

ABSTRACT OF THE DISSERTATION

for the degree of Doctor of Philosophy (PhD) on the topic:

Comprehensive assessment of serotonin metabolism in children with congenital heart defects complicated by pulmonary hypertension

Specialty: 8D10100 - Медицина

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Relevance of the study. Pulmonary arterial hypertension (PAH) is rightfully regarded as one of the most severe and prognostically unfavorable complications of congenital heart defects (CHD) in children. The pathogenesis is based on elevated pressure recorded in the pulmonary artery system. Under its influence, a process of progressive remodeling of the pulmonary vascular bed is initiated, which inevitably leads to increasing overload of the right heart chambers. The logical culmination of this chain of events is the development of chronic heart failure. Speaking of the scale of the problem and referring to epidemiological data, we observe that congenital heart defects (CHD) occur in approximately 8 infants per 1000 newborns. Moreover, if one follows the fate of these patients, it turns out that practically every third one of them, at one stage or another of the disease, encounters manifestations of pulmonary hypertension. The overwhelming majority of cases (86%) of secondary PAH fall on infants with transient PAH, including patients with correctable congenital heart defects. The development of PAH significantly worsens the clinical course of CHD, is associated with a high risk of irreversible vascular changes, and considerably increases mortality, especially in conditions of late diagnosis and untimely performance of radical surgical correction [1–4].

Despite significant progress in cardiac surgery and the introduction of modern methods of early correction of CHD, the problem of PAH in pediatric cardiology retains its relevance. Notwithstanding the successful elimination of the anatomical defect and the subsequent normalization of systemic hemodynamics, a certain proportion of patients still exhibit signs of pulmonary hypertension, varying in their degree of severity [5]. Such a clinical picture naturally fuels research interest, focusing it on the study of subtle molecular and biochemical mechanisms that initiate and sustain the pathological process. Of particular importance is the search for pathogenetically significant markers or biological indicators capable not only of objectively reflecting the dynamics of the disease, but also of serving as a criterion for the effectiveness of the therapy being administered.

In the pathogenesis of pulmonary arterial hypertension (PAH) developing against the background of congenital heart defects (CHD), the key triggering factor is a chronically existing pathological blood shunting. This refers to the shunting of blood both through intracardiac communications (defects of the interventricular or interatrial septum) and through extracardiac communications, for example, a patent ductus arteriosus. The chronic volume overload of the pulmonary circulation arising from this leads to a critical increase in shear stress on the endothelium of the vascular wall, provoking persistent spasm of the pulmonary arteries and gradually forming endothelial dysfunction. The cascade of pathological reactions triggered thereafter — such as medial hypertrophy, proliferation of smooth muscle cells, and progressive intimal thickening, which constitutes the morphological basis of pulmonary vascular remodeling — steadily reduces their reactivity. Having reached a certain stage of development, these structural changes acquire an irreversible character, making it impossible to restore normal pulmonary hemodynamics even with brilliantly performed surgical correction of the defect [5, 6].

One of the key factors in vascular remodeling in PAH is serotonin (5-hydroxytryptamine, 5-HT), which possesses pronounced vasoconstrictive and mitogenic effects. A number of studies have shown that an increase in the concentration of serotonin in the blood is associated with hyperplasia of smooth muscle cells of the vascular wall, enhanced expression of serotonin receptors and the serotonin transporter (SERT), as well as activation of intracellular signaling cascades that promote proliferation and remodeling of the pulmonary arteries. In patients with PAH against the background of CHD, certain changes in the serotonergic system have been described. At the same time, the majority of published works are cross-sectional in nature and do not allow a full assessment of the dynamics of changes in the serotonergic system in the pre- and postoperative period, which significantly limits the possibilities of the practical application of these indicators as markers for monitoring the condition of patients [7, 8].

