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Effect of patent ductus arteriosus on the heart in preterm infants

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Abstract

There continues to be controversy on the long-term effects of a patent ductus arteriosus (PDA) and its management. However, the hemodynamic effects of a large PDA in a preterm infant are well known. This article aims to provide insight into the adaptive changes and remodeling effects of a PDA on the myocardium in preterm infants.

KEYWORDS

congestive heart failure, neonatology, patent ductus arteriosus, pediatrics, preterm infant, surgical ligation, transcatheter device closure

1 | INTRODUCTION

An isolated patent ductus arteriosus (PDA) accounts for 5%-10% of all congenital heart diseases, affecting about 1 in 2000-5000 full-term live infants.[1] The incidence of PDA is inversely related to birth weight and gestational age. The ductus arteriosus remains open at a week of life in 65% of preterm infants born between 25 and 28 weeks of gestation and 87% of preterm infants born at less than 24 weeks of gestation.[2] The incidence is also higher in infants with various genetic syndromes including chromosomal abnormalities and single gene mutations.[3] The effect of a hemodynamically significant PDA on the heart is varied between preterm and term infants. Though there continues to be controversy on the significance of a PDA in long-term outcomes as well as in its management,[4] the hemodynamic effects are well documented. Not only is the magnitude of the shunt important but the duration of left-to-right shunting plays an important role in its effect on the heart.[5] Preterm infants experience sustained volume overload until ductal closure occurs. Due to the biomechanical stress from this volume overload, there are structural changes that occur in the preterm left ventricular myocardium.

2 | GENETICS

A better understanding of the possible genetic factors contributing to a PDA may help in devising specific strategies to treat the PDA and its effects on the heart. An autosomal dominant form of PDA resulting in distinctive facial features and hand abnormalities, Char syndrome ("heart-hand" syndrome), was reported in 2000 and is caused by mutations in the *TFAP2B* gene.[6] Some patients with this mutation have shown a high prevalence of PDA with mild facial abnormalities but no skeletal abnormalities of the hand, while others have had a PDA and a sleep disorder or only an isolated PDA. *PRDM6* functions as a transcriptional repressor of myocardin, GATA-6, and smooth muscle cell actin and myosins. These proteins are important for vascular smooth muscle cell (VSMC) differentiation and their development of contractile phenotypes. *PRDM6* mutations lead to *PRDM6* loss of function and result in early differentiation of VSMCs and their reduced proliferation. A rapid decline of *PRDM6* in the normal ductus arteriosus suggests that VSMC differentiation occurs in later developmental stages to promote contraction.[7] Sufficient *PRDM6* is necessary for the proliferation of these cells. Tfap2b—the Murine ortholog of *TFAP2B*—also results in impaired development of

