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Pulmonary Hypertension: Pathogenesis, Diagnosis and Management - Current Concepts and Future Perspectives

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Abstract

Background: Pulmonary hypertension (PH) is a complex and heterogeneous condition characterized by elevated pulmonary arterial pressure, increased pulmonary vascular resistance, and progressive right ventricular failure.

Objective: This review aims to summarize current knowledge on the pathogenesis, clinical presentation,diagnostic approaches,and treatment of PH,with particular emphasis on pulmonary arterial hypertension(PAH).

Methods:A narrative review of the literature was conducted,including recent clinical studies, review articles, and current guidelines addressing the pathophysiology, diagnosis, andmanagement of PH.

Results: Key mechanisms underlying PH include endothelial dysfunction, vascular remodeling,and dysregulation of the prostacyclin,nitric oxide,and endothelin pathways. Diagnostic strategies are based on non-invasive assessment and right heart catheterization. Current therapies improve exercise capacity and quality of life but do not reverse vascularremodeling.

Conclusions: Despite significant advances, PH remains associated with poor prognosis. Future research focusing on molecular mechanisms and novel therapeutic targetsmay enable more effective and personalized treatment strategies.

Keywords: *pulmonary hypertension; pulmonary arterial hypertension; pathogenesis; vascular remodeling; diagnosis; treatment; targeted therapy; biomarkers; risk stratification; right ventricular failure*

Introduction

Pulmonary hypertension (PH)represents a heterogeneous group of pathophysiologicaldisorders leading to a sustained increase in pulmonary arterial pressure and consequent right ventricular overload. In pulmonary arterial hypertension (PAH), a central role is played by

progressive narrowing of the distal pulmonary arteries,resulting from vasoconstriction, medial hypertrophy, intimal proliferation, and fibrosis [1].

These processes are further amplified by an inflammatory component, involving

increased expression of cytokines (including IL-1β, IL-6, and MCP-1) and infiltration of

inflammatory cells. Endothelial dysfunction and impaired angiogenesis also play a significant role,leading to loss of the microvascular bed and the formation of plexiform lesions. Duringdisease progression, a shift is observed from increased endothelial cell apoptosis to an

apoptosis-resistant and senescentphenotype [2].

Pathogenetic mechanisms vary depending on the underlying etiology of PH.In PHassociated with left heart disease,passive elevation of pulmonary venous pressure

predominates [1], whereas in chronic thromboembolic pulmonary hypertension (CTEPH),

persistent thrombotic obstruction and secondary vascular remodeling are of primaryimportance [1; 3], potentially modulated by genetic factors [3].

Prognostic assessment in PH is based on the evaluation of hemodynamic parameterssuch as right atrial pressure (RAP), cardiac index (CI), and mean pulmonary arterial pressure (mPAP), complemented by non-invasive indicators (NYHA/WHO functional class,

six-minute walk distance, echocardiographic parameters, and biomarkers). It should be

emphasized, however, that no single parameter provides sufficientprognostic value. Despite its widespread use, the six-minute walk distance (6MWD) test has limitations, including a learning effect and measurement variability. The minimal clinically important difference is estimated at approximately 33 m, and values exceeding 380–440 m are associated with a

more favorable prognosis [4].

Therapeutic strategies in PAH focus on modulation of three principal

pathophysiological pathways: the prostacyclin, nitric oxide, and endothelin pathways. In

clinical practice, treatment includes prostacyclin analogues and receptor agonists,

phosphodiesterase type 5 (PDE5) inhibitors, soluble guanylate cyclase stimulators, and

endothelin receptor antagonists. These therapies improve exercise capacity and quality of life; however, epoprostenol remains the only agent with a demonstrated survival benefit in

prospective studies.

In CTEPH, pulmonary endarterectomy is the treatment of choice. In patients who arenot eligible for surgery or who have persistent PH after the procedure, pharmacotherapy (e.g., riociguat) or balloon pulmonary angioplasty may be employed [2; 3]. In advanced stages of the disease, lung transplantation (or heart–lung transplantation) is considered, with outcomes being strongly dependent on the timing of referral and qualification.