Alongside the serotonergic system, our study included an examination of insulin-like growth factor-1 (IGF-1). IGF-1 is involved in the regulation of proliferation and differentiation. Insulin-like growth factor-1 (IGF-1) takes an active part in the control of proliferation and differentiation of endothelial cells, modulation of angiogenesis, and the realization of adaptive reactions of the vascular wall arising in response to mechanical or hypoxic stress. Analyzing the available literature, one can find data indicating changes in the concentration of IGF-1 in various forms of pulmonary hypertension. However, the results of these works, being extremely ambiguous, demonstrate a pronounced dependence on the age of patients, the stage of the pathological process, and the nature of the therapy being administered. Particularly fragmentary and limited are the data concerning the role of IGF-1 in the cohort of children with CHD complicated by PAH. Extremely scarce are also data on the dynamics of this factor after surgical correction of the defect, which dictates the need for targeted research in this direction [9].

The currently existing diagnostic and therapeutic approaches to the management of children with CHD and PAH focus predominantly on clinical and instrumental indicators. Biochemical and molecular markers that directly reflect the key links of pathogenesis, however, remain underutilized and insufficiently integrated into real clinical practice. Such a state of affairs makes especially relevant the carrying out of a comprehensive analysis of those regulatory systems that are involved in the formation and progression of pulmonary vascular pathology.

A comprehensive study of serotonin metabolism, its main metabolite (5-hydroxyindoleacetic acid — 5-HIAA) and IGF-1 in children with PAH, studied in dynamics before and after surgery, opens new prospects. Such an integrative approach allows not only to substantially deepen the understanding of the pathogenetic mechanisms responsible for the development and persistence of pulmonary hypertension in CHD, but also to identify potential biomarkers. The latter, in turn, could become a reliable tool for early diagnosis, objective prediction of the course of the disease, and, most importantly, for the quantitative assessment of the effectiveness of the surgical correction performed.

Aim of the Study - to conduct a comprehensive assessment of serotonin metabolism in children with congenital heart defects complicated by pulmonary hypertension.

Objectives of the Study:

1. To investigate the state of the serotonergic system in children with congenital heart defects complicated by pulmonary hypertension, based on indicators of serotonin metabolism, transport, and reception in blood plasma, the platelet pool, and urine.
2. To assess the level of insulin-like growth factor-1 (IGF-1) in plasma and platelets and to analyze its relationship with the parameters of the serotonergic system and the clinical and instrumental characteristics of the patients.
3. To develop integrated diagnostic indices based on the studied biochemical and molecular indicators and to evaluate their relationship with clinical and instrumental parameters to determine the diagnostic and prognostic significance of these indices.
4. To evaluate the relationship of the integrated indices with clinical and instrumental parameters and to determine the diagnostic and prognostic significance of these indices.

Scientific novelty. For the first time, a comprehensive study of the dynamics of serotonin metabolism and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in plasma and urine was conducted in young children with congenital heart defects (CHD) complicated by pulmonary arterial hypertension (PAH), both before and after surgical correction.

Our study convincingly demonstrated that patients suffering from PAH exhibit profound alterations in the concentrations of serotonin and its principal metabolite, 5-HIAA. These changes, reflecting the complex pathophysiological processes occurring within the pulmonary vascular bed and directly within the pulmonary vascular wall, deserve particular attention.

For the first time, we obtained data establishing a direct relationship between the level of circulating plasma serotonin and its transport activity mediated by platelets. Furthermore, a clear dynamic pattern of these parameters was identified, demonstrating characteristic changes following surgical intervention.

Although the literature has indicated a role for insulin-like growth factor-1 (IGF-1) in the regulation of vascular tone and remodeling, its behavior in PAH developing in children with CHD had remained unexplored. Our findings fill this gap, allowing IGF-1 to be considered an additional pathogenetically significant marker reflecting vascular wall remodeling processes in this complex category of patients.

For the first time, a comparative analysis of IGF-1 dynamics in relation to serotonin metabolism parameters was performed. This comparison enabled the identification of previously unknown pathogenetic mechanisms responsible for the progression of pulmonary hypertension even after successful surgical treatment.

