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PERSISTENT FETAL CIRCULATION: ROLE OF THE PATENTUS DUCTUS ARTERIOSUS (REVIEW)

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Abstract. The article examines the pathophysiological aspects of the patent ductus arteriosus in newborns, with an emphasis on its role in the development of persistent fetal circulation. The patentus ductus arteriosus (PDA), which is a shunt between the left pulmonary artery and the descending aorta, is a normal component of fetal circulation, but its persistence after birth can lead to serious hemodynamic disorders and delayed postnatal development. The first breath and an increase in oxygen levels in the blood initiate the closure of the duct, however, in premature infants this process may be disrupted, which leads to the development of a right-angle shunt and overload of pulmonary circulation. The article emphasizes the importance of early diagnosis and monitoring of this condition in premature infants, due to which more effective treatment can be provided to improve the outcomes and quality of life of patients. Analysis of the pathogenetic mechanisms associated with PDA and individual correction of therapy are key aspects in reducing the risk of complications and improving the survival of newborns with this pathology.

Keywords: patent ductus arteriosus, anatomy, pathological physiology, fetal communications

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ПЕРСИСТИРУЮЩЕЕ ФЕТАЛЬНОЕ КРОВООБРАЩЕНИЕ: РОЛЬ ОТКРЫТОГО АРТЕРИАЛЬНОГО ПРОТОКА (ОБЗОР)

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Резюме. В статье рассматриваются патофизиологические аспекты открытого артериального протока у новорожденных, с акцентом на его роль в развитии персистирующего фетального кровообращения. Открытый артериальный проток (ОАП), представляющий собой шунт между левой легочной артерией и нисходящей аортой, является нормальной составляющей фетального кровообращения, однако его персистенция после рождения может приводить к серьезным гемодинамическим нарушениям и задержке постнатального развития. Первый вдох и повышение уровня кислорода в крови инициируют закрытие протока, однако у недоношенных детей данный процесс может нарушаться, что ведет к развитию право-левого шунта и перегрузке легочного кровообращения. Статья подчеркивает важность ранней диагностики и мониторинга данного состояния у недоношенных, за счет чего можно обеспечить более эффективное лечение, позволяющее улучшить исходы и качество жизни пациентов. Анализ патогенетических механизмов, связанных с ОАП, и индивидуальная коррекция терапии являются ключевыми аспектами в снижении риска осложнений и улучшении выживаемости новорожденных с данной патологией.

Ключевые слова: открытый артериальный проток, анатомия, патологическая физиология, фетальные коммуникации

INTRODUCTION

Patent ductus arteriosus (PDA) is a connection between the left pulmonary artery and the descending aorta, located distal to the left subclavian artery, during the postnatal period [1, 2, 5, 13–15, 22, 26, 29].

Normally, in full-term neonates, the patent ductus arteriosus closes in 90% of cases within 48 hours and in 100% within 96 hours of life [2]. Structural and physiological immaturity of the ductus in pre-term neonates leads to its persistence.

Functioning of ductus arteriosus in postnatal period is inversely proportional to gestational age of premature neonate.

During the process of the cardiovascular system formation, six embryonic arches undergo changes during the first eight weeks of intrauterine development (Fig. 1). As the result, connections between the pulmonary artery and the descending aorta appear (Fig. 2) [3]. Proximal parts of these arches form pulmonary arteries, and the distal left arch becomes the ductus arteriosus.

Patent ductus arteriosus can vary in shape, size, and spatial relationship to adjacent structures, representing an important anatomical characteristic (Fig. 3). Currently, a number of classifications of PDA is created — from the first by J.P. Hubbard to the most frequently used angiographic (by A. Krichenko), and the modern one, described in the clinical guidelines of the Russian Ministry of Health [5]. The diversity of duct anatomy contributes to the understanding of the pathophysiological features of its clinical manifestations.

