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Pathogenetic Significance of Endothelial Dysfunction in Pulmonary Hypertension Associated with Congenital Heart Defects in Children: A Modern Literature Review

Ubaydullayeva O. X.

Tashkent State Medical University, Uzbekistan

Abstract

Relevance. Congenital heart defects (CHDs) are among the main causes of pulmonary hypertension and pulmonary vascular disease in children. Particularly in defects associated with systemic-to-pulmonary shunts, a prolonged increase in pulmonary blood flow, pulsatile load, and shear stress alter the functional state of the pulmonary vascular endothelium. As a result, attenuation of vasodilatory and antiproliferative systems, enhancement of vasoconstrictor and proliferative signaling, and progressive vascular remodeling may occur.

Objective. To analyze the main hemodynamic and molecular mechanisms of endothelial dysfunction in the development of pulmonary hypertension associated with CHDs in children based on contemporary scientific data and to evaluate their clinical significance.

Materials and Methods. This article presents a narrative literature review in which scientific studies published in PubMed/MEDLINE and PubMed Central databases between 2020 and 2026 were analyzed.

Results. Endothelial dysfunction is an important mechanism linking hemodynamic load and structural remodeling in pulmonary vascular disease associated with CHDs. Attenuation of the NO–sGC–cGMP and prostacyclin–cAMP pathways, increased endothelin-1 activity, oxidative stress, impaired BMPR2/TGF-β signaling, inflammation, and metabolic alterations promote pathological vascular remodeling. BNP and NT-proBNP are among the most extensively studied biomarkers in pediatric pulmonary hypertension; however, they are not specific markers of endothelial dysfunction.

Conclusion. In pulmonary hypertension associated with CHDs, endothelial dysfunction represents one of the central pathogenetic links in disease initiation and progression. Combined assessment of molecular biomarkers with invasive hemodynamics, PVRI, and right ventricular function represents a promising direction for future research.

Keywords: Congenital heart defects, children, pulmonary hypertension, pulmonary arterial hypertension, endothelial dysfunction, nitric oxide.

1. Introduction

Pulmonary hypertension (PH) is a hemodynamic condition that develops under the influence of various etiological and pathophysiological factors. According to contemporary criteria, PH is characterized by a mean pulmonary artery pressure (mPAP) greater than 20 mmHg at rest, measured during right heart catheterization [1].

In adults, the criteria for precapillary PH include mPAP >20 mmHg, pulmonary artery wedge pressure (PAWP) ≤15 mmHg, and pulmonary vascular resistance (PVR) >2 Wood units. In children, assessment of the pulmonary vascular resistance index (PVRI) is of particular importance because of the influence of body surface area on hemodynamic parameters. For pediatric PAH, a PVRI ≥3 WU·m² criterion is used [1–3]. PH in children is not simply a scaled-down form of the disease observed in adults. Congenital heart defects, impaired lung development, genetic disorders, and perinatal factors play an important role in the etiology of pediatric PH [3–6]. Therefore, the child's age, type of anatomical defect, shunt volume, pulmonary blood flow, PVRI, and right ventricular function should be assessed comprehensively. Pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) is not a uniform clinical condition. It includes PAH developing in the setting of large systemic-to-pulmonary shunts, Eisenmenger syndrome, PAH associated with small or incidental cardiac defects, as well as PAH that persists or develops after correction of the defect [1,2].

In hemodynamically significant left-to-right shunts, excessive blood flow enters the pulmonary circulation. Initially, the endothelium responds to this load with an adaptive vasodilatory response. However, long-term shear stress and pulsatile pressure may lead to disruption of endothelial homeostasis. As a result, vasodilatory, antithrombotic, and antiproliferative properties are weakened, while vasoconstrictor and proliferative signals become predominant [2,7].

The endothelium is not merely a passive inner lining of the vascular wall. It is a metabolically active system that regulates vascular tone, platelet function, coagulation, inflammation, angiogenesis, and cellular proliferation. Therefore, endothelial dysfunction is not limited to functional vasoconstriction but may also lead to structural remodeling of the pulmonary vascular wall.

Contemporary studies indicate that the pathogenesis of PAH cannot be limited to the classical nitric oxide (NO), endothelin, and prostacyclin pathways. Mechanisms such as BMPR2/TGF-β signaling, oxidative stress, immune-inflammatory processes, metabolic reprogramming, and endothelial-to-mesenchymal transition also contribute to the development of vascular remodeling [8–12].

Objective of the study. To analyze the main hemodynamic and molecular mechanisms of endothelial dysfunction in the development of pulmonary hypertension associated with congenital heart defects in children and to evaluate their diagnostic and clinical significance.

2. Methods

This article presents a narrative literature review in which scientific studies published in the PubMed/MEDLINE and PubMed Central databases between 2020 and 2026 were analyzed. Molecular data obtained from adult populations and experimental models were used only to explain biological mechanisms and were not directly accepted as pediatric clinical evidence.

