INTRODUCTION

Patent ductus arteriosus (PDA) accounts for 5 to 10% of all congenital heart diseases (CHD). It occurs more commonly in premature infants, where 8 out of 1,000 premature infants have PDA compared to 2 out of 1,000 of term infants. It is more common in females with a female to male ratio of 3:1[(1)].

PDA represents the persistence of a normal fetal structure between the left pulmonary artery and the descending aorta about 5 mm distal to the origin of the left subclavian artery. It allows most of the blood from the right ventricle (RV) to bypass the fluid filled lungs of the fetus which protects the RV from pumping against high resistance and thus preventing RV failure in utero [(2)].

When the newborn takes his first breath the lungs inflate and bradykinins released by the inflated lungs cause constriction of the smooth muscle of the ductus and reduce the blood flow through it. Normally the ductus closes within 12 to 24 hours and is sealed completely after 3 weeks.

PDA may be idiopathic or may be due to congenital rubella syndrome or some chromosomal abnormalities. Infants may be asymptomatic in small ducts or may present with recurrent respiratory tract infection, pneumonia in moderate ducts where in large ducts symptoms of congestive heart failure and failure to thrive may occur. Large ducts can also cause gradual development of pulmonary hypertension secondary to increase in pulmonary blood flow [(3)].

Available treatment modalities include surgical ligation in large ducts not suitable for interventional treatment and transcatheter closure for small to moderate sized ducts whether by coil embolization or occluder devices. Accurate assessment of the size, shape and anatomical type of the PDA represents a crucial step to choose the most suitable technique that will guarantee complete closure of the PDA without complications.[4]

2D echocardiography is an important diagnostic tool and is the mainstay for the diagnosis and evaluation prior to management. Cardiac catheterization is also used to revaluate the ductus prior to its percutaneous closure. With the recent introduction of 3D echocardiography with its unique ability to allow real time volumetric imaging and thus improving the accuracy of evaluating the cardiac chambers, the idea of using this unique capability in interrogating extra cardiac vascular structures like the PDA to optimize the management seems appealing[5].

AIM OF THE STUDY

To determine the feasibility, accuracy, and clinical applicability of real-time 3-dimensional echocardiography (RT3DE) in the evaluation of patent ductus arteriosus.

Chapter 1
Patent Ductus Arteriosus

The ductus arteriosus is a unique, dynamic vascular structure that functions as a prenatal bypass between pulmonary artery and aorta [(6)].

It accounts for about 5 to10% of congenital heart diseases (CHD). The prevalence of the patent ductus arteriosus (PDA) increases with increased maternal age and also is much more common in premature babies, and there is an association between the PDA and the neonatal respiratory distress syndrome. PDA is also more common in females with a ratio of 3:1[(5)].

The PDA usually closes after 48 hours in term infants and by 72 hours in 90% of infants> 30 weeks of gestation. However the anatomical obliteration of the ductus may not occur until several weeks after birth. It is unlikely for the ductus to close if it persisted beyond 1 year of age [(7)].

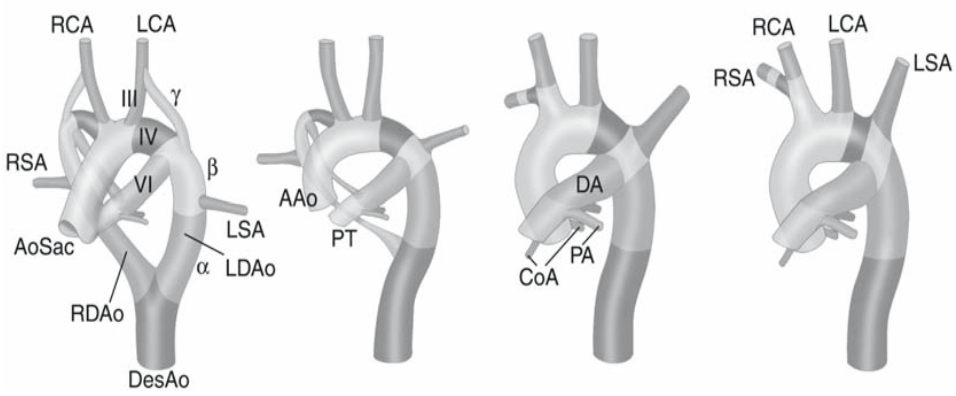
Embryogenesis:

The vascular system of the embryo starts from endothelial precursors forming an endothelial plexus in the splanchnic mesoderm. After folding of the embryo the endothelial plexus in the heart region becomes incorporated within the myocardium [(8)].

