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Platelet-serotonin Dynamics: Elucidating Their Role in Pulmonary Arterial Hypertension

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Abstract

Background and Objectives: Pulmonary arterial hypertension (PAH) is a significant complication in pediatric patients with congenital heart disease (CHD). The role of platelets and serotonin in the pathogenesis of PAH has been increasingly recognized. This study aims to investigate the correlation between platelet count, serotonin levels, and PAH in children with CHD, and to understand the impact of surgical intervention on these parameters.

Material and Methods: This study included 26 children with CHD and PAH (Group I) and an 11-child control group without PAH. Pre- and post-operative platelet counts, mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), and serotonin levels in plasma and platelets were measured. Group I underwent surgical correction for CHD, and the control group received no such intervention. Data were analyzed to determine the relationships between these hematological and biochemical markers and PAH.

Results: Group I showed higher pre-operative platelet counts and serotonin levels compared to the control group. Post-surgical data indicated a significant decrease in platelet serotonin levels, aligning more closely with the control group. The study also observed lower plasma serotonin levels in the control group, suggesting altered serotonin metabolism in PAH patients.

Conclusion: The study suggests a strong association between elevated platelet counts, increased serotonin levels, and the presence of PAH in children with CHD. Surgical correction of CHD appears to normalize these parameters, indicating a potential pathophysiological link. These findings emphasize the need for further research to understand the underlying mechanisms and to explore targeted therapeutic strategies for PAH in pediatric CHD patients.

Keywords: children, congenital heart defects, pulmonary arterial hypertension, platelets, serotonin

Introduction

Pulmonary Arterial Hypertension (PAH) in the context of Congenital Heart Defects (CHD) represents a critical intersection of two complex cardiovascular pathologies, each contributing to a multifaceted clinical presentation and progression. The pathophysiology of PAH in CHD encompasses a range of mechanisms, from molecular alterations to functional changes in the heart and lungs [1].

In the pediatric population, CHDs such as atrial and ventricular septal defects, patent ductus arteriosus, and more complex anomalies like Eisenmenger syndrome are significant contributors to the development of PAH. These congenital anomalies create abnormal connections between the systemic and pulmonary circulations or defects within the heart chambers, leading to altered hemodynamics. The increased blood flow through these abnormal pathways, particularly those that shunt blood from the systemic to the pulmonary circulation, results in elevated pressure in the pulmonary artery—a condition termed pulmonary hypertension [2].

The initial response of the pulmonary vasculature to increased blood flow and pressure is often compensatory. This response can include hypertrophy of the vascular smooth muscle cells and endothelial proliferation. However, these changes eventually become maladaptive, leading to progressive narrowing and stiffening of the pulmonary arteries. This phenomenon, known as vascular

remodeling, is a hallmark of PAH and is driven by complex interactions between endothelial cells, smooth muscle cells, and the extracellular matrix [3].

A key aspect of the pathophysiology of PAH in CHD is endothelial dysfunction. Normally, the endothelium plays a critical role in maintaining vascular tone by balancing vasoconstrictive and vasodilative substances. In PAH, this balance is disrupted, favoring vasoconstriction, inflammation, and thrombosis. Endothelial dysfunction in PAH is characterized by reduced production of nitric oxide (NO) and prostacyclin, both potent vasodilators, and an increased expression of endothelin-1, a potent vasoconstrictor. These changes contribute significantly to increased pulmonary vascular resistance, a defining feature of PAH [4].

The role of genetic and molecular factors in the pathogenesis of PAH in the setting of CHD is also increasingly recognized. Research has identified several genetic mutations and polymorphisms that may predispose individuals to more severe vascular remodeling and PAH. For instance, mutations in the BMPR2 gene, which plays a role in the regulation of pulmonary vascular growth and inflammation, have been identified in some patients with PAH [5].

Over time, the persistent elevation in pulmonary arterial pressure due to these combined mechanisms places an increased workload on the right ventricle. In an attempt to compensate, the right ventricle undergoes hypertrophy and dilation, changes that initially help maintain cardiac output. However, these adaptations can become maladaptive, leading to right ventricular dysfunction and failure, which are major determinants of prognosis in PAH associated with CHD [5].