3. Results and Discussion

Hemodynamic load and endothelial dysfunction. In children with systemic-to-pulmonary shunts, pulmonary blood flow and pulsatile pressure may be significantly higher than physiological values. Under these conditions, mechanical shear stress directly affects endothelial cell function. The rate of development of pulmonary vascular disease is determined not only by the presence of an anatomical defect, but also by the magnitude and duration of the shunt, the ratio of pulmonary to systemic blood flow, pressure load, and individual biological characteristics [2,3].

Initially, an increased blood flow induces a compensatory vasodilatory response. However, under conditions of persistent hemodynamic load, endothelial protective mechanisms become insufficient. This may be accompanied by vasoconstriction, hypertrophy and proliferation of smooth muscle cells, intimal changes, and accumulation of extracellular matrix [7,8]. As a result, pulmonary vascular resistance gradually

increases and right ventricular afterload rises. From this perspective, endothelial dysfunction represents an important pathogenetic link between hemodynamic load and structural pulmonary arteriopathy.

Imbalance of NO, endothelin, and prostacyclin. Nitric oxide (NO) is one of the key mediators of normal endothelial function. Through soluble guanylate cyclase (sGC), it increases the formation of cyclic guanosine monophosphate (cGMP), thereby promoting relaxation of pulmonary vascular smooth muscle. In addition, NO inhibits platelet aggregation and smooth muscle cell proliferation [7,13]. Endothelial injury, chronic hypoxia, and oxidative stress may reduce NO bioavailability. This leads not only to vasoconstriction but also to attenuation of antithrombotic and antiproliferative protection.

Endothelin-1 is a potent vasoconstrictor and mitogenic mediator. In PAH, enhanced endothelin signaling is associated with contraction, proliferation, and fibrotic remodeling of pulmonary vascular smooth muscle cells [7,13]. The prostacyclin pathway represents the third major component of endothelial protection. Through IP receptors, prostacyclin increases intracellular cAMP levels, thereby promoting vasodilation, reducing platelet aggregation, and limiting proliferative processes.

Therefore, according to the contemporary concept, endothelial dysfunction is not limited to decreased NO or increased endothelin-1. An imbalance among the NO–sGC–cGMP, endothelin, and prostacyclin–cAMP pathways constitutes an important pathogenetic basis of pulmonary vascular disease [7,13]. The clinical significance of these pathways is reflected in the fact that a substantial proportion of modern PAH-targeted therapies act specifically on the endothelin, NO–cGMP, and prostacyclin pathways [1,6].

Oxidative stress and contemporary molecular mechanisms. Oxidative stress plays an important role in the development of endothelial dysfunction. Excessive formation of reactive oxygen species reduces NO bioavailability, enhances inflammatory signaling, and promotes the formation of a proliferative cellular phenotype [8,12]. In recent years, BMPR2/TGF-β signaling has been actively investigated as one of the central molecular pathways in PAH pathogenesis. BMPR2 plays an important role in maintaining homeostasis of pulmonary vascular endothelial and smooth muscle cells. Attenuation of this signaling pathway is associated with cellular proliferation, resistance to apoptosis, and pathological remodeling [9].

Although BMPR2 mutations are among the major genetic causes of heritable PAH, functional downregulation of BMPR2 signaling may also occur in forms of PAH without detectable mutations. However, this mechanism cannot be regarded as clinically proven in all children with PAH associated with congenital heart disease. Endothelial-to-mesenchymal transition (EndMT) is also considered a potentially important mechanism of pulmonary vascular remodeling. During EndMT, endothelial cells lose some of their characteristic properties and acquire a mesenchymal phenotype with increased capacity for migration, proliferation, and matrix production [10]. EndMT is associated with hypoxia, oxidative stress, inflammation, and TGF-β signaling. At the same time, the quantitative clinical significance of this process in pediatric PAH-CHD remains insufficiently studied.

Inflammation and metabolic alterations. Increasing evidence supports the presence of an immune-inflammatory component in the pathogenesis of PAH. Accumulation of immune cells around remodeled pulmonary vessels and activation of inflammatory mediators indicate that the disease is not solely a hemodynamic disorder [11]. Increased expression of adhesion molecules such as ICAM-1 and VCAM-1 in endothelial cells facilitates leukocyte migration into the vascular wall. Cytokines may, in turn, enhance proliferative and fibrotic responses of endothelial cells, smooth muscle cells, and fibroblasts. Mitochondrial dysfunction and metabolic reprogramming have also been described in PAH. A shift of vascular cells from oxidative phosphorylation toward a more glycolytic metabolic phenotype may create favorable conditions for proliferation and resistance to apoptosis [9,12]. However, most of these mechanisms have been studied in adult PAH cohorts and experimental models. Therefore, there is currently insufficient evidence to use them as independent diagnostic criteria for pediatric PAH-CHD.

Structural vascular remodeling and operability. When endothelial dysfunction persists for a prolonged period, functional vasoconstriction is gradually replaced by, or becomes accompanied by, structural pulmonary arteriopathy.