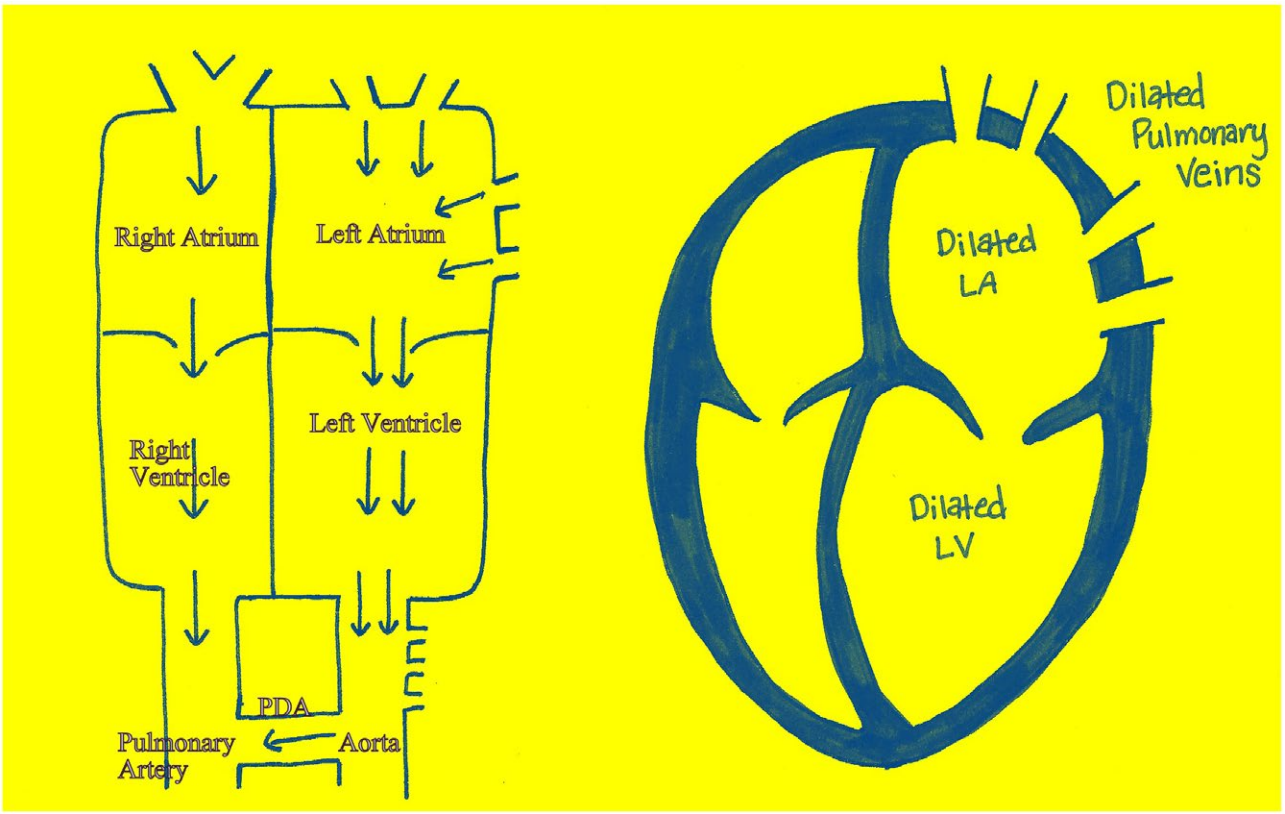

FIGURE 1 Left, Line diagram showing increased volume overload in the left atrium and ventricle. Right, Apical 4-chamber illustration showing the dilation of the pulmonary veins and the left atrium and ventricle. The left heart remodels to a larger and more spherical shape. Abbreviations: LA = left atrium; LV, left ventricle

the VSMC layer and patency of the ductus arteriosus in mice. PDA has been reported in a few subjects with thoracic aortic aneurysm and rare genetic variations in the myosin and actin encoding genes *MYH11* and *ACTA2*. Structural analyses of the aorta in these affected individuals have revealed large areas of medial degeneration with very low VSMC content.

3 | PHYSIOLOGY

The clinical importance of a large left-to-right shunt PDA is the effect over time of high-pressure systemic to pulmonary blood flow. The magnitude of left-to-right shunting in a large PDA is determined by the relationship between systemic and pulmonary vascular resistance (PVR). When the ductus arteriosus is large, the pressure differences between the aorta and the pulmonary artery remain the same after birth. Based on Ohm's law (pressure = flow × resistance), an increase in resistance through a vascular bed results in a decrease in blood flow through that bed and vice versa. Therefore, the magnitude of left-to-right shunt increases as the PVR physiologically decreases with time. However, the presence of a large systemic to pulmonary communication may retard the normal maturation of pulmonary vessels after birth due to pulmonary engorgement and decreased pulmonary compliance which is more prevalent in preterm infants.[8] Hence, the decrease in PVR may be prolonged over several weeks. The course of blood flow through systole and diastole in a typical PDA with pulmonary over-circulation is as follows: PDA, pulmonary arteries, pulmonary capillaries, pulmonary veins, left atrium, left ventricle, aorta, and PDA (Figure 1). A large left-to-right shunt through a PDA results in left atrial and left ventricular enlargement. The pulmonary veins and ascending aorta can also be dilated with a sufficiently large PDA. The left ventricular end-diastolic pressure increases as well as left atrial and pulmonary venous pressures. Whether an infant with a large PDA develops heart failure depends not only on the decrease in PVR but also on the ability of the left ventricle to handle the increased volume overload.[8]

4 | EFFECT ON THE HEART

4.1 | Remodeling of the left ventricle

The left heart remodels to a larger and more spherical shape and thus significantly increases in volume with both left atrial and left ventricular dilation (Figure 1). Most changes occur and peak in the first 4 weeks of volume overload, then plateau and return to the normal size, and shape over a 10-week course.[9] The wall thickness increases after 4 weeks of increased volume exposure. The myocardium will tolerate left ventricular overload

without failing at older gestations and further on from the time since birth.