Another aspect of the pathophysiology of PAH in CHD is the development of Eisenmenger syndrome in some patients. This syndrome represents an advanced form of PAH where prolonged high pressure in the pulmonary circulation causes a reversal of the initial left-to-right shunt to a right-to-left shunt. This shunting leads to cyanosis as oxygen-poor blood bypasses the lungs and enters systemic circulation, a situation that significantly complicates the clinical management and prognosis of these patients [6].

The progressive nature of PAH in the setting of CHD is also characterized by a decreased response to vasodilator therapy, unlike idiopathic PAH. This resistance to treatment is partly due to the fixed component of the increased pulmonary vascular resistance due to structural changes in the pulmonary vasculature. These pathophysiological changes culminate in increased pulmonary arterial pressure, right ventricular overload, and ultimately heart failure. Understanding these mechanisms is crucial for the development of targeted therapies and the improvement of clinical outcomes in this patient population [7].

Platelets in PAH pathogenesis. In the pathogenesis of PAH, platelets play a pivotal and multifaceted role, contributing significantly to the progression of this complex vascular disorder. Central to the formation of in-situ thrombi in the small pulmonary arteries, a characteristic feature of PAH, platelet activation and aggregation lead to increased pulmonary vascular resistance and pressure. This thrombotic activity is further exacerbated by the release of serotonin, a potent vasoconstrictor and pro-fibrotic agent, from the dense granules within the platelets. Upon activation, platelets expel serotonin into the pulmonary circulation, instigating not only vasoconstriction but also stimulating smooth muscle cell proliferation, thereby contributing to the pathological remodeling of pulmonary arteries [8, 9].

Serotonin in PAH pathogenesis. Serotonin, also known as 5-hydroxytryptamine (5-HT), is a multifunctional monoamine neurotransmitter that exerts significant influence in various physiological systems, including the vascular system. Its role in vascular biology is complex and multifaceted, impacting vascular tone, endothelial function, and contributing to vascular pathologies such as atherosclerosis, pulmonary hypertension, and more [10, 11, 12].

The study of platelet and serotonin dynamics offers a promising avenue for unraveling the complex etiology of PAH, potentially leading to more targeted and effective therapeutic strategies. Such research is not only pivotal for advancing our fundamental knowledge but also holds significant clinical implications in improving the management and outcomes of patients suffering from this challenging condition.

The aim of this study is to investigate the dynamics of platelets and serotonin in the etiology of PAH.

Materials and Methods

The study was authorized by ethic committee of Karaganda Medical University No. 37 dd. 29.03.2022. In this study, informed consent was obtained from the parents of all participating patients. Participant recruitment was conducted at the Karaganda City Cardiosurgery Center (Kazakhstan). The study cohort was stratified into two distinct groups. The I group comprised children diagnosed with CHDs complicated by PAH before and after surgical treatment. The II group included the control, consisting of healthy children free from CHD and PAH. Inclusion criteria for the I group encompassed the presence of a medically confirmed CHD, the presence (or absence, for the second group) of pulmonary hypertension, no current infectious complications, and an age range from 0 to 7 years, alongside parental or legal guardian consent for the child's involvement in the research. For the II group, the criteria were the absence of significant somatic pathologies, including CHD and PAH, no active infectious or inflammatory conditions, and an age range of 0 to 7 years, in addition to parental or guardian consent. The inclusion of a control group in our study was essential to establish a comparative reference point for evaluating the specific effect of the serotonin system on pulmonary hypertension. By comparing outcomes between the intervention group and the control group, we could effectively control for confounding variables and discern the true impact of serotonin dynamics on disease progression.

The sample size for our study was meticulously determined based on statistical considerations, including the desired level of confidence, margin of error, and expected variability of the data. This rigorous approach ensures that our study is adequately powered to detect significant differences or relationships with confidence.

Our primary research question was to investigate the influence of the serotonin system on the development of pulmonary hypertension in children with congenital heart defects. This question stems from a recognized gap in the literature regarding the understanding of the pathophysiological mechanisms underlying pulmonary hypertension in this specific patient population.

For laboratory analysis, several parameters were evaluated: the quantity of blood platelets and their specific attributes (including mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit) (PCT), along with the concentration of serotonin in both blood serum and platelets. The process involved using citrated whole blood for platelet

extraction and EDTA-plasma for obtaining Platelet Poor Plasma (PPP).

