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Children's heart and prematurity: a current view of the problem

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ABSTRACT

Improved survival of children born with low, extremely low and very low body weight in modern conditions due to increased nursing capabilities, optimization of treatment and increased efficiency of resuscitation measures has led to the need for greater understanding of the importance of assessing the cardiovascular system's state beyond the neonatal period. With approximately 10% of infants worldwide being born preterm, there is an increasing need for further research into optimal regimens, lifestyle and clinical interventions that can benefit and modify cardiovascular morphology and function in this growing population. Modern theoretical postulates on the physiology and pathophysiology of the child's heart include ideas about the key process of cardiac biomechanics — diastole, during which the earliest disturbances, that precede the formation of systolic dysfunction, occur. Assessment of the pumping properties of the left ventricle in systole and diastole is a fundamental methodological technique for an in-depth understanding of the pathophysiological mechanisms of cardiovascular system's emerging diseases, their early diagnosis and assessment of the complex therapy's effectiveness. However, despite the widespread use of standard echocardiography to assess systolic and diastolic function, its traditional parameters have limitations in terms of diagnostic accuracy and effectiveness in practice. Expanding knowledge about new pathogenetic mechanisms of the cardiac dysfunction formation in conditions of prematurity at the current stage of cardiology development using the "trace spot" technology (two-dimensional speckle tracking echocardiography) will be very useful for scientists studying the mechanics formation of the child's heart after premature birth, and for doctors of various specialties in early diagnosis of heart diseases.

Keywords: prematurity; child's heart; left ventricular mechanics; diastolic dysfunction.

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Детское сердце и недоношенность: актуальный взгляд на проблему

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АННОТАЦИЯ

Улучшение выживаемости детей, рождённых с низкой, экстремально низкой и очень низкой массой тела, в современных условиях вследствие повышения возможностей выхаживания, оптимизации лечения и повышения эффективности реанимационных мероприятий привело к необходимости большего понимания важности оценки состояния сердечно-сосудистой системы за пределами неонатального периода. Около 10% детей во всём мире рождаются недоношенными, следовательно, возрастает необходимость дальнейших исследований оптимальных режимов, образа жизни и клинических мероприятий, которые могут благотворно влиять и изменять морфологию и функционирование сердечно-сосудистой системы в этой растущей популяции. К современным теоретическим постулатам по физиологии и патофизиологии детского сердца относятся представления о ключевом процессе биомеханики сердца — диастоле, в ходе которой происходят наиболее ранние нарушения, предшествующие формированию систолической дисфункции. Оценка насосных свойств левого желудочка в систолу и диастолу — основополагающий методологический приём для углублённого понимания патофизиологических механизмов возникающих заболеваний сердечно-сосудистой системы, ранней их диагностики и оценки эффективности комплексной терапии. Однако, несмотря на широкое использование стандартной эхокардиографии для оценки систолической и диастолической функций, её традиционные параметры имеют ограничения в плане точности диагностики и эффективности использования в практике. Расширение знаний о новых патогенетических механизмах формирования дисфункции сердца в условиях недоношенности на современном этапе развития кардиологии при использовании технологии «след пятна» (двухмерной спекл-трекинговой эхокардиографии) будет весьма полезно научным работникам, изучающим вопросы становления механики детского сердца после преждевременных родов, и врачам различных специальностей при ранней диагностике заболеваний сердца.

Ключевые слова: недоношенность; детское сердце; механика левого желудочка; диастолическая дисфункция.

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ЭКО•ВЕКТОР

INTRODUCTION

Improved survival of children born with extremely low birth weight has led to a greater understanding of the importance of cardiovascular assessment beyond the neonatal period [1], owing to increased nursing capacity, treatment efficiency, and resuscitative measures. Premature delivery can lead to a distinct cardiac phenotype characterized by structural and functional abnormalities and reduced myocardial adaptation due to the immaturity of the heart [2, 3].

Preterm infants display a distinct cardiac phenotype in later life characterized by reduced volumes and disproportionate weight increases of the heart and reduced systolic and diastolic functions [1]. The structure and function of a child's heart can be affected by various factors before and after childbirth [2]. Several preterm-born mature individuals were exposed to glucocorticoids before delivery and/or during the neonatal period [2].

