PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH CONGENITAL HEART DISEASE: RATIONALE FOR MANAGEMENT ALGORITHM BASED ON A LITERATURE REVIEW

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Abstract. The substantial progress achieved in cardiology and paediatric cardiac surgery has led to a considerable increase of life expectancy of patients with congenital heart disease (CHD), and at the same time to growing number of adult patients developing pulmonary arterial hypertension (PAH) associated with congenital heart defects. Nowadays guidelines were developed and updated for PAH, but no expert recommendations exist for effective management of PAH associated with CHD. Thus, it is important to develop an algorithm for managing these patients, based on international standards and a comprehensive understanding of prognostic markers of worsening the course of pulmonary arterial hypertension (PAH), considering local cardiac tertiary hospitals' capabilities.

The aim. To highlight the pathophysiology and clinical characteristics of PAH-CHD patients, identify prognostic markers for its onset and progression, and develop a management algorithm for patients.

Results. The article presents the pathophysiology of PAH-CHD, the mechanisms of right ventricle adaptation to pressure overload, which determine the functional abilities of patients and prognosis, PAH formation, and progression after defects correction. The accurate identification of stages in PAH-CHD (volume overload, mixed, stage of pulmonary vascular disease) is essential for the timely determination of surgical intervention, selecting conservative treatment strategies, and predicting the outcomes of surgical defect correction. The type of defect, its size, and the volume of blood flow through the defect influence the onset and progression of PH-CHD. We review the pathophysiology and clinical features of PAH-CHD, as well as the reasons for the late diagnosis of heart failure at the stage of severe decompensation and irreversible remodelling of the lung vessels when diuretic therapy is not effective enough and inotropic support, circulatory mechanical support and heart / lung complex transplantation are required. The necessity of developing new scales for stratifying the risk of PAH-CHD is justified considering the particularities of the disease course and cardiac hemodynamic in different anatomical types of the defects. Based on this literature review, at the Municipal Enterprise «Dnipropetrovsk Regional Clinical Center for Diagnostics and Treatment» of the Dnipropetrovsk Regional Council the algorithm for managing patients with PAH-CHD was devised and implemented into clinical practice.

Conclusions. PAH is a common complication of CHD. The prevalence of PAH-CHD is substantial and it can manifest and progress even in patients with previously corrected heart defects. To effectively manage patients with PAH-CHD, an algorithm has been devised and implemented in clinical practice. It includes factors that have demonstrated associations with poor prognosis which are more than two hospitalizations for HF in the last year, pulmonary vascular resistance (PVR) (or index of PVR), mean pressure in the pulmonary artery, pulmonary capillary wedge pressure, left ventricular ejection fraction, heart failure with a reduced ejection fraction, right ventricle heart failure, NYHA FC, high risk of atrial fibrillation or flutter, 6-minute walking test distance, NTproBNP, highly sensitive C-reactive protein, B-lines on lung ultrasound, glomerular filtration rate, haemoglobin, platelet count, sodium, Model for End-Stage Liver Disease scale.

Keywords: pulmonary arterial hypertension, congenital heart disease, right heart catheterization, mean pulmonary artery pressure, Eisenmenger syndrome.

The substantial progress achieved in cardiology and paediatric cardiac surgery has led to a considerable increase of life expectancy of patients with congenital heart disease (CHD), and at the same time to growing number of adult patients developing pulmonary arterial hypertension (PAH) associated with congenital heart defects [1]. These patients require lifelong monitoring and treatment with the objective of early detection of disease progression and prevention of possible complications [1, 2, 3].

Therefore, it is important to develop an algorithm for managing these patients, based on international standards and a comprehensive understanding of prognostic markers of worsening the course of pulmonary hypertension, considering local cardiac tertiary hospitals' capabilities.

The aim. To highlight the pathophysiology and clinical characteristics of pulmonary arterial hypertension in congenital heart disease patients, identify prognostic markers for its onset and progression, and develop a management algorithm for patients.

Results. PAH-CHD is represented by a heterogeneous population of patients with various structural
changes of the heart, features of the evolution of pulmonary hypertension (PH), variable clinical manifestations, cardiovascular complications, and comorbidities [1]. PH is a condition with a mean pulmonary artery pressure (mPAP) greater than 20 mmHg at rest according to right heart catheterization (RHC) [2]. PAH-CHD belongs to the first clinical group of the PH classification (updated from Simonneau G. et al. [3]) and includes patients who, according to hemodynamic characteristics, have precapillary PH, defined by a pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and pulmonary vascular resistance (PVR) > 2 Wood units (WU). The distinction between pre- and post-capillary PH builds on measuring PAWP or end-diastolic pressure in the left ventricle. [2, 4].

