few days, compromising systemic or pulmonary blood flow in infants with duct-dependent defects.
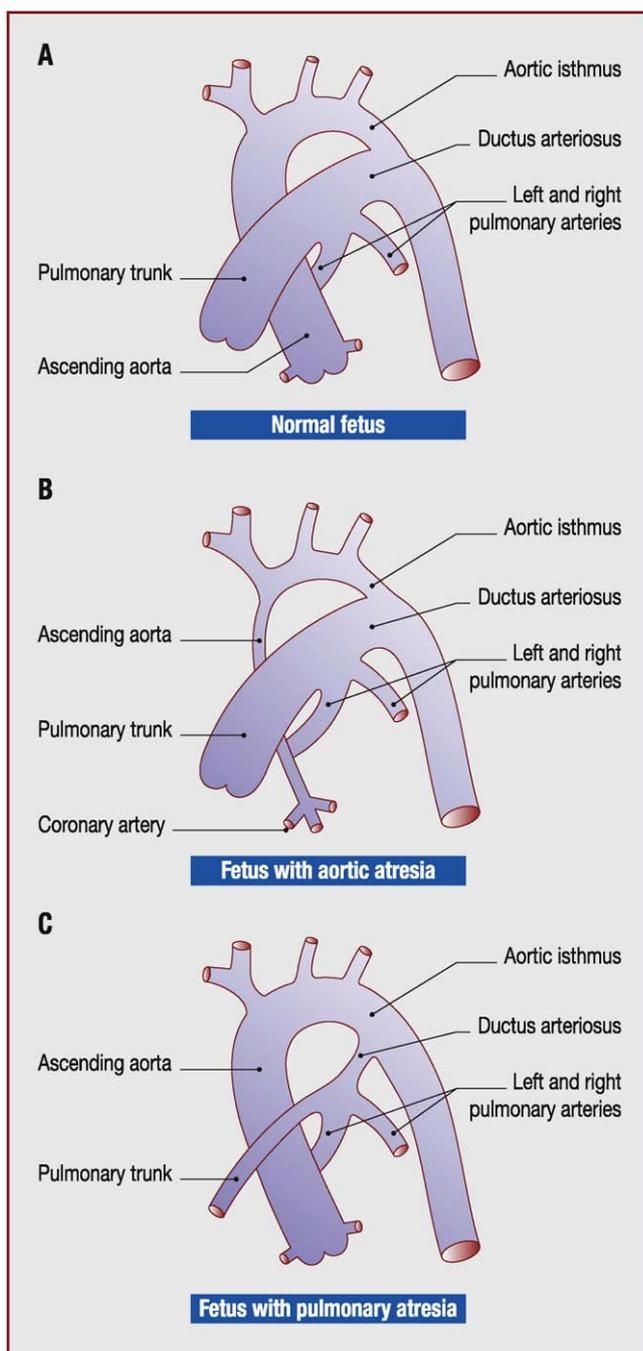
Figure 3. Relationships and sizes of the ductus arteriosus and the aorta, pulmonary trunk and pulmonary arteries. A: in a normal foetus. B: in a foetus with aortic atresia. C: in a foetus with pulmonary atresia.
[32].

Maintenance of ductal patency

The use of intravenous alprostadil (PGE1) to maintain ductal patency improved dramatically the management of newborns with duct-dependent congenital heart defects in the early 1980s [33]. It is usually very effective when given shortly after ductal constriction. The frequency of the most usual side effects, such as hypotension, apnoea, fever and pain, can be reduced greatly by using doses

< 0.01 μg/kg/min [34]. Other less frequent side effects, including gastric outlet obstruction and cortical hyperostosis, occur only after prolonged administration.

Concerns about the complications of long-term prostaglandin infusion have led physicians to seek alternative means to maintain ductal patency, specifically in the setting of hypoplastic left heart syndrome. The Loma Linda group, who had the greatest experience in the management of neonates waiting for transplantation, reported a promising preliminary experience of ductal stenting in five patients in 1993 [35]. Subsequently, other investigators concluded that although the ductal stent can be placed safely and does maintain ductal patency, subsequent pulmonary overcirculation is a major problem.

More recently, ductal stenting has also been applied as part of a hybrid catheter-surgical univentrical palliation strategy in patients with hypoplastic left heart syndrome [36]. The objective of this procedure, which combines percutaneous ductal stenting and surgical pulmonary artery banding, is to improve survival in patients who are considered at too high risk for the stage I Norwood intervention. The latest results reported a 50% survival rate, which is similar to the current results for the conventional Norwood stage I operation in similarly high-risk patients [37].

Conflict of interest statement

None.

References

[1] Heymann MA, Rudolph AM. Control of the ductus arteriosus. Physiol Rev 1975;55:62—78.
[2] Coceani F, Olley PM. The response of the ductus arteriosus to prostaglandins. Can J Physiol Pharmacol 1973;51:220—5.
[3] Bhattacharya M, Asselin P, Hardy P, et al. Developmental changes in prostaglandin E(2) receptor subtypes in porcine ductus arteriosus. Possible contribution in altered responsiveness to prostaglandin E(2). Circulation 1999;100:1751—6.
[4] Clyman RI, Chan CY, Mauray F, et al. Permanent anatomic closure of the ductus arteriosus in newborn baboons: the roles of postnatal constriction, hypoxia, and gestation. Pediatr Res 1999;45:19—29.
[5] Nora JJ. Multifactorial inheritance hypothesis for the etiology of congenital heart diseases. The genetic—environmental interaction. Circulation 1968;38:604—17.
[6] Martin RP, Banner NR, Radley-Smith R. Familial persistent ductus arteriosus. Arch Dis Child 1986;61:906—7.
[7] Satoda M, Zhao F, Diaz GA, et al. Mutations in TFAP2B cause Char syndrome, a familial form of patent ductus arteriosus. Nat Genet 2000;25:42—6.
[8] Gittenberger-de Groot AC, Strengers JL, Mentink M, et al. Histologic studies on normal and persistent ductus arteriosus in the dog. J Am Coll Cardiol 1985;6:394—404.
[9] Becker TE, Ensing GJ, Darragh RK, et al. Doppler derivation of complete pulmonary artery pressure curves in patent ductus arteriosus. Am J Cardiol 1996;78:1066—9.
[10] Espino-Vela J, Cardenas N, Cruz R. Patent ductus arteriosus. With special reference to patients with pulmonary hypertension. Circulation 1968;38:45—60.
[11] Bessinger Jr FB, Blieden LC, Edwards JE. Hypertensive pulmonary vascular disease associated with patent ductus arteriosus. Primary or secondary? Circulation 1975;52:157—61.