Diastole is a crucial process in cardiac biomechanics that leads to systole and, therefore, cardiac cycle. The earliest disturbances in cardiac biomechanics occur during diastole, preceding systolic dysfunction. The factors that contribute to left ventricle (LV) diastole include the following [4, 5]:

– Active isovolumic relaxation

– Passive viscoelastic and geometric (thickness, size, and shape) properties of the myocardium and cavities of LV and left atrium (LA)

– End-diastolic pressure (filling pressure) during atrial systole

– Status of the mitral valve and related structures

– LA systolic function

– LA transit function for pulmonary vein blood

– Duration and temporal pattern of diastole, pericardial status

– Rheological blood properties

Assessment of LV pumping properties during systole and diastole is a fundamental methodological technique for comprehensively understanding the pathophysiological mechanisms of emerging cardiovascular diseases, facilitating early diagnosis, and evaluating the effectiveness of complex therapies [6, 7]. However, despite the widespread use of standard echocardiography to assess systolic and diastolic functions, in this study, the traditional parameters have limitations regarding diagnostic accuracy and efficiency of use in practice [6, 7].

The development of cardiovascular system dysfunctions, including diastolic dysfunction, in premature-born children who received complex therapy during the neonatal period is intensely discussed in specialized literature [2, 7]. New mechanisms of diastolic dysfunction in premature newborns are being studied. Recent research has shown that hyperoxia can suppress cardiomyocyte proliferation in the pulmonary veins and LA, leading to impaired *de novo* synthesis of fatty acids and LA enlargement [8, 9].

Establishing reliable criteria, including laboratory determination of NT-proBNP[1] activity or instrumental application of noninvasive ultrasound technology such as two-dimensional (2D) strain speckle-tracking imaging, is crucial. Early diagnosis of cardiac dysfunction remains a relevant task in cardiology, including pediatric cardiology, for the early detection of emerging heart dysfunction. This is particularly critical given the current stage of scientific knowledge in cardiac biomechanics [7, 10, 11], as some premature-born individuals may exhibit subclinical signs of diastolic and systolic dysfunction [12, 13], which may not be apparent when using traditional parameters such as ejection fraction.

As the number of premature-born people increases worldwide [14], there is a growing need for research on optimal regimens, lifestyle, and clinical interventions that may positively affect cardiovascular morphology and function in this population [14].

Furthermore, previous studies have observed a correlation between preterm birth and increased mortality rates during infancy, childhood, and adolescence [14, 15]. A study found a twofold increase in mortality risk among preterm-born individuals, with a mean age of death of 28.8 (15.0–50.9) years [15]. Therefore, it is crucial to monitor this cohort and provide lifelong follow-up care [2, 16].

A thorough investigation of postnatal growth patterns, cardiac chamber development, and LV diastolic event formation during ontogenesis is warranted to address these questions, and for identifying effective criteria for early diagnosis of subclinical cardiac dysfunction in preterm infants.

HEART STRUCTURE AND FUNCTIONING IN PREMATURE-BORN CHILDREN AND ADULTS

The relationship between the heart's shape and its functioning has been a fundamental position in cardiology [17, 18], which has been supported by a multifactorial analysis of the influence of premature birth on heart formation during different periods of postnatal ontogenesis [19, 20]. Adverse LV remodeling in premature-born children and young adults is characterized by increased mass, decreased internal cavity diameter, and increased LV wall thickness. Additionally, LV function changes, including decreased systolic and diastolic functions and rotational function, have been observed [12, 13, 20, 21]. LV apex position (in the left-to-right direction), heart shape, LV length, and degree of prematurity have been identified as highly predictive factors for the early diagnosis of cardiovascular disease in premature-born young adults [22].