The accurate identification of stages in PAH-CHD (volume overload, mixed, stage of pulmonary vascular disease) is essential for timely determination of surgical intervention, selecting conservative treatment strategies, and predicting the outcomes of surgical defect correction. The volume overload stage is characterized by a significant arteriovenous blood flow into the pulmonary circulation and mild vasospasm without an increase in PVR. Correcting the defect at this stage results in the complete normalization of pulmonary artery pressure. In mixed stage of PAH-CHD, an elevation in pulmonary artery (PA) pressure occurs due to spasms in the pulmonary vessels, serving as a protective response that restricts arteriovenous blood flow. Vasoconstriction represents a vital adaptive mechanism of the body. The phase of pulmonary vascular disease is distinguished by irreversible morphological alterations in the pulmonary vessels [1, 4].

The type of defect, its size, and the volume of blood flow through the defect influence the onset and progression of PAH-CHD. Depending on the location of the pathological blood shunt between the heart chambers with low or high pressure, CHD can be categorized into pre- and post-tricuspid defects, as well as complex defects involving a post-tricuspid shunt. The terms "restrictive" and "non-restrictive" for post-tricuspid defects are defined by the ratio of the defect size to the diameter of the aorta (aortic valve). The pressure difference between the systemic and pulmonary circulation determines the direction of the shunt [4], which can be arteriovenous, bidirectional, or venoarterial (Eisenmenger syndrome (ES)).

Pre-tricuspid defects, such as atrial septal defect, partial atrioventricular canal, and partial anomalous pulmonary venous return, represent low-pressure shunts with arteriovenous shunting. The volume overload on the right ventricle (RV) and pulmonary circulation, under conditions of low pressure, does not result in a rapid increase in PA pressure. PAH develops later, and its progression is attributed to the severity of structural changes in the pulmonary vessels and a decrease in RV contractility. Only 2% of patients with atrial septal defect develop PAH [5, 6].

Post-tricuspid non-restrictive defects, such as ventricular septal defect, patent ductus arteriosus, and aortopulmonary septal defect, constitute high-pressure shunts with arteriovenous shunting. Left ventricular (LV) volume overload under high-pressure conditions leads to PH in the first years of life. Without timely correction, irreversible pathological changes in the pulmonary vessels cause an increase in PVR, leading to a subsequent alteration in the direction of blood flow and the development of ES. Cossio-Aranda J. et al. demonstrated the significance of defect size in PAH development. Among patients with a ventricular septal defect smaller than 1.5 cm, ES was diagnosed in approximately 3% of cases, whereas with a larger defect size, this syndrome - in the absence of appropriate correction - was observed in every case [3]. The PAH in ES is associated with vasoconstriction, medial wall hypertrophy, and remodeling of the pulmonary vasculature [7]. Volume and pressure overload leads to pulmonary vascular endothelial damage and dysfunction, synthesis of vasoconstrictors (endothelin-1 and thromboxane), and reduction of vasodilators (prostacyclin, nitric oxide, vasoactive peptide, and prostaglandin I2). In a study by Rubens C. et al., circulating endothelin levels correlated with PAH severity and poor outcome [8]. Activation of vascular elastase and matrix metalloproteinases, degradation of the extracellular matrix, and the release of FGF and TGF-β1 collectively contribute to the hypertrophy of smooth muscle cells, their proliferation, and the formation of neo-intima [9]. The study by Breuer J. et al. highlighted an elevation in the level of the vasoconstrictor serotonin and impaired intrapulmonary expression of TGF-β1 receptors [10]. Platelet and leukocyte aggregation to the damaged endothelium induces inflammation and thrombus formation. The consequence of endothelial dysfunction and vascular remodeling in the pulmonary arteries is an increase in PVR and right ventricular heart failure (HF) [11].