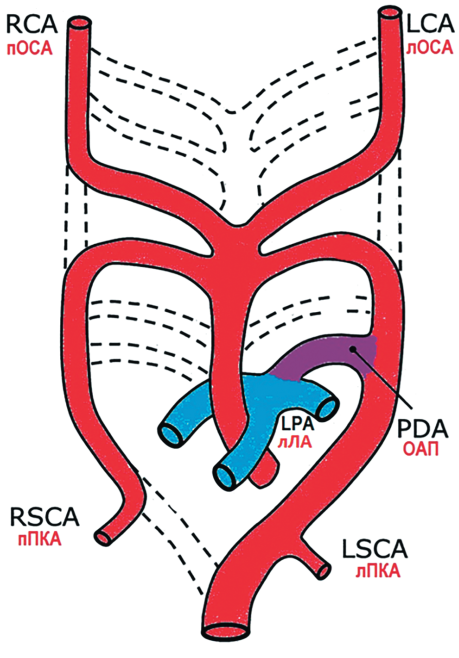

Fig. 1. **The distal left sixth embryonic arch normally persists and becomes the PDA, bridging the left pulmonary artery to the descending aorta. LPA — left pulmonary artery; LCA — left carotid artery; LSCA — left subclavian artery; PDA — patent ductus arteriosus; RCA — right carotid artery; RSCA — right subclavian artery [2]**

Рис. 1. **Дистальная левая шестая эмбриональная дуга в норме сохраняется и становится ОАП, соединяя левую легочную артерию с нисходящей аортой. лЛА — левая легочная артерия; лОСА — левая общая сонная артерия; лПКА — левая подключичная артерия; ОАП — открытый артериальный проток; пОСА — правая общая сонная артерия; пПКА — правая подключичная артерия [2]**

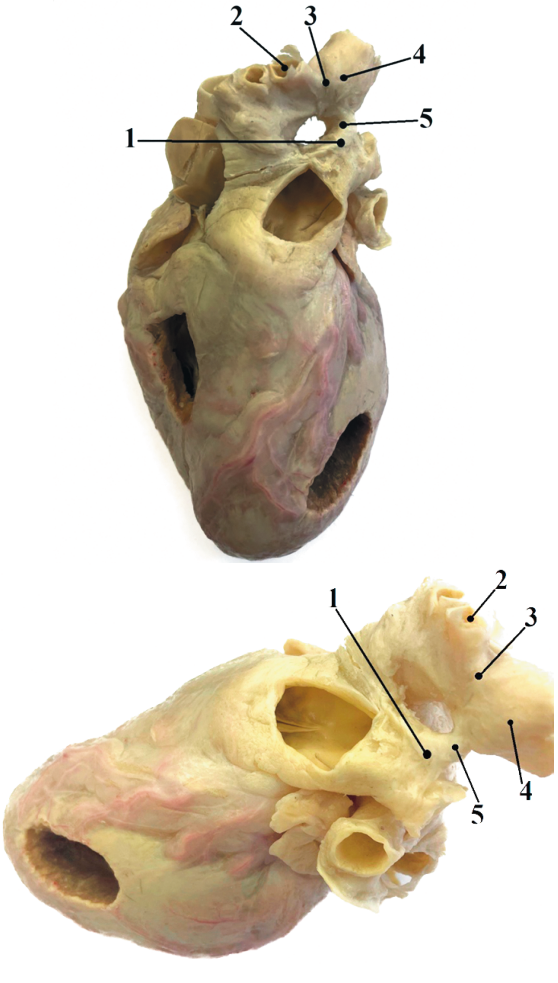

Fig. 2. **Natural heart preparation made by polymer embalming with preserved open ductus arteriosus: 1 — left pulmonary artery; 2 — left subclavian artery; 3 — isthmus of the aorta; 4 — descending aorta; 5 — patentus ductus arteriosus. The heart preparation was made by Professor I.V. Gaivoronsky**

Рис. 2. **Натуральный препарат сердца, изготовленный методом полимерного бальзамирования с сохраненным открытым артериальным протоком: 1 — левая легочная артерия; 2 — левая подключичная артерия; 3 — перешеек аорты; 4 — нисходящая аорта; 5 — открытый артериальный проток. Препарат сердца изготовлен профессором И.В. Гайворонским**