When analyzing earlier studies devoted to PAH in children, one cannot fail to notice their fragmented nature: individual parameters of the serotonergic system, including serotonin concentration, the level of its metabolite (5-HIAA), or the activity of the serotonin transporter (SERT), were studied in isolation. However, a comprehensive assessment of serotonin metabolism as a unified, integrative system in children with CHD complicated by PAH has not previously been undertaken (at

least in the scientific literature available to us). In the present study, this gap has been addressed: for the first time, an integrated investigation encompassing the key components of serotonin metabolism and tracking their dynamics both before and after surgical correction of the defect is presented.

Taken together, the obtained results not only provide a new perspective on the role of the serotonergic system and IGF-1 in the development and progression of PAH in children with congenital heart defects, but also significantly expand current understanding of the metabolic aspects of vascular remodeling and open additional opportunities for assessing the effectiveness of surgical intervention.

Certificates of intellectual property were obtained: No. 55841 dated March 17, 2025, “Prospects for the Use of Insulin-Like Growth Factor-1 (IGF-1) in Molecular Technologies for the Diagnosis and Treatment of Pulmonary Hypertension in Children”; and No. 66780 dated January 28, 2026, “The Use of 5-Hydroxyindoleacetic Acid (5-HIAA) as a Method for Early Diagnosis and Prognosis of Pulmonary Hypertension in Children” (Appendices B and G).

Practical significance. The practical value of our study is primarily determined by the possibility of using the obtained results to improve the diagnosis, monitoring, and accuracy of prognostic assessment of the course of pulmonary arterial hypertension (PAH) that develops in children with congenital heart defects (CHD). Equally important is the potential application of these findings for the objective evaluation of the effectiveness of surgical correction of the defect, representing a promising direction for future research.

During the course of the study, we identified specific biochemical markers that are sufficiently sensitive and reflect both the severity of hypertensive changes within the pulmonary circulation and the dynamics of vascular remodeling processes. Determination of serotonin concentrations and its principal metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in blood plasma and urine before and after surgery may serve as a reliable tool for assessing the effectiveness of surgical treatment as well as the reduction of pulmonary hypertension. In addition, this approach enables postoperative monitoring and facilitates the timely detection of persistent pulmonary hypertension.

Particular emphasis should be placed on the diagnostic and prognostic significance of the identified biomarkers in children with CHD complicated by PAH. The use of these indicators in clinical practice provides an opportunity to implement a personalized approach to patient management, more accurately determine the risk of residual pulmonary hypertension, and predict long-term outcomes of surgical correction with greater confidence.

Completely novel data were also obtained regarding the dynamics of insulin-like growth factor-1 (IGF-1) in this category of patients. The identified patterns allow IGF-1 to be considered a potential marker that is highly responsive to vascular wall remodeling processes. When incorporated into standard diagnostic algorithms, analysis of IGF-1 dynamics may significantly optimize the management strategies of patients who have undergone surgical correction of congenital heart defects.

It is evident that a comprehensive investigation of serotonin metabolism and its derivatives, supplemented by the analysis of IGF-1, opens new opportunities for a more

refined and accurate assessment of the condition of the pulmonary vascular bed. Such an approach makes it possible not only to detect developing secondary pulmonary hypertension in a timely manner but also to implement measures aimed at preventing its further progression.

The results obtained in our study will undoubtedly find practical application in clinical practice, particularly in the work of cardiologists, cardiac surgeons, and pediatricians who encounter this complex pathology on a daily basis. Furthermore, the principal findings and conclusions of the study have already been integrated into the educational process of the Non-Commercial Joint-Stock Company “Karaganda Medical University,” thereby contributing to the training of future healthcare professionals.

The implementation of the diagnostic and prognostic approaches proposed in this study into routine healthcare practice will contribute to improving the quality of medical care provided to patients with CHD, reduce the risk of residual pulmonary hypertension, and ultimately increase the effectiveness of surgical treatment in this severe category of patients.