A prospective population-based longitudinal cohort study recorded a decrease in LV end-diastolic and end-systolic volumes and cardiac output (4.8 ± 1.2 vs. 5.1 ± 1.4 l/min; $p = 0.03$) in volunteers aged 26–30 years who were born with

[1] NT-proBNP is the N-terminal fragment of the prohormone brain natriuretic peptide.

extremely low body weight, compared to controls [22]. Subclinical changes in LV and LA structure and function were found in preschool-aged children (5–6 years old) born <37 weeks of gestation with birth weight <1500 g (mean gestational age: 28.6 ± 2.7 weeks; mean body weight, 1042 ± 247 g). The premature group exhibited significantly smaller LV end-diastolic and end-systolic dimensions (31.2 vs. 33.5 mm, $p = 0.048$, and 20.0 vs. 21.6 mm, $p = 0.024$, respectively) and lower LV diameter with end-diastolic and end-systolic volumes (38.8 vs. 46.3 mL, $p = 0.024$, and 12.8 vs. 15.6 mL, $p = 0.008$, respectively) than the full-term group [23].

The preterm infants who were born <29 weeks of gestation and were 1 year old had lower values of right ventricular (RV) function parameters ($p < 0.01$) than their full-term peers. Additionally, RV morphology parameters (signs of remodeling) were higher in preterm infants. These findings show that subclinical dysfunction and RV morphology changes are a distinct pathology of prematurity that persists even after bronchopulmonary dysplasia and pulmonary hypertension have resolved [24, 25].

At age 6.5 years, individuals born extremely premature (with extremely low birth weight) exhibit a reduced right atrium, altered RV shape, and higher pulmonary vascular resistance compared to those born prematurely [26].

The specific mechanism behind the subclinical dysfunction of the RV and its persistent morphological changes up to 1 year of age in preterm infants remains unknown. Changes in hemodynamic load conditions after delivery and the loss of structural and functional organization of the fetal myocardium in the third trimester of pregnancy may play a role [24, 25].

A study using magnetic resonance imaging (MRI) examined the cardiac structure and function of premature-born young adults aged 23–28 years with a birth weight <1850 g [27]. Another study on individuals aged 18–40 years who were born prematurely with a low birth weight (gestational age: 32.8 ± 3.2 weeks) was conducted [28]. Both studies revealed that preterm birth leads to a decrease in the RV cavity and its ejection fraction [28]. Multimodal cardiac imaging has shown that young adults born moderately premature (mean gestational age: 32.8 ± 3.2 weeks) exhibit structural and functional changes in the RV that are independent of pulmonary physiology [29].

Based on echocardiography data, premature-born individuals with very low birth weight exhibit smaller RV cavity sizes and RV function changes [30]. A study of individuals aged 26–30 years with a history of preterm birth (birth weight <1500 g) who underwent four-dimensional MRI of the heart revealed a decrease in RV length. Additionally, flow in the RV cavity, particularly during diastole, was found to be altered in those born preterm [31].

In a one-stage cohort study of premature-born adolescents and young adults (≤32 weeks) with a birth weight <1500 g, cardiac MRI demonstrated a significant decrease in the biventricular dimensions of the heart chambers, and changes in deformation were recorded [20, 31].

LV myocardial mass and its index were measured in preterm infants with birth weight ranging from 588 to 3380 g and gestational age from 24 to 35 weeks. The results showed that the mass and index ranged from 2.94 ± 0.70 g and 37.08 ± 8.22 g/m^2 at a body surface area of 0.07–0.08 m^2 to 8.27 ± 2.13 g and 48.57 ± 13.56 g/m^2 at a body surface area of 0.17–0.19 m^2, respectively [32]. The mass and index increased more strongly after birth than in full-term peers [20, 33]. Delayed fetal intrauterine development is accompanied by a decreased RV and systolic dysfunction in the postnatal period [34].

Diffuse fibrosis of the LV myocardium, which is correlated with the degree of prematurity, has been documented in premature-born young people with LV structural and functional changes [3, 35]. This may be the cause of the cardiac remodeling previously described. Furthermore, diastolic dysfunction is associated with diffuse myocardial fibrosis and the degree of prematurity [35].

According to, preterm-born individuals experience myocardial dysfunction more frequently than healthy full-term peers [18]. This dysfunction can lead to LV dysfunction, which can cause increased LA pressure, which in turn can result in stasis in pulmonary veins and subsequently lead to increased RV afterload.