MORPHOFUNCTIONAL CHARACTERISTICS OF PATENT DUCTUS ARTERIOSUS CLOSURE

By the end of the first day of life, a healthy newborn has established both circulatory systems functioning: the pulmonary (lesser) and the systemic (greater) circulation. The functioning of the pulmonary circulation is determined by the low resistance of the pulmonary vessels against the background of increased synthesis of endogenous vasodilators (nitric oxide, prostacyclin), triggered by an increase in the oxygen content in the blood, rhythmic expansion of the lungs during breathing and tactile stimulation [6]. The establishment of normal lung volume, adequate alveolar ventilation-perfusion matching, and timely clearance of fetal lung fluid collectively promote physiological reduction in pulmonary vascular resistance, thereby enhancing pulmonary circulation function.

Persisting fetal circulation is a reversible pathology leading to right-to-left shunting of blood through the patent ductus arteriosus and/or foramen ovale, i.e. in the most general terms, the newborn retains signs of fetal circulation, which is manifested in a delay in normal postnatal development. If the pulmonary circulation, which has just started functioning, is overloaded from birth (excess fluid, prematurity, infections, etc.), then there is a risk of developing a persistent left-right shunt — a functioning patent ductus arteriosus (FPDA).

A number of authors claim that normally the duct closes immediately after birth and associates this with the newborn's first breath. It is believed that the trigger for closure is most likely the influx of oxygen (O_2) into the tissue. However, the exact mechanism of ductal obliteration remains unclear. Several Japanese researchers have reported in their studies [7] the presence of ATP-sensitive and voltage-gated potassium channels that function as oxygen sensors in ductal