The hematological investigations involved assessing the platelet count and various platelet indices (mean platelet volume, the coefficient of variation in platelet volume, plateletcrit) using the Hematology analyzer Mindray 3200. The extraction of platelets was carried out from the citrated plasma.

For the immunoassay analysis, particularly for measuring serotonin levels, the study employed ELISA kits manufactured by Cloud-Clone Corp.

In terms of statistical methodology, normal quantitative data were expressed using the mean (M) and standard deviations (SD), providing a comprehensive statistical overview of the collected data.

Results

Group I, consisting of 26 pediatric patients, exhibited a median age of 9 months. The age spectrum extended from a minimum of 1 month to a maximum of 6 years. This group demonstrated an equitable gender distribution, with a 50:50 ratio of male and female participants. Each child in this group was clinically diagnosed with congenital heart disease. The prevalence of specific cardiac anomalies varied: atrial septal defect (ASD) was observed in 38% of the cases, ventricular septal defect (VSD) in 7%, patent ductus arteriosus (PDA) in 2%, and a combination of these defects in an additional 7%. Regarding pulmonary arterial hypertension (PAH), 11.5% of the subjects presented with a high degree of severity, whereas the remainder exhibited moderate to mild levels . Surgical intervention was undertaken for all individuals to mitigate the risk of right ventricular failure.

Pre-operative hematological and biochemical parameters were recorded. The average platelet count stood at 328.28 thousand/µl, with a median value of 344.00 thousand/µl. Additional parameters, such as median mean platelet volume (MPV) at 7.30 fl, platelet distribution width (PDW) at 15.70%, and plateletcrit (PCT) at 0.23%, were noted (p-value = 0.005). Serotonin levels, both in plasma and platelets, were quantified before surgery. Plasma serotonin fluctuated between 2.31 ng/ml and 193.54 ng/ml, averaging at 41.72 ng/ml. Platelet serotonin concentrations varied from 1.90 ng/ml to 230.21 ng/ml, with an average of 21.09 ng/ml (p-value = 0.05).

Table 1 Characteristics of the Study Groups

Characteristic	Group I	Group II
Age Range	1 month - 6 years	6 months - 7 years
Gender Distribution	50% male, 50% female	45% male, 55% female
Diagnosis	Congenital Heart Disease	None (No Heart Disease)
Prevalence of Cardiac Anomalies	- Atrial Septal Defect (ASD): 38%	Control group
	- Ventricular Septal Defect (VSD): 7%	Control group
	- Patent Ductus Arteriosus (PDA): 2%	Control group
	- Combination of Defects: 7%	Control group
Pulmonary Arterial Hypertension (PAH)	- 11.5% with high severity	Control group
	- 88.5% moderate to mild levels	Control group
Surgical Intervention	Yes	No

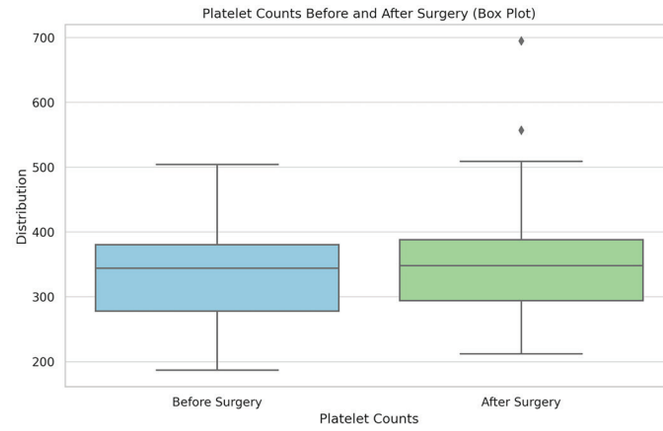

Figure 1 - The number of people with ASD in the respondent's environment

Figure 2 - The number of people with ASD in the respondent's environment

Figure 3 - The number of people with ASD in the respondent's environment

Post-surgical assessments revealed significant changes. The average platelet count increased to 377.25 thousand/µl, with a median of 348.00 thousand/µl. There were slight alterations in MPV (median of 7.70 fl), PDW (15.60%), and PCT (0.25%) (p-value = 0.005). Postoperative plasma serotonin levels were observed in the range of 4.10 ng/ml to 174.19 ng/ml, with a mean value of 50.80 ng/ml. In contrast, platelet serotonin concentrations were noted to be between 1.30 ng/ml and 14.20 ng/ml, averaging at 8.70 ng/ml (p-value = 0.05).