Some studies have demonstrated that 2D speckle-tracking echocardiography can be used to assess LA function in children, including those born prematurely [23, 36, 37, 38]. It was found that premature-born children have reduced longitudinal LA deformation (43.9% vs. 52.8%, $p < 0.0001$) and increased LA stiffness index (0.17 vs. 0.14, $p < 0.0001$) [23]. Further, 2D speckle-tracking echocardiography revealed weaker LA contraction and decreased reservoir and conduit function in children born <30 weeks of gestation [38]. Additionally, premature-born children had significantly smaller maximum and minimum LA volumes [23].

Infants diagnosed with severe bronchopulmonary dysplasia were born with a significantly lower mean gestational age of 27.4 ± 2.1 weeks and mean birth weight of 971.3 ± 305.8 g compared to those with mild (30.0 ± 0.9 weeks, 1237.3 ± 132.2 g) and moderate (29.6 ± 1.3 weeks, 1203.2 ± 214.4 g) bronchopulmonary dysplasia. The study found that premature-born children with severe bronchopulmonary dysplasia had a significantly lower peak longitudinal deformation level in the right atrium (26.3 ± 10.1%) compared to those with moderate (32.4 ± 10.9%) or mild (31.9 ± 8.3%) bronchopulmonary dysplasia. Moreover, the decrease in peak longitudinal deformation of the right atrium was significantly correlated with the duration of artificial ventilation [39].

Infants born prematurely and with signs of bronchopulmonary dysplasia exhibit reduced diastolic function [40], longitudinal RV deformation [41], and changes in rotational mechanics and LV apex deformation velocity [40]. A study has shown an association between late preterm birth (34–36 weeks of gestation) and increased risk of cardiometabolic issues, heart failure, cardiovascular diseases, death from cardiovascular diseases, and thromboembolism in adulthood

[42]. Additionally, the risk of coronary heart disease debut in adulthood is correlated with the child's body size at birth [42].

Evidence indicates that preterm-born individuals are at an increased risk for lifetime cardiovascular issues, including coronary heart disease at age 30–43 years. Thus, additional long-term cardiovascular surveillance should be provided for this vulnerable population.

MECHANISMS OF REMODELING AND FORMATION OF CARDIAC DYSFUNCTION IN PREMATURITY

Immaturity of the child's heart

Clinical pathomorphologic studies of the heart in children at gestational age 23 and 36 weeks and experimental studies confirm the decrease in the number of cardiomyocytes, their immaturity, and reduced division, along with myocardial infiltration by lymphocytes and mast cells, indicating inflammation and damage. Clinical studies confirm differences in the structure of cardiomyocytes between premature and full-term infants [45–47].

Focal hypertrophy of cardiomyocytes with large hyperchromic nuclei, focal wave-like deformation of cardiomyocytes, and signs of myocytolysis are observed in fetal RVs and live-born LVs. The prevalence of these characteristics varies from single-cell structures and their separate groups to the involvement of extensive areas of the myocardium, which indicates hypoxic damage [47, 48].

Fetuses and newborns born between 25 and 37 weeks of gestation and to mothers with intrauterine developmental delay syndrome are believed to have heart mass deficit with myocardial structural rearrangement [50, 51]. Furthermore, they may exhibit subendocardial fatty degeneration of cardiomyocytes, signs of micromyocytolysis, and microvascular ischemia [52].

Under conditions of prematurity with hypoxia [53], features of the fibrous skeleton [54], trabecular apparatus [55], microvascular channels [56], and anomalies in coronary artery may develop in the pediatric heart due to immaturity of cardiomyocytes (predominance of β-myosin isomer, thin myofibrils, insufficient function of calcium channels, reduced activity of mitochondrial enzymes, and L-carnitine insufficiency) [51].

Infant heart damage resulting from hypoxia and hyperoxia

Hypoxia is a significant cause of long-term adverse effects on the cardiovascular system [57–59]. Fetal hypoxia can result in intrauterine growth restriction, perinatal morbidity, and mortality. The long-term effects of intrauterine growth restriction on cardiovascular disease in adulthood are well-established [57–59].