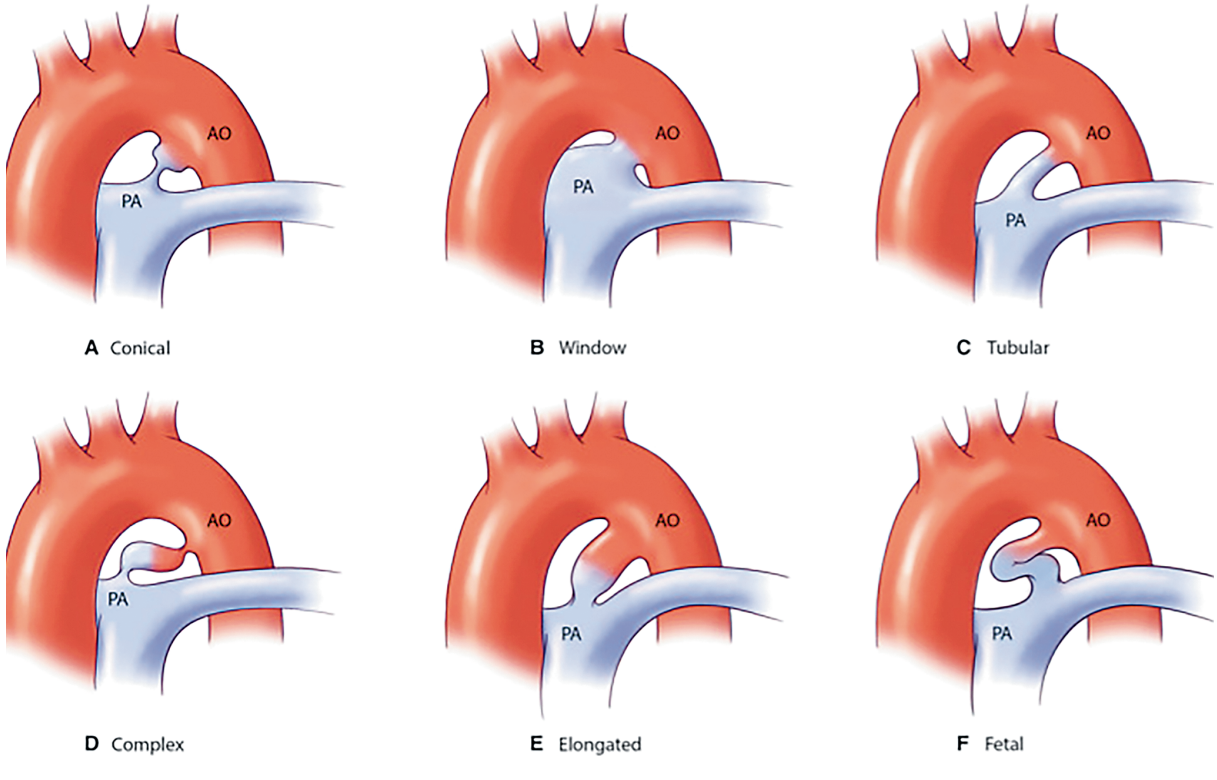

Fig. 3. **Configuration of patentus ductus arteriosus: type A ("conical") ductus, with defined aortic ampulla and constriction near the pulmonary artery (PA) end; type B ("window") ductus, with short length and constriction at the aortic end (wide PA end); type C ("tubular") ductus, without constrictions at the aortic or pulmonary ends; type D ("saccular") ductus, with constricted aortic and pulmonary ends and a wide center; type E ("elongated") ductus, which is narrow with a constricted pulmonary end; and type F ("fetal") ductus, which is found largely in premature infants and is long, wide, and tortuous. AO — aorta [4]**

Рис. 3. **Форма открытого артериального протока: проток типа A («конусообразный») с четко выраженной ампулой аорты и сужением вблизи конца легочной артерии (ПА); проток типа B («окно») с короткой длиной и сужением на конце аорты (широкий ПА); проток типа C («трубчатый»), без сужений на аортальном или легочном концах; проток типа D («мешковидный») с суженными аортальным и легочным концами и широким центром; проток типа E («удлиненный»), который является узким с суженным легочным концом; и проток типа F («фетальный»), который встречается в основном у недоношенных детей и является длинным, широким и извилистым. AO — аорта [4]**

tissue (based on *in vitro* [8] and *in vivo* [9] experiments). The closure of these channels triggers ductal spasm and subsequent PDA obliteration [9, 10].

Mutations in genes encoding ATP-sensitive potassium channels (ATPC), potassium inwardly-rectifying channels (KCNJ8), ATP-binding cassette (ABCC9), which encode a vascular-specific subtype of ATPC — $K_{ir}6.1$ (integral membrane protein and inward-rectifying potassium channel)/SUR_2B (sulfonylurea receptor 2), are found in patients with Cantu syndrome. This syndrome, in turn, is associated with a hemodynamically significant patent ductus arteriosus [11].

It is known that with this combination of pathologies, hemodynamically significant PDA does not respond to treatment with non-steroidal anti-inflammatory drugs, in particular indomethacin, and requires surgical correction.

Prostaglandin E, along with oxygen, plays an important role in the functioning of PDA during the intrauterine period and its closure in early postnatal period. Serum Prostaglandin E concentration decreases after birth [11]. U. Yokoyama et al. demonstrated that, during the prenatal (intrauterine) period, Prostaglandin E and its receptor EP_4 promote the neointima formation in the ductus arteriosus area and inhibits formation of elastic fibers (elastogenesis), preparing the process of duct closure after birth [12].

Patent ductus arteriosus is a key structure of fetal circulation. Its functioning is often observed in extremely premature infants and is accompanied by significant disturbacnes in central and regional hemodynamics [13–15]. PDA in preterm newborns is of particular importance and often influences their survival. At the same time, prematurity is an independent global problem in both healthcare and economics. According to Russian authors, only 24% of extremely preterm infants with birth weights below 1,000 grams demonstrated normal development on follow-up [16, 17]. Their health is influenced not only by prematurity, but also by the intensive care provided [18–20].

In newborns with very low and extremely low birth weight, impaired closure of the ductus arteriosus are frequently observed, resulting from multiple contributing factors [21–24]. The primary factors are believed to be immature ductal tissue and elevated circulating prostaglandin levels [25, 26].