The control group, comprising 11 children aged between 6 months and 7 years (median age 3 years), included 45% male and 55% female subjects. Baseline hematological measurements in this cohort showed an average platelet count of 287.45 thousand/μl, with a median of 299.00 thousand/μl. The control group's median MPV was registered at 8.30 fl, PDW at 14.20%, and PCT at 0.22% (p-value = 0.005). Serotonin levels in this group also varied, with plasma levels ranging from 7.30 ng/ml to 41.05 ng/ml (mean 17.24 ng/ml) and platelet serotonin concentrations spanning from 10.58 ng/ml to 34.76 ng/ml (mean 20.26 ng/ml, p-value = 0.05).

Discussion

In the realm of cardiovascular physiology, platelets and serotonin, particularly platelet-derived serotonin, play a critical role. Beyond their well-known functions in hemostasis, these elements are integral to the development of the cardiovascular system and the pathogenesis of PAH.

In PAH, where endothelial dysfunction is prominent, platelets adhere to the damaged endothelial cells, amplifying vasoconstriction and fostering vascular remodeling – processes that are central to the disease's pathogenesis. Beyond their role in coagulation and vasoconstriction, platelets also partake in inflammatory processes. They release pro-inflammatory cytokines and engage in crosstalk with leukocytes, thus maintaining an inflammatory milieu within the pulmonary vasculature, which is increasingly acknowledged as a critical component in the development of PAH [13, 14, 15].

Additionally, platelets secrete growth factors such as Platelet-Derived Growth Factor (PDGF) and Transforming Growth Factor-Beta (TGF-β), both of which are implicated in the pathological remodeling of pulmonary arteries. These growth factors promote the proliferation and migration of smooth muscle cells and fibroblasts, culminating in the detrimental remodeling that typifies PAH [16].

One of the critical functions of serotonin in vascular biology is the regulation of vascular tone. Serotonin exerts its effects on blood vessels through a diverse array of receptors, predominantly through the 5-HT1 and 5-HT2 receptor families. The 5-HT1 receptors, particularly the 5-HT1B and 5-HT1D subtypes, are known to mediate vasoconstriction in certain blood vessels, including coronary arteries. Conversely, the 5-HT2 receptors, especially 5-HT2A, are associated with both vasoconstriction and vasodilation, depending on the vascular bed and the state of the endothelium. The net effect of serotonin on vascular tone is context-dependent, influenced by factors such as the type of blood vessel, the local concentration of serotonin, and the relative expression of its receptors [17, 18].

In healthy endothelium, serotonin typically induces vasodilation, mediated through the release of endothelium-derived relaxing factors like nitric oxide (NO) and prostacyclin. This vasodilatory effect is often attenuated in conditions where endothelial function is impaired, such as in atherosclerosis or hypertension, leading to a more pronounced vasoconstrictive response to serotonin [18].

The endothelium plays a crucial role in maintaining vascular homeostasis. Serotonin influences endothelial function in several ways. It modulates the expression of various endothelial adhesion molecules, which are pivotal in the recruitment of leukocytes during inflammation. Furthermore, serotonin can stimulate endothelial cell proliferation and migration, processes essential for angiogenesis and vascular repair [18].

In pathological conditions these normally reparative actions can contribute to disease progression. For instance, in atherosclerosis, serotonin may promote the proliferation and migration of endothelial cells and smooth muscle cells, contributing to plaque formation and vascular remodeling. Additionally, serotonin's interaction with platelets, which are rich in serotonin content, facilitates thrombosis by enhancing platelet aggregation. This pro-thrombotic effect of serotonin further implicates it in the pathogenesis of various cardiovascular diseases [18, 19, 20].