Antenatal hypoxia promotes cardiac epigenetic reprogramming, which increases the risk of cardiovascular disease and vulnerability to ischemia and reperfusion injury later in life [60].

Prolonged hypoxia leads to the activation of free radical oxidation processes, lipid peroxidation, antiradical defense mechanism depletion, stimulation of Ca^{2+} capture by mitochondria, dissociation of tissue respiration and oxidative phosphorylation processes, and oxidative damage to enzymes, proteins, and nucleic acids. The toxic effect of ion channels on the myocardium [58, 59] and their contribution to interstitial fibrosis can lead to cardiovascular pathology in later stages of postnatal development [59].

According to clinical studies and experimental data, hypoxic damage to the fetal myocardium and intrauterine development disorders result in decreased proliferation and cardiomyocyte fund [61, 62]. Inhibition of their maturation [63] and increase in the proportion of mononuclear cardiomyocytes, signs of focal dystrophy, and focal cardiosclerosis, along with autonomic dysfunction in the future, can lead to persistent vegetative and visceral disorders [51, 61, 64].

Anteroposterior and/or inferolateral LV wall ischemia, combined lesions of the papillary muscles and interventricular septum, and subendocardial lesions are the most common characteristics of hypoxic and preterm newborns [65, 66]. Additionally, fetuses and premature infants have been found to have lesions of the trabecular apparatus, persistent myocardial ischemia, and foci of myocardial necrosis and/or scarring [69–78].

Myocardial lesions in preterm infants exposed to hypoxia ranged from small areas of subendocardial damage to larger areas of necrosis scattered throughout the myocardium [76, 78–81].

The apical region and papillary muscles were prone to necrotic lesions [80] and, in some cases, rupture of the papillary muscles [82, 83], which are sometimes fatal [84], favored by nuances of structure [85, 86] and blood supply (including the apex) [87].

Under conditions of hypoxia exposure, aneurysm and coronary artery lesions have been noted in the pediatric heart. These lesions range from zones of acute focal necrosis to severe proliferative lesions of the intima and medial defects [88]. Additionally, vacuolar degeneration of cardiomyocytes has been observed. Myocardial damage is caused by the destruction of cardiomyocyte microtubules, increased opening time of L-type calcium channels, intracellular calcium overload, elevated inflammatory cytokine expression, and increased matrix metalloproteinase activity [78].

Childhood myocardial ischemia can be caused by various factors, including asphyxia, congenital heart defects, viral infections, Rhesus conflict, thromboembolism, and insufficient perfusion [55] and, in some cases, coronary occlusion [90]. The walls of coronary arteries often exhibit endothelial edema, detachment, destruction, apoptosis, and thrombosis of intramural arteries and veins (subepicardial and subendocardial layers) [91].

Bamber et al. and Breatnach et al. concluded that hypoxia affects heart tissue in premature and preterm newborns, including those with post-hypoxic encephalopathy. This is manifested by changes in LV torsional mechanics due to hypoxic heart damage [66, 89] and systolic and diastolic dysfunction. Experimental data shows that this dysfunction is associated with myosin molecule degradation in oxygen