The main morphological changes include:

- medial hypertrophy;
- intimal proliferation and fibrosis;
- adventitial remodeling;
- increased extracellular matrix deposition;

- narrowing of the lumen of distal pulmonary arteries;
- plexiform lesions in advanced cases.

As these structural changes progress, pulmonary vascular resistance increases not only because of dynamic vasoconstriction, but also due to anatomical narrowing and obliteration of the vascular lumen [7,8]. This is of major clinical significance because the severity of pulmonary vascular disease is one of the key factors in assessing the feasibility of surgical or interventional correction of congenital heart defects.

Particularly in patients with borderline PVRI, relying solely on echocardiographic findings is insufficient. Right heart catheterization and invasive hemodynamic assessment continue to play a central role in determining operability [2,3,6]. Therefore, the concepts of "reversible" and "irreversible" pulmonary vascular disease should not be viewed as two strictly separate states. The vasoconstrictor component and some early structural changes may be reversible to a certain extent, whereas the potential for reversibility is markedly limited in advanced intimal fibrosis and obliterative arteriopathy.

Table 1. Main pathogenetic mechanisms of endothelial dysfunction in PAH-CHD

Pathogenetic pathway	Main alteration	Main consequence
NO–sGC–cGMP	Decreased NO bioavailability	Vasoconstriction and attenuation of antiproliferative protection
Endothelin-1	Enhanced vasoconstrictor signaling	Vasoconstriction and proliferation
Prostacyclin–cAMP	Attenuation of protective signaling	Reduced vasodilatory and antithrombotic effects
Oxidative stress	Increased ROS	Endothelial dysfunction and reduced NO signaling
BMPR2/TGF-β	Disruption of signaling balance	Pathological proliferation
EndMT	Alteration of the endothelial phenotype	Fibrosis and vascular remodeling
Inflammation	Cytokine and immune activation	Perivascular inflammation
Metabolic reprogramming	Glycolytic phenotype	Proliferation and resistance to apoptosis

Clinical significance of biomarkers of endothelial dysfunction. Understanding the mechanisms of endothelial dysfunction is important for identifying new biomarkers. However, at present, there is no single reliable endothelial biomarker for determining operability or disease severity in pediatric PAH-CHD. BNP and NT-proBNP are among the best-studied blood biomarkers for PH in children. In a systematic review and meta-analysis published in 2024, the pooled sensitivity of these markers for detecting pediatric PH was 0.81, specificity was 0.87, and the AUROC was 0.91 [14].

However, BNP and NT-proBNP primarily reflect myocardial and right ventricular wall stress rather than endothelial dysfunction itself. Therefore, they cannot be used as independent markers to replace cardiac catheterization or PVRI. Endothelin-1, NO metabolites, ICAM-1, VCAM-1, VEGF, and other inflammatory or angiogenic markers are considered pathogenetically promising. However, pediatric age-specific reference ranges and standardized clinical cutoff values are not available for most of them [15].

In 2024, the diagnostic potential of new markers such as 5-hydroxyindoleacetic acid (5-HIAA) and insulin-like growth

factor-1 (IGF-1) was investigated in children with PH associated with congenital heart disease [16]. Although the obtained results are of interest, validation in large independent pediatric cohorts is required before these markers can be introduced into broad clinical practice. Therefore, the most promising future approach may be based not on a single biomarker, but on a multimodal assessment model combining invasive hemodynamics, PVRI, right ventricular function, and several biological markers.

4. Conclusion

In pulmonary arterial hypertension associated with congenital heart disease, endothelial dysfunction is one of the major pathogenetic mechanisms linking hemodynamic load and progressive pulmonary vascular remodeling. Excessive blood flow and shear stress arising in the setting of systemic-to-pulmonary shunts initially lead to impairment of endothelial function. Subsequently, attenuation of the NO–sGC–cGMP and prostacyclin pathways, enhancement of endothelin signaling, oxidative stress, alterations in the BMPR2/TGF-β system, inflammation, and metabolic reprogramming support pathological vascular remodeling.

As these processes progress, initially functional vasoconstrictor changes are accompanied by structural alterations such as medial hypertrophy, intimal fibrosis, and obliterative arteriopathy. Therefore, in children with congenital heart disease, early identification of pulmonary vascular disease before progression to an advanced structural stage is of particular clinical importance.

At present, BNP and NT-proBNP are among the best-studied biomarkers in pediatric PH; however, they are not specific for endothelial dysfunction. The pediatric clinical significance of endothelin-1, NO metabolites, adhesion molecules, angiogenic markers, and metabolic biomarkers requires further validation. In future studies, prospective evaluation of endothelial biomarkers in combination with cardiac catheterization data, PVRI, right ventricular function, and long-term clinical outcomes may contribute to the improvement of individualized diagnostic and therapeutic strategies in pulmonary hypertension associated with congenital heart disease.

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