When diagnosing a patent ductus arteriosus in full-term neonates, several contributing factors have been identified: chronic fetal hypoxia, structural abnormalities in the ductal wall, impaired oxygen-induced vasoconstriction, prostaglandin (PG) system dysregulation, intrauterine growth restriction, maternal use of NSAIDs (ibuprofen or indomethacin) which act as PGE_2 antagonists [26].

The basis for the development of all pathophysiological processes in PDA is a left-to-right shunt of blood from the aorta to the pulmonary artery, which is primarily due to low pulmonary arteriolar resistance [26, 27].

Until recently, fetal communication, which was vital for the fetus, becomes a serious problem for the newborn, in the absence of other pathologies. The presence of a left-right shunt (which can reach a volume of 40–70% of the minute blood volume of the left ventricle) [28] in the first hours and days of life leads to an increase in the volume of circulating blood in the pulmonary circulation and volume overload of the left ventricle [26]. The nature and severity of hemodynamic changes depend on the size of the ductus, total pulmonary vascular resistance, and the duration of pathological left-to-right shunting. This process leads to pulmonary hypertension. Without treatment, this condition progresses to shunt reversal, resulting in right-to-left flow.

The issue of PDA functioning in preterm neonates has been highlighted by a number of international and domestic researchers and represents a separate disease category. This is primarily due to pathophysiological features of the PDA course. A sharp decrease in pulmonary vascular resistance during several days (particularly when using surfactant) differs from that in full-term neonates, in whom total pulmonary vascular resistance (TPR) decreases more slowly [29].

All these features, in pre-term newborns with functional PDA, lead to the onset of clinical signs within the first days of life. High blood pressure, increased pulmonary blood flow, increased permeability of the capillary wall, and pathological changes in metabolism in premature infants contribute significantly to vascular leakage and, consequently, to accumulation of fluid in the lungs [30].

Changes in lungs and pulmonary vessels determine the occurrence of pulmonary hypertension in the pulmonary circulation (PC). To a greater extent, they are associated with arterial blood flow into the venous bed and overflow of the vessels of the pulmonary artery system, which leads to functional and morphological changes. The first stage, which occurs before structural changes, is a stage of functional changes. It is presented as spasm of arterioles. The occurrence of this process, as already mentioned above, is associated with the overflow of blood into the pulmonary artery, as well as increased pressure on the walls of the vessels, irritation of the neuroreceptor apparatus of the latter and generalized spasm of the arterioles.

According to F.Ya.Kitaev (1931), N.B. Slonim et al. (1954) [34, 35], W. Whitaker et al. (1956) [36, 37], spasm of arterioles is the protective barrier that prevents lung capillaries from becoming overfilled with blood. In modern medical practice, these pathological processes can be controlled with ganglionic blockers and sympatholytics. However, without treatment and control, pathological processes rapidly