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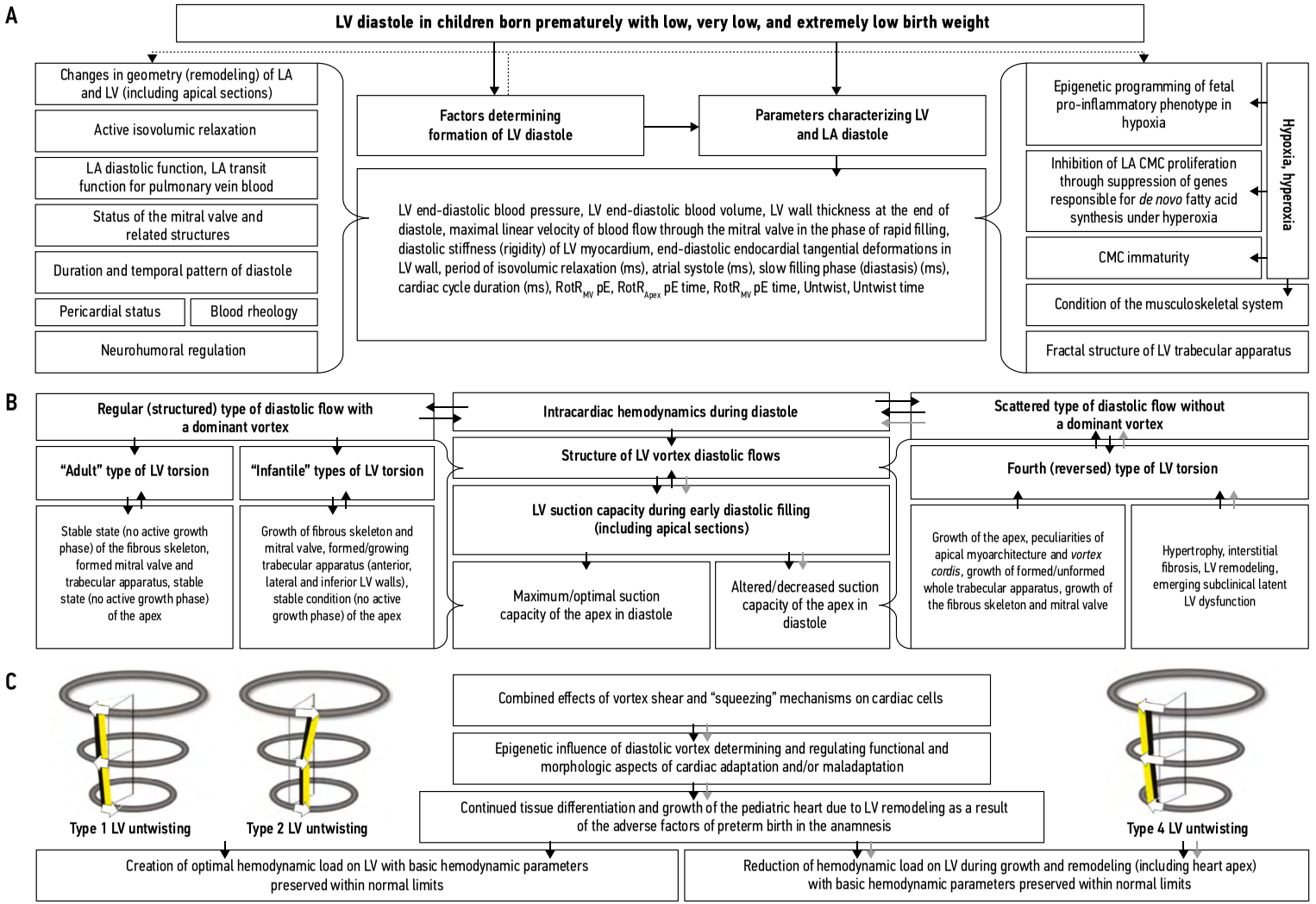

Fig. 1. Mechanisms of formation of diastole and diastolic vortex flows of the left ventricle (LV), their complex effects in infants and preschoolers born prematurely with low, very low and extremely low body weight, during postnatal growth and ongoing tissue differentiation of the heart (hypothesis). A. Mechanisms of formation and parameters characterizing LV diastole. B. Characteristics of intracardiac diastolic flows and types of LV twist into systole. C. Variants of LV untwist into diastole with various models of rotational movement in LV systole and complex effects of intracardiac hemodynamics. LA — left atrium; CMC — cardiomyocytes

Рис. 1. Механизмы формирования диастолы и диастолических вихревых потоков левого желудочка (ЛЖ), их комплексные эффекты у детей раннего и дошкольного возраста, рождённых недоношенными с низкой, очень низкой и экстремально низкой массой тела, в процессе постнатального роста и продолжающейся тканевой дифференцировки сердца (гипотеза). А. Механизмы формирования и параметры, характеризующие диастолу ЛЖ. В. Характеристика внутрисердечных диастолических потоков и типов скручивания ЛЖ в систолу. С. Варианты раскручивания ЛЖ в диастолу при различных моделях вращательного движения в систолу ЛЖ и комплексные эффекты внутрисердечной гемодинамики. ЛП — левое предсердие; КМЦ — кардиомиоциты

deficiency. The regenerative abilities of the pediatric heart are indisputable [89].