Provisions submitted for defense.

1. Disturbances of serotonergic regulation in pulmonary arterial hypertension in children with congenital heart defects are characterized by a change in serotonin distribution, manifested by a decrease in its intraplatelet deposition with a tendency to increase circulating levels (more than 3 times relative to control) in the absence of stable intergroup differences in the concentration of the membrane transporter SERT. These features reflect dysregulation of serotonin deposition and transport processes as one of the pathophysiological mechanisms of this disease.
2. Serotonin metabolism in pulmonary arterial hypertension in children with congenital heart defects is characterized by an imbalance in its catabolism and excretion, which is manifested by a decrease in the concentration of 5-hydroxyindoleacetic acid (5-HIAA) in blood plasma (1.4 times) while increasing its excretion in urine (6.6 times). The identified features indicate an imbalance between the circulating and metabolic links of the serotonergic system.
3. Pulmonary arterial hypertension in children with congenital heart defects is associated with a decrease in the level of insulin-like growth factor-1 (IGF-1) in blood plasma (1.9 times) in the absence of statistically significant changes in its intraplatelet content, which indicates the predominant role of the systemic pool of growth factors in the pathogenesis of this disease.
4. The formation of integrated diagnostic indices based on indicators of the serotonergic system and IGF-1, such as 5-HIAA platelets/plasma (increased 1.5 times), SERT/serotonin (increased 1.6 times), and IGF-1 plasma/platelets (decreased 14.9 times) in patients compared to controls, makes it possible to quantitatively characterize the intercompartmental redistribution of metabolites and growth factors in pulmonary arterial hypertension in children with congenital heart defects.
5. Assessment of the relationship between the obtained integrated indices and clinical-instrumental parameters allows us to determine their high diagnostic and prognostic significance in pulmonary arterial hypertension in children with congenital heart

defects, which is confirmed by the presence of strong correlations with hemodynamic parameters and high sensitivity and specificity according to ROC analysis.

Implementation of the research results. The results of this study have been implemented into the educational process at the Department of Pediatrics with a course in Neonatology through the use of the obtained scientific data in teaching the discipline "Pediatrics in General Medical Practice" to 6th-year students of specialty 6B10102 - "Medicine", and the discipline "Inpatient Treatment of Children and Adolescents" for 5th-year students of specialty 6B10108 - "Pediatrics". The main provisions and conclusions of the work have been integrated into thematic lectures, practical classes, and clinical case discussions (Appendices A, B).

Personal contribution of the author. The doctoral candidate independently performed the selection and analysis of scientific literature, developed the research plan, formulated the aims and objectives, developed the study design, determined the inclusion and exclusion criteria for patients, as well as collected clinical material and prepared medical documentation. The laboratory part of the study was carried out jointly with research staff of the laboratory of the Institute of Life Sciences, Akhmaltdinova L.L., Avdienko O.V. The doctoral candidate performed statistical data processing, interpretation of the results obtained, formulation of conclusions, and writing of the dissertation text.

The study was conducted within the framework of the grant project IRN AR14871767 "Development of innovative molecular technologies for the diagnosis and evaluation of the effectiveness of treatment of pulmonary arterial hypertension in preschool children" 2022-2024, in which the doctoral candidate acted as the principal investigator at all stages of the work.

Approbation of the work. The main provisions of the study were reported and discussed at the following scientific events:

34th European Pediatrics Conference (Zurich, Switzerland, October 9-10, 2023), where the doctoral candidate presented an oral report on "Study of Serotonin Metabolism in Children with Congenital Heart Defects"; 10th Congress of the European Academy of Paediatric Societies (EAPS 2024) (Vienna, Austria, October 17-20, 2024), where the doctoral candidate presented an oral report on "Biomarkers for Diagnosing and Monitoring Pulmonary Hypertension in Children with Congenital Heart Defects"; XX International / XXIX All-Russian Pirogov Scientific Medical Conference of Students and Young Scientists (Moscow, March 2025), where the doctoral candidate presented an oral report on "Insulin-like growth factor-1 as an indicator of the effectiveness of surgical treatment of congenital heart disease complicated by pulmonary arterial hypertension."