Epidemiology and Clinical Significance of Pulmonary Hypertension

Global Prevalence

Pulmonary hypertension (PH) affects approximately 1% of the general population [6; 7], and up to 10% among individuals over65 years of age [7]. Accurate assessment of disease prevalence remains challenging due to evolving diagnostic criteria, including the lowering ofthe mean pulmonary arterial pressure (mPAP) threshold to >20 mmHg and the introduction of pulmonary vascular resistance (PVR) ≥ 3 Wood units, both of which have contributed to

increased detection rates [6].

The most common forms of PH are those associated with leftheart disease (Group 2) and lung diseases (Group 3), which also account for the majority of PH-related mortality [6]. The prevalence of pulmonary arterial hypertension (PAH) is estimated at several tens of cases per million population,whereas the overall prevalence of PH may reach several hundred

cases per 100,000 individuals [6].

In high-income countries, an increasing incidence has been observed, along with a shift in the age at diagnosis to approximately 65 years [7]. In low- and middle-income

countries, infectious diseases and rheumatic conditions play a more prominentrole, while in

the pediatric population PH remains a rare disorder [6]. Limited access to advanced

diagnostic modalities, particularly right heart catheterization, contributes to underestimation of the true disease burden [6].

Geographic and Demographic Differences

The clinical profile and etiology of pulmonary hypertension exhibit significant

regional variation. In high-income countries, PH associated with left heart disease (LHD-PH) predominates, accounting for up to 69% of cases. Within this group, heart failure with

preserved ejection fraction (HFpEF) is of particular importance, especially among older individuals [6].

In low- and middle-income countries, infectious diseases (e.g., HIV), rheumatic fever, and untreated congenital heart defects play a more prominent role [6]. Differences are also

observed in pulmonary arterial hypertension (PAH): in developing countries, it is more

frequently associated with congenital heart disease or schistosomiasis, whereas in developed countries, idiopathic forms and those related to connective tissue diseases predominate [6].

PH associated with lung diseases and LHD-PH are among the most common and carry the highest mortality, whereas chronic thromboembolic pulmonary hypertension (CTEPH) occurs less frequently [6].

Socioeconomic factors havea substantial impact on disease course. Limited access to diagnostic procedures and treatment is associated with poorer prognosis,increased rates of hospitalization, and higher mortality. Furthermore, the lack of population-based registries andlimited availability of invasive diagnostic procedures contribute to underestimation of the

true burden of the disease,particularly in resource-limited settings [6; 8].

Classification of Pulmonary Hypertension

Pulmonary Arterial Hypertension (PAH)

Pulmonary arterial hypertension (PAH)represents a form ofpre-capillary pulmonaryhypertension and is defined by a mean pulmonary arterial pressure (mPAP) >20 mmHg,

pulmonary arterial wedge pressure (PAWP) ≤15 mmHg, and pulmonary vascular resistance (PVR) ≥3 Wood units [9; 2]. The revision of diagnostic criteria, compared with the previous threshold of mPAP ≥25 mmHg, has improved diagnostic sensitivity and enabled earlier

identification of affected patients [2].

PAH encompasses a heterogeneous group of conditions, including idiopathic,

heritable, drug-induced forms, as well as those associated with connective tissue diseases,

HIV infection, portal hypertension, and congenital heart disease [9; 11]. The disease spectrum also includes rare entities such as pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) [3].

Diagnosis is based on right heart catheterization, which allowsfor detailed

hemodynamic assessment and performance of acute vasoreactivity testing. This evaluation isessential for selecting appropriate therapeutic strategies, including eligibility for calcium

channel blocker therapy [12].

The pathophysiology of PAH involves progressive remodeling and obliteration of thepulmonary vascular bed, leading to increased pulmonary vascular resistance and right

ventricular failure. Environmental factors also play a significant role, including exposure to drugs and toxins (e.g., fenfluramine, methamphetamine, dasatinib) [9].