Babies born at <34–36 weeks of gestation have been found to experience changes in autonomic regulation of the heart that persist until adulthood (23 years) [92]. This is due to hypoxic myocardial damage resulting in localized myocardial dystrophy that develops before full recovery of function or formation of cardiosclerosis [93]. These factors contribute to an increased risk of cardiovascular disease in this clinical group [92].

Hyperoxia has been shown to suppress cardiomyocyte proliferation in the pulmonary veins and LA [8]. The most significant loss of pulmonary vein cardiomyocytes occurs directly in the lung under hyperoxia, and gradual cell loss was observed in LA [94]. Hyperoxia causes a decrease in cardiomyocytes that surround the pulmonary veins, extending from the LA and penetrating into the lung lobes, which assist in pumping oxygen-rich blood from the lungs. The loss of these cardiomyocytes impairs blood flow, leading to early age dilation of pulmonary arterioles and veins [94].

Neonatal hyperoxia suppresses genes needed for *de novo* synthesis of fatty acids in atrial cardiomyocytes and LA tissue explanted from human infants, inhibiting LA cardiomyocyte proliferation. Fatty acid synthase and stearoyl-CoA desaturase were found to be suppressed [8, 94].

According to, neonatal hyperoxia impairs the structure and function of mitochondria in LV cells [95]. This is evidenced by fragmented organelles, loss of cristae structure, destruction of inner and outer membranes, reduced mitochondria size, and decreased ability for oxidative phosphorylation. Additionally, lower protein expression of electron transport chain subunits, including complexes I, III, IV, and V, was observed.

Furthermore, Lewandowski et al. showed that the shortened LV and reduced LV cavity size in preterm infants during the postnatal period may be associated with interruption of LV development and changes in blood flow observed in preterm labor. The last trimester of pregnancy is crucial for fetal heart growth [20]. Furthermore, alterations in intracardiac blood flow patterns may impact modifications in the position of the LV apex [20] and its contractile function.

LV myocardial wall thickening in the basal and apical segments and papillary muscles may be due to cardiomyocyte hypertrophy and/or interstitial fibrosis. This thickening correlates with gestational age and affects the formation of contractility of the pediatric heart, including diastolic events in the conditions of prematurity in anamnesis [33].

The manifestation of contractility disorders in a child's heart, resulting from the mechanisms previously described, is a plausible and substantiated event. This is supported by the medical history of children who were born with low, very low, and extremely low body weight [7, 96, 97].

Contemporary cardiomechanics presents an axiom regarding the relationship between systolic and diastolic dysfunctions [98]. The pathophysiologic basis of this relationship, in conditions of hypoxic exposure, is considered aberrant calcium homeostasis, which involves changes in the release and absorption of intracellular calcium. Moreover, theoretical postulates about the genesis of the mechanical component of the formation of global diastolic function, especially in early diastole, are relevant, as they are beneficial in establishing the "suction" phenomenon [98].

According to modern scientific data, the explanation of the special regularities of LV contractility formation in premature infants is based on the morphological LV changes in children born with low, very low, and extremely low body weight. These changes are described in detail by Cox et al. [33]. According to, the process of dysfunction formation can be extensive [99]. Additionally, the clinical onset of the pathology may occur in the distant future (Figure 1).

Premature-born patients with low, very low, and extremely low body weight require long-term observation in outpatient settings. During childhood, they should be monitored by a neonatologist and pediatrician and by a general practitioner and cardiologist in adulthood.

ADDITIONAL INFORMATION

Author contributions. E.N.P. — development of the concept, analysis and synthesis of literature data, preparation and editing of the text, approval of the final version of the article; M.V.K. — concept development, research, preparation and editing of the text, approval of the final version of the article; G.V.N. and E.O.A. — conducting research, collecting and analyzing literature data; R.S.K. — general management of the research group's activities, concept development, approval of the final version of the article.

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Conflict of interest. The authors declare that there is no conflict of interest in the presented article.

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