The omphalomesenteric vessels enter the heart at the

venous pole, while the arterial pole becomes connected to the dorsal aorta by the symmetric pharyngeal arch arteries. Pharyngeal arch patterning (Figure 1) is influenced by neural crest cells, smooth muscle cells and by the neural system surrounding the arches. The ductus arteriosus derives from the distal portion of the left sixth pharyngeal arch artery while the proximal portions of the sixth pair of embryonic aortic arches persist as the proximal branch pulmonary arteries [(6)].

During pharyngeal arch remodeling the ductus acquires a muscular vessel wall, whereas the surrounding great arteries become elastic arteries [(9)].



AAo = ascending aorta, AoSac = aortic sac, CoA = coronary arteries, DA =ductus arteriosus, DesAo = descending aorta, PA = pulmonary artery, PT = pulmonary trunk, LDAo = left descending aorta, LCA = left carotid artery, LSA = left subclavian artery, RCA = right carotid artery, RDAo = right descending aorta, RSA = right subclavian artery; III, IV, and VI refer to the branchial arches.

Figure (1): Pharyngeal arch patterning from branchial arches to mature arteries [(8)].

A number of teratogens are known to influence the development of the duct, including rubella, alcohol, amphetamines, and the anticonvulsant hydantoin, with the duct

being most sensitive from 18 to 60 days of gestation [10].

Anatomy of the ductus:

The ductus arteriosus connects the pulmonary artery to the descending thoracic aorta 2 to 10 mm from the aortic origin of the subclavian artery. It's 5 to 10 mm long and tends to be shorter in adults. The aortic orifice is wider and narrows en route to the pulmonary end [11].

The duct is related to the left main bronchus posteriorly, while anteriorly it is crossed by the vagus nerve. This gives off the left recurrent laryngeal nerve, which encircles the duct before ascending behind the aortic arch into the neck [12].

Microscopic structure of the ductus:

In terms of its microscopic structure, the duct is a muscular artery endowed with an intima, media and adventitia, differing markedly from the adjacent pulmonary trunk and aorta [13].

While the media of the aorta is composed mainly of circumferentially arranged elastic fibers, the media of the duct consists largely of spirally arranged smooth muscle cells, some with circular and others with longitudinal orientation, with an increased content of hyaluronic acid [14].

The intimal layers are thicker than those of the adjoining vessels, and contain increased amounts of mucoid substance [15].

In the newborn, the tissues are rather loosely arranged,

with a well-defined internal elastic lamina that may be single or focally duplicated, with small interruptions encountered regularly [15].

No collagen is seen in the media by light microscopy, but abundant material that stains positively for acid mucopolysaccharides is observed between the muscle and elastic laminas [16].

Electron microscopy reveals fine collagen fibrils lying between adjacent lamellas of smooth muscle cells and elastin [13].

It is known that vessels cannot close by isolated contraction of circularly arranged muscle, so coincident shortening of the less abundant longitudinally arranged muscle fibres is critical to ensure effective closure of the ductus arteriosus [14].

The duct is innervated mostly by adrenergic fibres, supplying largely the adventitia and outer media, with cholinergic fibres being extremely sparse or totally absent [15].

Vessels are also found in its walls that may have a role in fuelling contraction at birth. Some degree of hyperaemia of these vessels is common in newborn infants [15].

Eccentrically placed intimal cushions, or mounds composed of smooth muscle and elastic tissue, have been described by many authors, with suggestions made that the formation of these mounds precedes normal ductal closure at

birth [14,15].

Variation in duct morphology:

The ductus arteriosus may persist in a wide variety of sizes and configurations. The duct can also vary considerably in its shape.

Study of a large number of angiograms from patients with PDA undergoing interventional closure showed that the most frequent pattern was to find a constriction at the pulmonary end of the duct. This pattern was seen in two-thirds of cases. In just under one-fifth, a constriction was found at the aortic end of the duct, and in just under one-tenth, the lumen was unrestricted. In just under one twentieth, there was a constriction at both ends, whilst the remaining patients showed bizarre patterns not lending themselves to classification. Ducts could also become aneurysmal and elongated [17]. (Figure 2)