PAH is a rare disease, with a prevalence of approximately 26 cases per million adults and an incidence ranging from 1.1 to 7.5 cases per million per year [7; 2]. It is more common in women [10], although the mean age at diagnosis is increasing.

Treatment targets the three principal pathophysiological pathways: prostacyclin, nitric oxide, and endothelin. It includes phosphodiesterase type 5 (PDE5) inhibitors, soluble

guanylate cyclase stimulators, endothelin receptor antagonists, and prostacyclin analogues

[10; 9; 2]. Supportive management includes, among others, oxygen therapy, diuretics, and

anticoagulation [14; 15]. In advanced cases, lung transplantation or heart–lung transplantation may be considered, as well as interventional procedures such as atrial septostomy in selected patients [5].

Pulmonary Hypertension Associated with Left Heart Disease

Pulmonary hypertension associated with left heart disease (PH-LHD) is the most

common form of PH and results from a passive increase in pulmonary venous pressure

secondary to elevated left atrial and/or left ventricular pressure. In the early stages, these

changes are reversible; however, chronic overload may lead to secondary pulmonary vascular remodeling and the development of a combined pre- and post-capillary phenotype [3; 14].

The most common causes of PH-LHD include heart failure (both with reduced and preserved ejection fraction), valvular heart disease, and less frequently, inflow or outflow

obstruction of the left ventricle.Pulmonary hypertension frequently coexists with heart

failure, including HFpEF, where it may be present in up to approximately half of patients [3].

Management of PH-LHD is primarily focused on treatment of the underlying

condition, particularly optimization of heart failure therapy. This includes the use of diuretics,angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), β-blockers, and mineralocorticoid receptor antagonists.

To date, therapies specific for PAH have not demonstrated efficacy in this patient population, and their use may be associated with adverse effects [10; 14]. Elevated

pulmonary vascular resistance (PVR) and transpulmonary gradient (TPG) constitute important risk factors in patients being evaluated for heart transplantation [14].

Pathogenesis of Pulmonary Hypertension

The pathogenesis of pulmonary hypertension (PH)involves complex interactions

between hemodynamic, cellular, and molecular mechanisms, leading to increased pulmonary vascular resistance (PVR) and progressive right ventricular failure. Regardless of etiology, the common consequence of these processes is sustained right ventricular overload and

gradual decompensation.

Hemodynamic Changes

Elevated Pulmonary ArterialPressure

Elevated pulmonary arterial pressure represents a common endpoint of various

pathophysiological processes that increase right ventricular afterload. In pulmonary arterial hypertension (PAH), a central role is played by increased pulmonary vascular resistance

(PVR), resulting from vasoconstriction, arterial wall remodeling,inflammation, and in situ thrombosis [14; 15].

Endothelial dysfunction leads to an imbalance between vasodilatory mediators(nitric oxide, prostacyclin) and vasoconstrictive factors (endothelin-1), promoting sustained

vasoconstriction. Additionally, alterations in ion channel function enhance Ca^{2+} influx into smooth muscle cells, further promoting vasoconstriction and cellularproliferation [6].

In other forms of PH, different mechanisms predominate. In PH associatedwith left heart disease (PH-LHD), the increase in pressure is passive and secondary to elevated

left-sided cardiac pressures, with the potential progression to a combined pre- and

post-capillary form(CpcPH) under chronic overload conditions [14]. In PH associated with lung diseases, key contributors include hypoxic vasoconstriction, loss of the capillary bed,and the effects of toxic factors. In chronic thromboembolic pulmonary hypertension

(CTEPH),mechanical obstruction of the pulmonary vasculature by organized thrombi is ofprimary importance [14].

Regardless of etiology,chronic elevation of pulmonary pressure initially leads to

compensatory right ventricular hypertrophy, followed by progressiveright ventricular failure. Reduction of afterload may improve right ventricular function; however, in advanced stages, irreversible structural changes occur, including fibrosis and microvascular dysfunction [16; 6].