The mechanism of PAH development in complex congenital heart defects, including post-tricuspid shunts (such as common truncus arteriosus, complete form of the atrioventricular canal, etc.), is generally similar to simple post-tricuspid defects. In cyanotic CHD (transposition of the great vessels, a functional single ventricle, etc.) pulmonary vascular disease is further aggravated by in-situ thrombosis, and in the case of transposition of the great vessels – the detrimental effect of oxygenated blood on the pulmonary arteries [9]. The clinical classification of PAH associated with CHD is provided in the recommendations of the European Society of Cardiology (ESC) [2, 4].

The development of PAH in patients with a previously corrected defect is attributed to the progression of pulmonary vascular remodeling, which proceeds despite the surgical treatment of the anomaly. According to data in research by Jančauskaitė D. et al., residual PH was frequently noted in individuals with a combined CHD shunt or elevated PVR before surgical intervention and was associated with worse long-term outcomes [12].

Valvular heart defects can contribute to PH, categorized under group 4 of the PH classification, and are regarded as associated with the left side of the heart [2].

Recent studies have highlighted the role of genetics and epigenetics in the onset and progression of PAH. In the study by Roberts K.E., 6% of PAH-CHD patients exhibited mutations in the BMPR2 gene, which are linked to familial and idiopathic PAH [13]. In the research by Na Zhu et al., mutations in the SOX17 gene were observed in 3.2% of PAH-CHD cases. Within the PAH cohort without CHD, polygenic variants of SOX17 were identified in 0.7% of cases, designating it as a risk gene for PAH-CHD development [14].

RHC with a vasoreactivity test is recommended for all patients with PAH-CHD. It is used to confirm the diagnosis, evaluate the hemodynamic variant and severity of PAH, and also to determine treatment tactics [1, 2, 4, 15].
The RV adaptation to pressure overload determines the functional capacities of patients with PAH-CHD and serves as a prognostic marker. Right-sided HF in patients with PAH-CHD results from inadequate blood supply to the heart and/or elevated systemic venous pressure. In the early stage of HF, the energy reserve of the RV is still preserved. However, there are already disturbances in immunological and adrenergic responses, which resemble the phenotype of the foetal RV. Over time, adaptive reserves are depleted, leading to development of systolic dysfunction. As a consequence, the right chambers of the heart expand; at the stage of terminal heart failure, lung or even heart-lung complex transplantation may be necessary [16]. There is limited research on the criteria for preclinical changes in the RV.

A comprehensive assessment of adaptation mechanisms for various defects is important. For example, with the same PVR values, patients with ES retain RV function longer and have better survival rates compared to patients with idiopathic PAH [16, 17]. This is explained by the long-lasting foetal hypertrophied phenotype, which prevents RV dilatation, and right-to-left shunting, which allows the pressure in the pulmonary artery to be tolerated above the systemic one [13].

Symptoms and signs of HF occur in 30% of patients with CHD [18]. According to the 2023 ESC guidelines for the management of patients with HF, decompensated HF is defined as a period of chronic HF characterized by worsening or emergence of HF symptoms and requiring hospitalization [19]. However, patients with PAH-CHD in the hypervolemic stage get used to restrictions on physical exertion due to adapting their “everyday” activity to their capabilities. They do not give due importance to the increase in dyspnoea. At this stage, there are no distinctive symptoms or signs of HF. As a result, the diagnosis is typically established during severe decompensation and irreversible changes in the pulmonary vascular bed. At this point, diuretic therapy is not effective enough, and isotropic support, mechanical circulatory support, and heart/lung complex transplantation are required [18].

Over a quarter of patients diagnosed with ES have I or II FC of HF at the time of diagnosis [20, 21]. Despite lower mortality rates in patients with ES and FC I or II compared with FC III or IV, they remain significant [22]. In the placebo-controlled EARLY trial, where small septal defects or PDA were present in 21% of patients with FC I-II, it was shown significant reductions in PVR and slowed disease progression after six months of bosentan treatment. These findings suggest an enhanced prognosis with early diagnosis of PAH-CHD and timely therapy [23].