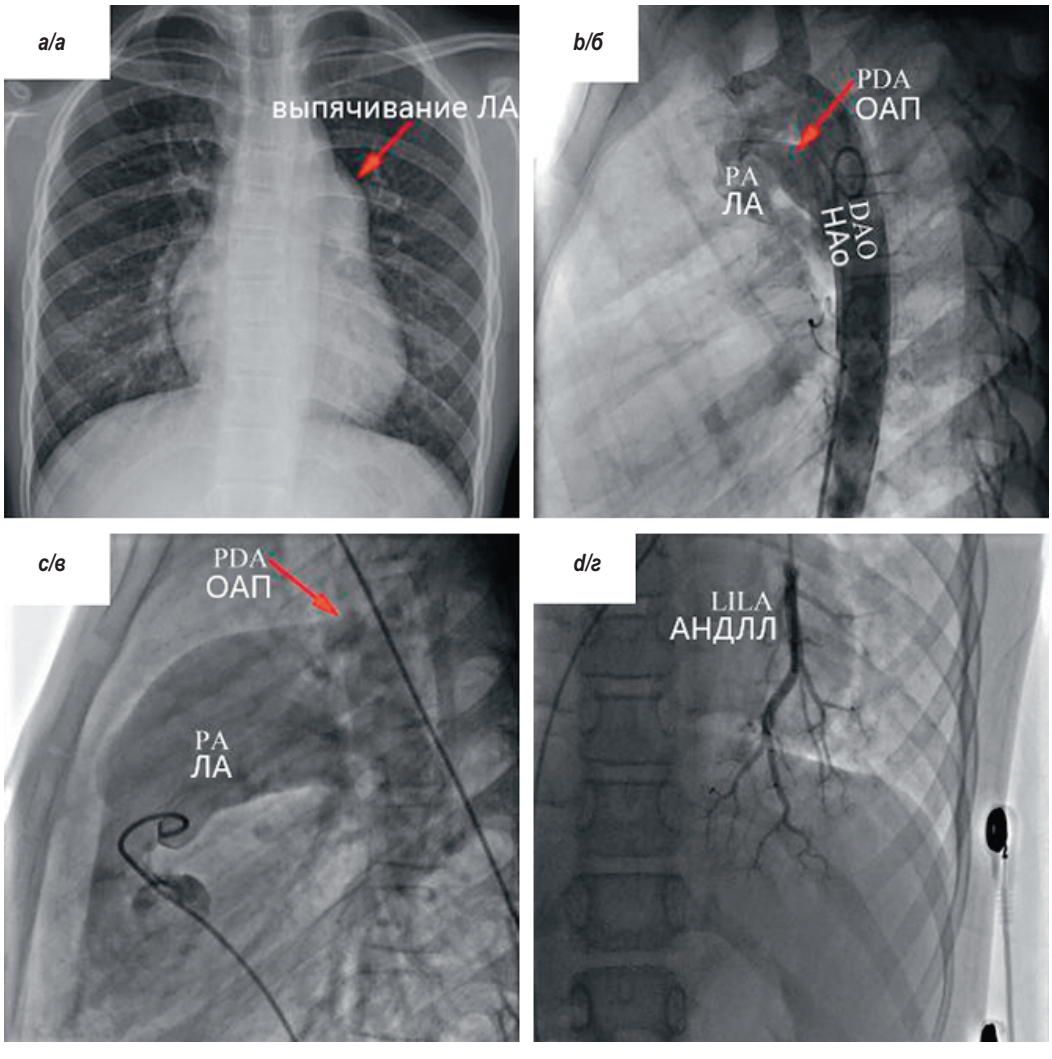

Fig. 4. **A clinical case of pulmonary hypertension in combination with an open ductus arteriosus: *a* — on chest X–ray, an arrow indicates a bulge of the pulmonary artery at the upper left border of the heart (cardiac shadow); *b* — Descending aortography revealed a large PDA; *c* and *d* — pulmonary arteriography showed a large PDA and decreased pulmonary capillary filling. LILA — left inferior lobe artery; PA — pulmonary artery; DAO — descending aorta; PDA — patent ductus arteriosus [31]**

Рис. 4. **Клинический случай легочной гипертензии в сочетании с открытым артериальным протоком: *а* — на рентгенографии органов грудной клетки стрелкой указано выбухание легочной артерии у верхней левой границы сердца (сердечной тени); *б* — на аортографии выявлен больших размеров ОАП; *в* и *г* — на легочной артериографии виден больших размеров ОАП в сочетании со сниженным наполнением легочных капилляров. АНДЛЛ — артерия нижней доли левого легкого; ЛА — легочная артерия; НАо — нисходящая аорта; ОАП — открытый артериальный проток [31]**

progress to structural changes in lung tissue and vasculature — Eisenmenger syndrome (Fig. 4) [38–41].

CONCLUSION

A functioning patent ductus arteriosus in a premature and full-term newborn contributes to the development of the above complications and significantly, under certain conditions, worsens the quality of life of a newborn, up to the development of a fatal outcome. Diagnosis and determination of the significance of structural and hemodynamic disorders in a child determines the doctor's attitude to the choice of the most life-saving treatment methods.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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