[12] Zuberbuhler JR, Neches WH, Park SC. Infectious endocarditis--an experience spanning three decades. Cardiol Young 1994;4:244—51.

[13] Sadiq M, Latif F, Ur-Rehman A. Analysis of infective endarteritis in patent ductus arteriosus. Am J Cardiol 2004;93:513—5.

[14] Rashkind WJ, Mullins CE, Hellenbrand WE, et al. Nonsurgical closure of patent ductus arteriosus: clinical application of the Rashkind PDA Occluder System. Circulation 1987;75:583—92.

[15] Cambier PA, Kirby WC, Wortham DC, et al. Percutaneous closure of the small (less than 2.5 mm) patent ductus arteriosus using coil embolization. Am J Cardiol 1992;69:815—6.

[16] Pass RH, Hijazi Z, Hsu DT, et al. Multicenter USA Amplatzer patent ductus arteriosus occlusion device trial: initial and one-year results. J Am Coll Cardiol 2004;44:513—9.

[17] Giroud JM, Jacobs JP. Evolution of strategies for management of the patent arterial duct. Cardiol Young 2007;17(Suppl. 2):68—74.

[18] Sullivan ID. Patent arterial duct: when should it be closed? Arch Dis Child 1998;78:285—7.

[19] Koch J, Hensley G, Roy L, et al. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. Pediatrics 2006;117:1113—21.

[20] Kluckow M, Evans N. Ductal shunting, high pulmonary blood flow, and pulmonary hemorrhage. J Pediatr 2000;137:68—72.

[21] Marshall DD, Kotelchuck M, Young TE, et al. Risk factors for chronic lung disease in the surfactant era: a North Carolina population-based study of very low birth weight infants. North Carolina Neonatologists Association. Pediatrics 1999;104:1345—50.

[22] Clyman RI, Roman C, Heymann MA, et al. How a patent ductus arteriosus effects the premature lamb's ability to handle additional volume loads. Pediatr Res 1987;22:531—5.

[23] Kluckow M, Evans N. Early echocardiographic prediction of symptomatic patent ductus arteriosus in preterm infants undergoing mechanical ventilation. J Pediatr 1995;127:774—9.

[24] Heymann MA, Rudolph AM, Silverman NH. Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. N Engl J Med 1976;295:530—3.

[25] Lin YJ, Tsai YJ, Chen JS, et al. Renal effects and urinary excretion of prostaglandin following indomethacin therapy in premature infants with patent ductus arteriosus. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 1995;36:104—7.

[26] Grosfeld JL, Chaet M, Molinari F, et al. Increased risk of necrotizing enterocolitis in premature infants with patent ductus arteriosus treated with indomethacin. Ann Surg 1996;224:350—5, discussion 55-7.

[27] Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2008:CD003481.

[28] Schmidt B, Davis P, Moddemann D, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 2001;344:1966—72.

[29] Laughon MM, Simmons MA, Bose CL. Patency of the ductus arteriosus in the premature infant: is it pathologic? Should it be treated? Curr Opin Pediatr 2004;16:146—51.

[30] Chorne N, Leonard C, Piecuch R, et al. Patent ductus arteriosus and its treatment as risk factors for neonatal and neurodevelopmental morbidity. Pediatrics 2007;119:1165—74.

[31] Kabra NS, Schmidt B, Roberts RS, et al. Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: results from the Trial of Indomethacin Prophylaxis in Preterms. J Pediatr 2007;150:229—34, 34 e1.

[32] Rudolph AM. The ductus arteriosus and persistent patency of the ductus arteriosus. Congenital diseases of the heart. 3rd ed. Chichester, UK: Wiley-Blackwell; 2009, p. 115—47.

[33] Moodie DS. Medical management of infants and children with congenital heart disease. Cardiovasc Clin 1981;12:177—86.

[34] Kramer HH, Sommer M, Rammos S, et al. Evaluation of low dose prostaglandin E1 treatment for ductus dependent congenital heart disease. Eur J Pediatr 1995;154:700—7.

[35] Ruiz CE, Gamra H, Zhang HP, et al. Brief report: stenting of the ductus arteriosus as a bridge to cardiac transplantation in infants with the hypoplastic left-heart syndrome. N Engl J Med 1993;328:1605—8.

[36] Michel-Behnke I, Akintuerk H, Marquardt I, et al. Stenting of the ductus arteriosus and banding of the pulmonary arteries: basis for various surgical strategies in newborns with multiple left heart obstructive lesions. Heart 2003;89:645—50.

[37] DiBardino DJ, McElhinney DB, Marshall AC, et al. A review of ductal stenting in hypoplastic left heart syndrome: bridge to transplantation and hybrid stage I palliation. Pediatr Cardiol 2008;29:251—7.