One of the most objective parameters indicating the severity of HF is the indicator of oxygen consumption during a cardiopulmonary test. However, in many patients with PAH-CHD, peak oxygen consumption is reduced due to detaining resulting from exercise restrictions, insufficient cardiac reserve, and the limitations advised by doctors [24]. In a study by Diller G.P., the maximum oxygen consumption in 20 patients with ES, where 70% were in FC I or II, was recorded at 11.5 ± 3.6 ml/kg/min [25]. Patients in FC I-III exhibit peak oxygen consumption comparable to adults without CHD in the same FC but, on average, are 26 years older [26]. Thus, a single baseline assessment of the FC of HF as well as absolute values for assessing functional capacities in patients with PAH-CHD have low diagnostic value. In contrast, the comparison of these parameters on follow-up visits of patient observation is a more accurate prognostic tool. Further studies are needed to determine clear criteria for diagnosing or tracking the progression of HF – especially at the stage of volume overload – in PAH-CHD.

Risk stratification and predicting the progression of PAH are integral components of the diagnostic algorithm. Numerous studies have explored prognostic factors in PAH-CHD. In the REVEAL registry, factors associated with better 4-year survival in patients with PAH-CHD included the 6-minute walk test (6MWT), N-terminal brain natriuretic peptide (NTproBNP) level <50 pg/ml, and the presence of vasoactivity [20]. In a study by Schuurig M.J. et al., NTproBNP >500 pg/ml and TAPSE <15 mm were identified as predictors of mortality in patients with PAH-CHD [23]. Ramung S. et al. found predictors of poor survival to include age, elevated creatinine levels, decreased DLCO, and reduced FEV1 [27]. In a recent study, Schuijt M.T. et al. HF FC progression, exercise desaturation, 6-MWT distance, NTproBNP, and TAPSE were markers of mortality in 92 patients with PAH-CHD [28]. In a multicenter study by Kempny A. et al. involving 1098 patients with ES, five independent predictors of mortality were identified: age, presence of a pre-tricuspid shunt, low saturation, presence of pericardial effusion, and arrhythmia [29].

Guidelines offer different criteria for defect closure, and the patients’ management of borderline hemodynamic is still controversial [2, 4, 30]. In addition, it is noteworthy that, as per the Dutch registry, nearly 15% of patients developed PAH after successful CHD correction in childhood [31]. This emphasizes the importance of current registries in shaping a contemporary strategy to identify individuals at a high risk of developing PAH after the surgical closure of defects. It consequently could impact the management of patients with operable CHD.

The highlighted pathophysiological distinctions between the forms of PAH-CHD (for example, the prognosis and response to therapy are significantly different in ES and PAH after the defect correction) and PAH of other etiologies underscore the need to modify the risk stratification table of the ESC/ERS 2022 recommendations for the PAH management [2].

Routine check-ups for patients with PAH-CHD should include risk stratification using the 2022 ESC/ERS criteria. Additionally, mandatory assessment should incorporate parameters indicative of poor prognosis, such as two and more hospitalizations for HF within last year, declining 6-MWT distance and SpO2 over time, B-lines on lung ultrasound, elevated NTproBNP, C-reactive protein exceeding 2.98 mg/l, platelet count, glomerular filtration rate less than 50 ml/min/1.73 m2, haemoglobin, sodium, and a risk score on the Model for End-Stage Liver Disease (MELD) scale exceeding 11 points [2, 23, 29, 32-34].

Guidelines discourage the routine use of oral anticoagulants in ES patients and state that they should be considered in case of atrial fibrillation and pulmonary artery thrombosis, in the absence of major bleeding. Considering the deleterious effects of losing sinus rhythm, European consensus documents for arrhythmia management in adults with CHD advocate a rhythm control strategy as the initial approach with further use of pharmacological and...
Interventional strategies to prevent arrhythmia recurrence [4, 35].

Thus, the decision to initiate PH therapy in patients with ES and FC II should be informed by risk stratification rather than solely relying on the FC of HF. Based on this literature review, at the municipal enterprise «Dnipropetrovsk Regional Clinical Center for Diagnostics and Treatment» of the Dnipropetrovsk Regional Council the algorithm for managing patients with PAH-CHD (Fig. 1) was devised and implemented into clinical practice.