The following abstracts have been published: in the collection of scientific works of the X Anniversary Congress "Pulmonary Hypertension – 2022" (Russia, Moscow); XII All-Russian Congress "Pediatric Cardiology – 2022" (Russia, Moscow, December 8-10, 2022); a poster report "Clinical case of pulmonary arterial hypertension in a child with congenital heart disease: difficulties of diagnosis and treatment" was presented at the VI Central Asian International Scientific and Practical Conference "Education of the Future: Wind of Change" (Karaganda, Kazakhstan, April 20-21, 2023); the abstract

"The role of the platelet component and the serotonin system in the development of pulmonary arterial hypertension in children with congenital heart defects" was published in the collection of abstracts of the All-Russian Congress "Pulmonary Hypertension – 2023" (Russia, Moscow, December 14-15, 2023); the abstract "The effect of excess serotonin in the embryonic period of ontogenesis on the activity of the membrane serotonin transporter in early postnatal ontogenesis" was published based on the materials of the XXIV Congress of the I.P. Pavlov Physiological Society (St. Petersburg, September 11-15, 2023); the abstract "Features of serotonin metabolism and expression of insulin-like growth factor-1 in children with congenital heart defects complicated by pulmonary hypertension" II All-Russian Conference "Samoylov Readings" (Russia, Kazan, 30.01.2026).

Publications on the topic of the dissertation. On the topic of the dissertation, 6 scientific works have been published, including: 2 articles in scientific publications of Kazakhstan recommended by the Committee for Quality Assurance in Science and Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan, 3 articles in international scientific journals included in the Scopus database, 1 monograph; 2 certificates of entry of information into the state register of rights to copyright-protected objects.

Study design, materials and methods:

Study design - a prospective longitudinal comparative study (prospective cohort analysis). The choice of this model is determined by the aim of assessing dynamic changes in the concentration of biomarkers in biological fluids (plasma, platelets, urine) in the same cohort of patients before and after surgical correction of CHD. The prospective nature of data collection ensured a high level of control over the process and minimized the risks of retrospective bias.

The study protocol was reviewed and approved by the Local Ethics Committee of Karaganda Medical University (Protocol No. 37 dated 29.03.2022). The interests and rights of all minor participants were protected by obtaining written informed consent from their parents or legal representatives.

The formation of the sample took place from June 2022 to December 2024. The children were divided into three groups:

- Group I (n=46) - formed from children with a verified diagnosis of CHD complicated by PAH at the cardiac surgery department of the public enterprise "Multidisciplinary Hospital No. 2 of Karaganda." All patients in this group underwent a baseline examination (time point T1) before planned surgical intervention.
- Group II (n=32) - formed from the original cohort and included children who completed longitudinal follow-up and were re-examined in the planned postoperative period (time point T2). The dropout of 14 patients was due to organizational and logistical reasons for follow-up.
- Group III (n=24) - comparison group (control). To determine reference values of the studied biomarkers and conduct a comparative analysis, a group of conditionally healthy children, comparable in age and sex, was assembled. The control group was examined once.

Statistical analysis was performed using the IBM SPSS Statistics software package (version 26.0). Since the distribution of most indicators deviated from normal, data are presented as median (Me) and interquartile range [25th; 75th percentiles]. When statistically significant differences were detected ($p < 0.05$), the Mann-Whitney U test was used for pairwise comparison of independent groups, and the Wilcoxon signed-rank test was used to assess differences between related samples.

Spearman's rank correlation coefficient was used to assess the relationship between parameters. The diagnostic efficiency of the studied biomarkers was evaluated using receiver operating characteristic analysis (ROC analysis) with calculation of the area under the curve (AUC), optimal cut-off point, sensitivity, and specificity. In all types of analysis, differences were considered statistically significant at $p < 0.05$.

