PULMONARY HYPERTENSION IN CHILDREN WITH CONGENITAL HEART DEFECTS

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Abstract*. To conduct a correlation analysis between immunological and echocardiographic parameters in children with pulmonary hypertension associated with congenital heart defects (CHD).*
Keywords*: pulmonary hypertension, heart, echocardiographic parameters.*

Objective: To conduct a correlation analysis between immunological and echocardiographic parameters in children with pulmonary hypertension associated with congenital heart defects (CHD).

Methods: 85 patients with CHD were followed dynamically, of which 61 were infants with CHD and pulmonary hypertension (study group) and 24 were children with CHD but without pulmonary hypertension (control group). The study was conducted at the clinical base of Tashkent Pediatric Medical Institute.

Results: Immunological biomarkers and morpho-functional parameters of the right heart were identified as potential predictors of pulmonary hypertension development in children with CHD. Endothelial dysfunction markers showed strong positive and negative associations with morpho-functional right heart parameters, allowing for early detection of pulmonary hypertension in patients with congenital malformations. Pediatric hypertensive vascular lung disease, associated with congenital heart defects (CHD), is a condition characterized by an average pulmonary artery pressure (PA) of ≥ 20 mmHg at rest, as determined by cardiac catheterization, and a general pulmonary resistance (OHL) of ≥ 3 units/m² for CHD with biventricular hemodynamics.

The development of hypertensive vascular lung disease in CHD depends on the anatomical variation, the size of the defect, and the volume of blood flow through the defect. Children with certain anatomical variants, such as uncorrected common arterial trunk or transposition of main vessels with double outlet right ventricle or non-restrictive ventricular septal defect (VSD), are at an increased risk for the earliest development of pulmonary vascular disease.

Other groups at risk include children with atrial septal defects. The rate of progression of pulmonary vascular disease may also depend on genetic predisposition.

Materials and Methods: During the period between 2019 and 2022, a total of 85 children with congenital heart defects (CHD) were examined and followed up, of which 61 were infants with CHD and pulmonary hypertension (PH) and 24 were children with CHD but without PH (clinical base at the TashPMI clinic). In all children, clinical symptoms of the condition, the degree and functional class of PH, hematological parameters, coagulation profile, echocardiographic findings, and markers of endothelial dysfunction were evaluated and analyzed.

Markers of endothelial dysfunction, including ET-1, vascular endothelial factor grooving (VEFG), and interleukin-1 (IL-1), were measured in the blood serum samples of patients using enzyme immunoassays (ELISAs) on an automated immunochemiluminescence analyzer (HUMAREADER HS, Biomedica, Germany). Additionally, the concentration of the N-terminal fragment of the pro-brain natriuretic peptide (BNP) in blood serum was measured using the same

automated immunochemiluminometer (HUMAREADER HS). Correlation analysis was conducted using Pearson's method to identify the statistical relationships between two or more variables.

The study findings: The analysis of right heart indicators was performed using ultrasound assessment of the heart and major vessels, as well as determination of pulmonary vascular resistance severity. It was observed that as arterial hypoxemia severity and Npro-BNP levels increase, so does vascular wall stiffness in the small vessel pathway, and correspondingly, increases in pulmonary artery pressure (Figure 1).

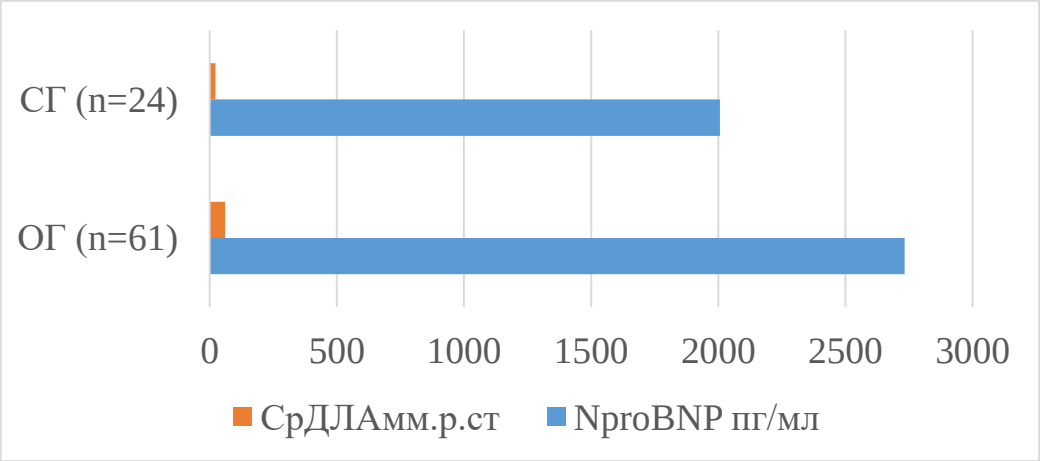

Figure 1: Pulmonary hypertension indicators in children with congenital heart defects.

Thus, in patients from the main group, the mean value of systolic pressure in the pulmonary artery (SDLA) was 55 mmHg. Arterial hypoxemia was most pronounced, with oxygen saturation at rest being 89.8%. Based on the findings of most researchers, echocardiography can be used in patients with CHD and pulmonary hypertension to assess the parameters of the right heart, identify early changes in the right ventricle, and determine the feasibility of surgical correction for the defect. Additionally, the rate of progression of right ventricular dysfunction can also be monitored [1, 3, 4]. When assessing the diameters of the right atrium, a significant increase in size was noted, with a twofold increase compared to the control group and a 1.6-fold increase compared with the comparison group. The diameter of the right ventricle also increased significantly, more than twofold, due to the development of myocardial hypertrophy.