4.2 | Development of left ventricular hypertrophy

Not all hemodynamically significant PDAs will cause left ventricular hypertrophy. If the PVR declines precipitously after birth, there will be rapid volume overload on the ventricle leading to failure with an inadequate time frame for the development of hypertrophy. In other words, when there is a more gradual regression of the changes in PVR after birth, it may provide the time and opportunity for adequate hypertrophy to occur to allow the left ventricle to handle the load.[8]

4.3 | Preservation of cardiac function

Recent studies by Waal et al have confirmed previous findings that the increased preload in infants with a PDA is followed by an increase in stroke volume, indicating that the Frank-Starlings mechanics are intact.[9] The left ventricular filling pressure is thought to be higher due to a less compliant preterm heart with the inability of altering its diastolic properties early in gestation.[10] The cardiac function is preserved predominantly by increasing the ejection fraction and base to apex wall shortening. Studies using rate-corrected velocity of fiber shortening and wall stress at peak systole have shown that the left ventricular contractility does not change.[11]

There are 2 mechanisms that have been postulated for the ability of the left ventricle to manage the increased preload without increasing contractility in preterm infants with a large PDA. The first mechanism is by lowering the afterload. In preterm infants with a PDA, the arterial blood pressure and effective arterial elastance are lower, but the ventricular elastance is unchanged.[9] This leads to the decoupling of the ventricular and arterial systems. In aging hypertensive populations, it is known that when there is an increased arterial elastance and a decrease in ventricular elastance (ie, decoupling of the ventricular and arterial systems with increased ventriculo-arterial coupling), there is decreased energy efficiency.[12] Infants with a PDA have decoupling with reduced ventriculo-arterial coupling with no changes in left ventricular stiffness. Hence, the PDA itself may be serving as an adaptation when the heart is incapable of increasing the contractility to maintain function.[9] The second mechanism in managing the preload without increasing the contractility is possibly related to the patent foramen ovale (PFO) which is present in most preterm infants.[13] Due to elevated left ventricular filling pressures, there is more left-to-right shunting at the PFO which leads to increased right ventricular output.[14]

4.4 | Other factors determining cardiac function

1. **Coronary blood flow:** The adequacy of coronary blood flow may be a factor in determining the ability of the left ventricle to provide cardiac output in the presence of a large PDA. Coronary blood flow is dependent on the perfusion pressure which is the difference between the aortic diastolic pressure and the diastolic pressure in the ventricle. Since the intramyocardial pressure is as high as the aortic pressure in the systole, coronary blood flow occurs predominantly during diastole. With a large PDA in a neonate, the aortic diastolic pressure is reduced and the left ventricular diastolic pressure is increased and hence there is a marked reduction in the perfusion pressure. In addition to the perfusion pressure being decreased, the faster heart rates and mild prolongation of left ventricular systolic ejection time decrease the overall duration of the diastole and consequently decrease coronary blood flow.[8] This decrease in coronary blood flow in the presence of a significant left-to-right shunt which increases ventricular work may decrease the oxygen delivery to the sub-endocardial region of the myocardium as evidenced by an electrocardiogram, demonstrating ST segment depression and T-wave flattening/inversion in the precordial leads.
2. **Hemoglobin level:** The physiologic nadir/drop in hemoglobin occurs around 2 months of age. A large hemodynamically significant PDA has increased oxygen requirements due to the increased ventricular work from the persistent left-to-right shunting and ineffective pulmonary blood flow. The drop in the hemoglobin level further accentuates the reduction of oxygen supply to the myocardium. The tissue oxygen requirements of the body also increase when the hemoglobin levels are low and this puts an additional strain on the left ventricle to provide more systemic blood flow.
3. **Pulmonary vascular resistance**: High PVR may prevent the early development of left ventricular failure or may decrease its severity initially. Factors that maintain a high PVR after birth such as high altitude and lung disease in prematurity are noted to have a lower incidence of heart failure. More importantly, when the lung disease has been treated, the precipitous decrease in PVR may lead to the development of left-sided heart failure. Over time, an infant with a large PDA with high pressure, high volume left-to-right shunting that survives cardiac failure will eventually show improvement in heart failure manifestations due to the development of increasing PVR and hence a decrease in the left-to-right shunt. Thus, if left untreated, a large PDA may lead to irreversible pulmonary vascular obstructive disease (Eisenmenger syndrome) by 2–3 years of age.[8]

5 | CONCLUSIONS

A large PDA in a preterm infant effects noteworthy remodeling of the preterm left ventricle. These changes occur early unless the PVR is significantly elevated in the neonatal period. Most changes peak in the first 4 weeks of volume overload, then plateau and return to the normal size, and shape over a 10-week course. Wall thickness increases after 4 weeks of increased volume exposure. Though these changes in shape and size are considered adaptive, a prolonged duration and an increased magnitude of left-to-right shunting from a PDA can compromise the oxygen delivery to the myocardium. These factors must be taken into consideration

during decision making for PDA closure and one must be aware that mere left ventricular dilation is not the only effect of the PDA on the myocardium.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

All listed authors fulfilled the authorship criteria: (1) substantial contributions to the research design, or the acquisition, analysis, or interpretation of the data; (2) drafting the paper or revising it critically; and (3) approval of the submitted and final versions.

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