**Figure 1. Management of patient with PAH-CHD at the municipal enterprise «Dnipropetrovsk Regional Clinical Center for Diagnostics and Treatment» of the Dnipropetrovsk Regional Council». Notes: * - Congenital heart diseases, that can be associated with PAH according to clinical classification of pulmonary arterial hypertension (updated from Simonneau et al. [2, 4]); ** - in patients with a typical and atypical angina and very high cardiovascular risk or a high cardiovascular risk males older 40 years / females in menopause. *** - in patients with GFR > 30 ml / min / 1.73 m², BMI < 30 kg / m², euthyroidism. WU – Wood units, PVR – pulmonary vascular resistance, iPVR – index of PVR, mPAP – mean pressure in the pulmonary artery; PCWP – pulmonary capillary wedge pressure; LV EF – left ventricular ejection fraction; HFrEF – heart failure with a reduced ejection fraction; RV HF – right ventricle heart failure; FC – functional class; 6MWT – 6-minute walking test; AF – atrial fibrillation; hCRP – highly sensitive C-reactive protein; MELD – Model for End-Stage Liver Disease; GFR – glomerular filtration rate; MCS – mechanical circulatory support; RRT – renal replacement therapy.

**Conclusions.** The prevalence of PAH-CHD is substantial, and the condition can manifest and progress even in patients with previously corrected heart defects. To effectively manage patients with PAH-CHD, an algorithm
has been devised and implemented in clinical practice considering local cardiac tertiary hospitals’ capabilities. It includes factors that have demonstrated associations with poor prognosis which are more than two hospitalizations for HF in the last year, PVR (or iPVR), mPAP, PCWP, LV EF, HfREF, RV HF, NYHA FC, high risk of AF or flutter, 6-MWT distance, NTproBNP, hCRP, B-lines on lung ultrasound, glomerular filtration rate, haemoglobin, platelet count, sodium, MELD scale.

Conflict of interest. The authors declare no conflict of interest and no financial interests in the preparation of this article.

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ЛЕГЕНЕВА АРТЕРИАЛЬНА ГІПЕРТЕНЗІЯ, АСОЦІЙОВАНА ІЗ ВРОЖДЕННИМИ ВАДАМИ СЕРЦЯ: ОБГРУНТУВАННЯ АЛГОРИТМУ ВЕДЕННЯ НА ОСНОВІ ОГЛЯДУ ЛІТЕРАТУРИ

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Резюме. Суттєвий прогрес, досягнутий у кардіології та кардіохірургії, призвів до значного зростання поширеності легеневої артеріальної гіпертензії, асоційованої з врожденими вадами серця (ЛАГ–ВВС). Тож постає актуальною розробка алгоритму ведення хворих на основі міжнародних стандартів і комплексного розуміння прогностичних маркерів погіршення перебігу легеневої артеріальної гіпертензії (ЛАГ) з урахуванням можливостей місцевих кардіологічних закладів третинного рівня.

Мета. Висвітлити патофізіологію та клінічні характеристики пацієнтів із ЛАГ–ВВС, визначити прогностичні маркери їх початку й прогресування і розробити алгоритм ведення пацієнтів.

Результати. У статті представлено патофізіологію ЛАГ–ВВС, формування і прогресування ЛАГ після корекції вад, клінічні особливості та причини пізньої діагностики серцевої недостатності. На основі вказаних у літературному огляді в Комумальному підприємстві «Дніпропетровський обласний клінічний центр діагностики та лікування» Дніпропетровської області в розроблено та впроваджено в клінічну практику алгоритм ведення хворих на ЛАГ–ВВС.

Висновки. ЛАГ є довоєнним ускладненням ВВС, яка може формуватись і прогресувати навіть після корекції дефектів. Для ефективного ведення пацієнтів із ЛАГ–ВВС розроблено та впроваджено в клінічну практику алгоритм, він охоплює фактори, які продемонстрували зв’язок із позаний прогнозом, а саме: більше ніж дві госпіталізації стосовно серцевої недостатності впродовж останнього року, легеневий судинний опір (ЛСО) (або індекс ЛСО), середній тиск у легеневій артерії, тиск закинювання легеневих капілярів, фракція викиду лівого шлуночка, серцева
недостатність зі зниженою фракцією викиду, правошлуночкова серцева недостатність, функціональний клас за NYHA, високий ризик фібриляції або тріпотіння передсердь, дистанція, що пройдена під час 6-хвилинного тесту, NT-proBNP, високочутливий С-реактивний білок, В-лінії на УЗД легень, швидкість клубочкової фільтрації, гемоглобін, кількість тромбоцитів, натрій, оцінка стадії захворювання печінки за шкалою MELD.

**Ключові слова:** легенева артеріальна гіпертензія, вроджена вада серця, катетеризація правих відділів серця, середній тиск у легеневій артерії, синдром Ейзенменгера.

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