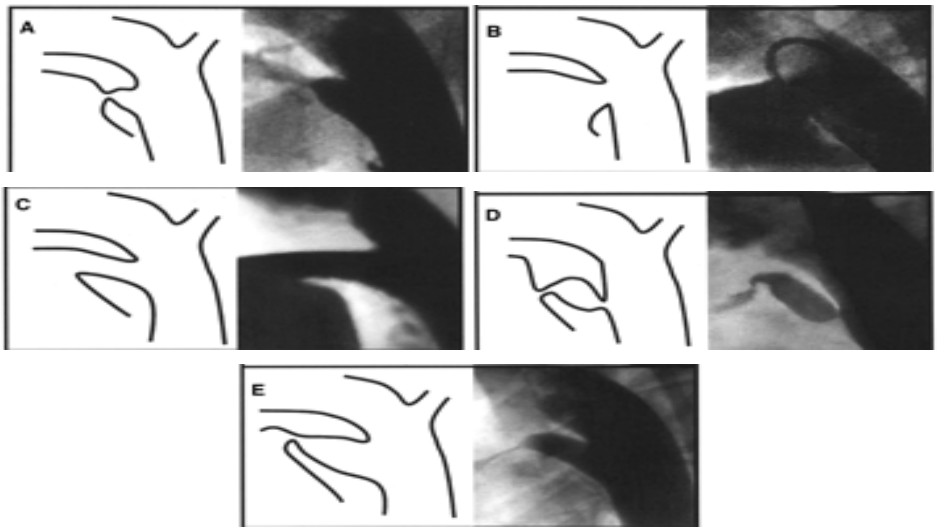


Figure (2): Variations in PDA configuration illustrated with the

classification of Krichenko et al. The configurations are sketched on the left, and examples of lateral angiograms for each type are on the right.

A, Type A ("conical") ductus, with well-defined aortic ampulla and constriction near the pulmonary artery end. B, Very large type ("window") ductus, with very short length. C, Type C ("tubular") ductus, which is without constrictions. D, Type D ("complex") ductus, which has multiple constrictions. E, Type E ("elongated") ductus, with the constriction remote from the anterior edge of the trachea [(17)].

Function of the fetal ductus:

During fetal life; direction of the blood flow through the ductus is from the pulmonary artery to the aorta, after birth and ventilation of the lungs the pulmonary vascular resistance (PVR) which was initially high in the fetal life will markedly drop and so if the ductus is to be persistent the flow will be from the high pressure aorta to the lower pressure pulmonary artery [(18)].

In fetal life the ductus is necessary to divert blood from the high resistance pulmonary vascular bed which receives 5 to 8% of the right ventricle (RV) blood so the ductus protects the RV from the high PVR of the fluid filled lungs if the ductus constricts this will cause RV failure and hydrops [(19)].

Factors maintaining the ductus patent in utero:

Patency is maintained by the relatively low fetal oxygen tension and cyclooxygenase-mediated products of arachidonic acid metabolism, primarily prostaglandin [PGE_2] and

prostacyclin[PGI_2].[14] Produced both locally, in ductal tissue, and circulating, these mediators cause vasodilation through interaction with prostanoid receptors [20,21].

Ductal maturation and closure:

Significant structural changes of the vascular morphology preparing the ductus for postnatal closure start in late gestation. [9,22] With further development intimal cushions appear. At term the internal elastic lamina has become fragmented and the intimal cushions are pronounced. Intimal thickening together with oxygen-dependent constriction functionally closes the ductus during the first hours after birth [22,23]. Levels of prostaglandin and prostacyclin fall because of metabolism in the functioning lungs, and elimination of the placenta [24,16].

Anatomical obliteration follows functional closure. The process begins with necrosis of the inner wall, followed by the formation of dense fibrous tissue [24]. Eventually, the duct becomes converted into a fibrous strand, the arterial ligament, which may become calcified. Anatomical obliteration may take several weeks to complete [24,25].

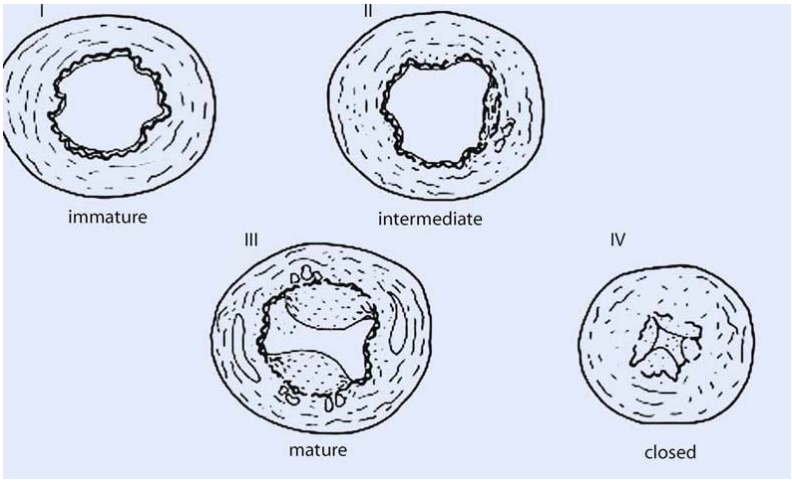


Figure (3): Ductal maturation stages [25,26].