The expansion of the cardiac chambers was facilitated by stretching of the atrial-ventricular ring of the tricuspid valve, with its size being twice that of the control level. Additionally, an increase in the diameter of the pulmonary artery trunk was observed, exceeding the values in children from the control group by more than twofold. In both groups of patients, the functional status of the endothelium was assessed by determining several functional characteristics, including levels of endothelin-1, the pro-inflammatory cytokine interleukin-1, and vascular endothelial growth factor, in relation to the severity of polycythemia and hypoxemia, as measured by blood gas analysis and other indicators. Of the blood coagulation system, we have identified markers that contribute to the development of pulmonary hypertension in our study participants due to the mechanisms described above. (Figure 2). As the endothelium becomes more affected, LH progresses and the levels of ET-1 in the plasma increase. It has been determined that damage to endothelial cells, as the disease advances, is accompanied by an increase in endothelin-1. In the main group, this indicator was 27.8-28.6% higher than the values in the control group ($p < 0.01$), and in patients in the comparison group it was 167.2% higher. ($p < 0.05$) The concentration of the

pro-inflammatory cytokine IL-1 showed a significant increase ($p < 0.001$) in the study group. All subjects had a high level of VEFG. Additionally, correlations between markers of endothelial dysfunction and hemodynamic, morpho functional, and biochemical parameters were identified for the purpose of future clinical applications (Table 1).

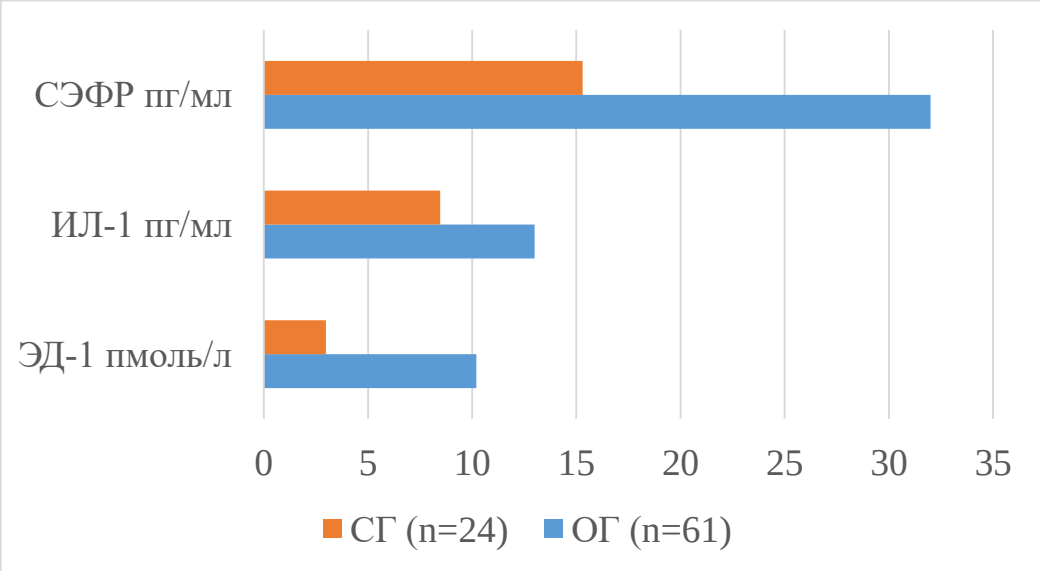

Figure 2: Markers of Endothelial Dysfunction in Children with LH-CHD

Table 1.

Correlation analysis of morpho functional parameters of the right ventricle and markers of endothelial dysfunction

	ED-1	IL-1	VEFG	SPPA (mmHg)	RA	DSPA	RV	Npro-BNP
Npro-BNP	0,956	0,843	0,934	0,867	0,74	0,574	0,849	-
IL-1	0,781	-	0,783	0,744	0,66	0,402	0,729	0,843
ED-1	-	0,781	0,823	0,758	0,66	0,572	0,801	0,956
VEFG	0,823	0,783	-	0,919	0,78	0,546	0,838	0,934

Note: ED-1 = endothelial dysfunction marker 1, IL-1 = interleukin-1, VEFG = soluble fraction of von Willebrand factor, SPPA = systolic pressure in the pulmonary artery, RA, DSPA = pulsatile pressure in the systemic artery, Npro = N-terminal prohormone of B-type natriuretic peptide, Npro-BNP = N-proBNP. Correlation analysis revealed a strong positive association between markers of endothelial dysfunction, namely endothelin-1 and N-pro-BNP. Another significant marker is VEFG, which showed a strong positive correlation with interleukin-1 and D-dimer. This indicates that the inflammatory response in pulmonary arterioles is increasing and leading to intimal hyperplasia, which in turn results in increased blood clotting and thrombus formation. Furthermore, the N-proBNP marker correlates with indicators of right-sided cardiac function, particularly with an increase in right ventricular size. This makes it possible to detect the development of pulmonary hypertension and right heart failure at an early stage. Additionally,

several statistically significant associations have been identified in the data presented in the table. And these connections serve as indicators that aid in the early detection of the development of pulmonary hypertension in children with congenital heart disease and the identification of these conditions in the outpatient setting.

Conclusion: Immunological biomarkers and morpho functional parameters of the right heart may serve as prognostic indicators for the development of pulmonary hypertension in children with CHD. Markers of endothelial dysfunction, such as ET-1, VEFG, IL-1, and NproBNP, have shown strong positive and negative correlations with morpho functional parameters of the right heart, allowing for an early diagnosis of pulmonary hypertension in children with congenital abnormalities.

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