Conclusions:

1. Changes in the parameters of the serotonergic system were revealed, manifested by a violation of the compartmental distribution of serotonin with relative preservation of membrane transport. The concentration of serotonin in the blood plasma of patients with CHD complicated by PAH was characterized by higher values compared to the control group (Me 32.27 and 31.00 ng/ml vs. 10.10 ng/ml), in the absence of significant differences between the pre- and postoperative periods. At the same time, a statistically significant decrease in the concentration of serotonin in platelets was found compared to healthy children ($p=0.049$), whereas the concentration of SERT in the platelet pool did not differ significantly between groups ($p>0.05$). The obtained data indicate a dissociation between circulating serotonin and its intracellular deposition.
2. It was found that the concentration of 5-HIAA in the blood plasma of patients with CHD and PAH was lower compared to the control group (Me 8.20 and 8.81 ng/ml vs. 11.33 ng/ml; $p=0.02$). At the same time, the level of 5-HIAA in urine was significantly higher in children with CHD and PAH before surgery compared to the control group (Me 6.55 vs. 1.00 ng/mmol creatinine; $p=0.026$) and was characterized by a decrease after surgical correction. The concentration of 5-HIAA in platelets did not differ statistically significantly between groups, indicating a predominant involvement of serotonin catabolism and excretion processes with relative stability of the intraplatelet metabolite depot.
3. A statistically significant decrease in the level of IGF-1 in the blood plasma of patients with CHD complicated by PAH was revealed compared to the control group. The median concentration of IGF-1 was 8.90 ng/ml before surgery and 11.42 ng/ml after surgery vs. 17.01 ng/ml in conditionally healthy children ($p=0.000074$). The concentration of IGF-1 in platelets did not differ significantly between groups ($p>0.05$), despite a trend towards higher values before surgical correction, indicating a predominant involvement of the circulating pool of growth factor in the pathogenetic mechanisms of pulmonary arterial hypertension.
4. The diagnostic value in assessing metabolic disorders in PAH was confirmed by integrated indices: 5-HIAA platelets/plasma, SERT/serotonin, and especially IGF-1 plasma/platelets (AUC=0.929; sensitivity 95%, specificity 86%), reflecting the intercompartmental redistribution of the studied biomarkers.

5. The established correlations between biomarkers of the serotonergic system, integrated indices, and hemodynamic parameters reflect their pathophysiological significance in PAH. Thus, the level of IGF-1 in blood plasma and the IGF-1 plasma/platelets index demonstrated an inverse correlation with estimated systolic pressure in the pulmonary artery ($r=-0.44$ and $r=-0.65$, respectively; $p<0.05$), indicating a relationship between IGF-1 deficiency and redistribution with increasing pulmonary hypertension. Serotonin metabolism indicators were characterized by multidirectional correlations with hemodynamic parameters: the concentration of 5-HIAA in blood plasma correlated inversely with estimated systolic pressure in the pulmonary artery ($r=-0.42$; $p<0.05$), whereas the level of 5-HIAA in urine and the integrated indices 5-HIAA plasma/urine and 5-HIAA platelets/plasma had a direct correlation with this parameter ($r=0.49$; $r=0.52$ and $r=0.49$, respectively; $p<0.05$), reflecting increased serotonin catabolism and an imbalance between biological media during PAH progression.
6. According to ROC analysis, the greatest diagnostic accuracy in detecting pulmonary arterial hypertension in children with congenital heart defects was characterized by the level of 5-HIAA in urine (AUC=0.871), the concentration of IGF-1 in blood plasma (AUC=0.781), and the IGF-1 plasma/platelets index (AUC=0.929), which indicates the high sensitivity and specificity of these indicators and their correlation with the degree of vascular remodeling.

Scope and structure of the dissertation. The dissertation contains 103 pages of typewritten text, consists of an introduction, a literature review, a main part (materials and methods of research, results of own research), a conclusion with conclusions, 28 tables, 12 figures, and a bibliography including 113 sources.

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