Etiology of patent ductus arteriosus:

PDA may be idiopathic, it is more common in premature infants, infants of diabetic mothers, infants of mothers who drink alcohol and as in most CHD chromosomal abnormalities especially trisomy 21 causes PDA. Maternal use of phenytoin and amphetamines is also associated with increased incidence of PDA [21].

Genetic Factors:

PDA occurs with increased frequency in several genetic syndromes, including those with defined chromosomal aberrations (such as trisomy 21 and 4p– syndrome), single-gene mutations (such as Carpenter's syndrome and Holt-Oram syndrome), and X-linked mutations (such as incontinentia pigmenti) [27].

The genetic mechanism of patent ductus in some patients may be autosomal recessive inheritance with incomplete penetrance [28].

Genetic studies suggest that the abnormalities in Char syndrome (an inherited disorder with PDA, facial dimorphism, and hand anomalies) result from derangement of neural crest cell derivatives [29].

Pathophyisology of patent ductus arteriosus:

There are two main factors controlling the hemodynamics in a patient with PDA:

a. Shunt volume and size of the PDA

b. Pulmonary vascular resistance

In cases of pulmonary hypertension due to PDA, two categories of patients exist: [30]

The first are infants where the physiological drop of pulmonary artery pressure never occurred (persistence of the fetal hemodynamic pattern). The second is the one where, after a period of relatively normal pressure, a progressive pulmonary hypertension supervenes.

In patients with a large PDA, the aorta and pulmonary artery are essentially in free communication; the systolic pressure in the pulmonary artery is equal to that in the aorta. Left ventricular volume overload results from recirculation through the lungs, with pulmonary congestion resulting from increased pulmonary flow and/or left ventricular failure [30,31].

As with all left-to-right shunts, with PDA three major, interrelated factors control the magnitude of shunting: The diameter and length of the ductus arteriosus, which governs the resistance offered to flow; the pressure difference between the aorta and the pulmonary artery; and the systemic and pulmonary vascular resistances [31].

Clinical picture:

Persistent Patency in full Term Infants:

Unlike the ductus arteriosus in premature infants, in whom failure of closure is due to physiologic developmental retardation, the ductus arteriosus in full-term infants is abnormal, and failure to constrict is probably related to a significant structural abnormality [32-36].

Manifestations:

In mature infants and older children, the factors determining the clinical features are the same as in premature infants, namely, the size of the communication, the relationship between pulmonary and systemic vascular resistances, and the ability of the myocardium to handle the extra volume load [33,37].

Small Ductus Arteriosus:

With a small communication, PVR and therefore pulmonary arterial pressure normally decrease after birth. However, because the resistance to flow across the ductus arteriosus is high, only a small left-to-right shunt develops.

Pulmonary blood flow is increased only minimally, and left ventricular failure does not occur. Precordial activity usually is normal with no increased apical impulse [(34)].

The only significant abnormal auscultatory finding may be the presence of a murmur. The important features of the characteristic continuous murmur are the late systolic accentuation and continuation through the second sound into diastole [(37)].

Moderate Ductus Arteriosus:

In infants, a moderate left-to-right shunt may produce symptoms related to left ventricular failure. Poor feeding, irritability, and tachypnea may be present, and weight gain is often slow. The systemic arterial pressure is widened with a low diastolic pressure. The precordium is hyperdynamic, and left ventricular enlargement produces a thrusting apical impulse. Both the first and second sounds may be difficult to hear, because they often are masked by a loud murmur. The continuous murmur is more intense, has more extensive radiation, and generally is well heard posteriorly [(37)].

Large Ductus Arteriosus:

Infants with a large PDA are invariably symptomatic. They are irritable, feed poorly, fail to gain weight normally, tire easily" particularly while feeding" and sweat excessively. They have increased respiratory effort and respiratory rates, also aggravated by feeding, and are prone to develop recurrent upper

respiratory infections and pneumonia [24].

Many of the typical physical signs may be absent when there is severe left ventricular failure. However, tachycardia and tachypnea are present, and if there is pulmonary edema, rales will be heard throughout the lung fields [33].

The peripheral pulses are bounding with a rapid upstroke and a wide pulse pressure unless there is severe left ventricular failure when the pulse volume decreases [33].

The precordium is markedly hyperdynamic, and clinical evidence of cardiac enlargement is present. A systolic thrill is often palpable.

The first and second heart sounds are accentuated, and a third sound ordinarily is heard at the apex [37].

Cyanosis, often more pronounced in the lower than in the upper limbs, begins to appear, initially only with exertion, but eventually becoming continuous as persistent right-to-left shunting across the ductus arteriosus occurs [34].

Table (1): The clinical picture of PDA can also be divided into 4 grades according to the progression of pulmonary hypertension and the degree of shunting: [30]