A particularly notable aspect of serotonin's role in vascular biology is its contribution to pulmonary vascular remodeling, a key feature of PAH. In the pulmonary vasculature, serotonin can induce smooth muscle cell proliferation and hypertrophy, leading to the narrowing of pulmonary arteries and increased pulmonary vascular resistance. This effect is mediated through various serotonin receptors, with the 5-HT2B receptor being particularly implicated in pulmonary smooth muscle cell proliferation [17, 18].

The serotonin transporter (SERT) also plays a crucial role in this context. Enhanced SERT activity in pulmonary arterial smooth muscle cells leads to increased uptake of serotonin, promoting cell proliferation and contributing to vascular remodeling [21].

Experimental studies, both in vitro and in animal models, have provided substantial evidence supporting serotonin's role in vascular biology. These studies have shown how alterations in serotonin signaling can contribute to various vascular diseases. For instance, mice lacking the 5-HT2B receptor exhibit reduced pulmonary vascular remodeling in response to hypoxia, highlighting the receptor's role in PAH [17, 18, 19, 20].

Beyond its role in vascular pathology, serotonin also contributes to normal vascular development and angiogenesis. Serotonin receptors are expressed in embryonic vascular tissues, suggesting a role for serotonin in vascular patterning and development. In angiogenesis, serotonin can stimulate the proliferation and migration of endothelial cells, essential for the formation of new blood vessels. This role has potential therapeutic implications in conditions where angiogenesis is desirable, such as in wound healing or ischemic heart disease.

The analysis revealed a notable difference in platelet levels between the control group and children with CHDs complicated with PAH. Specifically, the platelet count in the control group was approximately 30% lower than that observed in the CHD-PAH cohort. This disparity suggests a potential correlation between elevated platelet levels and the pathogenesis of PAH. Platelets, known for their primary role in hemostasis and thrombosis, also contribute significantly to inflammatory and proliferative processes, which are central to the development of PAH. Their involvement in PAH pathogenesis likely encompasses various mechanisms, including the modulation of vascular tone, promotion of endothelial dysfunction, and facilitation of smooth muscle cell proliferation.

Following surgical correction of congenital heart defects, a marked reduction in pulmonary hypertension was observed, accompanied by a nearly threefold decrease in platelet serotonin concentration. This finding underscores the significant role of serotonin in the pathogenesis of PAH. Serotonin, a potent vasoconstrictor and mitogen for smooth muscle cells, contributes to vascular remodeling, a hallmark of PAH. Elevated serotonin levels in platelets may enhance their release upon activation, further exacerbating vascular changes. Additionally, serotonin's influence on platelet aggregation could amplify the prothrombotic state, characteristic of PAH, promoting pulmonary vascular remodeling and increased pulmonary vascular resistance.

Furthermore, the study observed that the concentration

of serotonin in plasma was, on average, twice as low in the control group compared to the CHD-PAH group (figure 5). This finding indicates a systemic alteration in serotonin metabolism in patients with PAH, possibly reflecting its increased uptake and storage in platelets or its augmented production and release in response to chronic hypoxemia and endothelial dysfunction characteristic of CHD.

These observations suggest a complex interplay between platelets, serotonin, and the pulmonary vasculature in the context of PAH associated with CHD. However, it is imperative to acknowledge that these findings represent a preliminary exploration into a multifaceted and intricate pathophysiological process. Further research is essential to delineate the specific mechanisms by which platelets and serotonin contribute to the onset and progression of PAH in the context of congenital heart disease. Such studies should aim to elucidate the molecular pathways involved, evaluate the impact of various therapeutic interventions targeting platelet function and serotonin metabolism, and ultimately guide the development of more effective treatments for PAH in pediatric patients with CHD. The integration of advanced molecular techniques, longitudinal clinical studies, and interdisciplinary collaboration will be crucial in advancing our understanding of this complex disease process.

Conclusion

Our research highlights serotonin's role within the complex etiology of pulmonary hypertension. It is essential for future research to delve deeper into this relationship, examining the multifaceted mechanisms by which serotonin may contribute to pulmonary hypertension and validating these findings in broader cohorts. In essence, while our research opens new avenues for exploring serotonin and platelets dynamics as a biomarkers in pulmonary hypertension, it firmly establishes the foundation for subsequent, more extensive investigations to confirm these observations and their clinical relevance.

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