Impact on Right Heart Load

Chronic elevation of pulmonary arterial pressure leads to a progressive increase inright ventricular (RV) afterload [6]. Initially, adaptive mechanisms predominate, including concentric hypertrophy and enhanced RV contractility; however, prolonged overload results in ventricular dilation, reduced systolic function, and loss of ventriculo-arterial coupling [2].

Increased RV wall stress contributes to interventricular asynchrony, impaired left

ventricular filling, and a reduction in cardiac output [16]. Concurrently, secondary

pathological processes develop, including myocardial ischemia, fibrosis, inflammation, and a decrease in capillary density [6].

Reduction of afterload remains the key determinant of improved RV function;

however, its effectiveness depends on the reversibility of structural changes. Interventions such as atrial septostomy may temporarily reduce RV load at the expense of hypoxemia, while other strategies (e.g., modulation of the autonomic nervous system or cardiac

resynchronization) remain under investigation [5; 16].

Cellular and Molecular Processes

Vascular Remodeling

Pulmonary vascular remodeling is a multifactorial process involving complex

interactions between endothelial cells, smooth muscle cells, and fibroblasts, with significant contribution from the immune system. A key initiating event is endothelial dysfunction,

which leads to activation of proliferative and inflammatory signaling pathways [2].

Disruptions in BMPR2 and transforming growth factor-β (TGF-β) signaling play a central role.Loss of BMPR2function promotes proliferation of vascular cells,whereas

increased TGF-β activity enhances vascular wall remodeling. These processes are

accompanied by inflammatory cell infiltration and increased expression ofpro-inflammatorycytokines [2].

During disease progression, there is a loss of small pulmonary vessels and the

formation of plexiform lesions,resulting from the transition of endothelial cells to an

apoptosis-resistant and hyperproliferative phenotype. Impaired angiogenesis, pericyte

dysfunction, and alterations in regulatory pathways (including VEGF and PDGF signaling) further contribute to microvascular rarefaction [2]. Additionally, metabolic reprogramming of vascular cells (the Warburg effect) is observed.

Collectively, these processes lead to thickening of the vascular wall layers, deposition of extracellular matrix,and narrowing of the vascular lumen,ultimately resulting in a

sustained increase in pulmonary vascular resistance and pulmonary arterial pressure [2; 14].

Endothelial Dysfunction

Endothelial dysfunction in pulmonary hypertension represents one of the key

pathogenetic mechanisms underlying PH. It is characterized by an imbalance between

vasodilatory and vasoconstrictive factors, as well as mediators of cellular proliferation [2; 14].

Endothelial cell injury leads to reduced production of nitric oxide and prostacyclin, alongside increased synthesis of endothelin-1 and thromboxane A2, thereby promoting

vasoconstriction and smooth muscle cell proliferation [14].

These alterations are accompanied by impaired angiogenesis, platelet activation, and the development of a pro-inflammatory and prothrombotic milieu.Additionally,

dysregulation of signaling pathways (including BMPR2 and TGF-β) further contributes to vascular remodeling and loss of normal vascular architecture [2; 14].

Clinical Presentation

The clinical presentation of pulmonary hypertension (PH)is heterogeneous and

depends on both the stage of disease and its underlying etiology. Early symptoms are

nonspecific, often leading to delayed diagnosis, whereas advanced stages are dominated by features of right ventricular failure.

Early Symptoms

In the early stages of PH, symptoms are subtle and frequently resemble those of other cardiac or pulmonary conditions. The most common initial manifestation is progressive

exertional dyspnea, resulting from the limited ability of the right ventricle to augment cardiac output and the increased resistance withinthe pulmonary circulation [18; 7]. This is often

accompanied by fatigue and reduced exercise tolerance.

Some patients experience nonspecific chest pain, which may berelated to right

ventricular strain or distension of the pulmonary artery. Episodes of presyncope or exertionalsyncope may also occur and can indicate more advanced hemodynamic impairment [18].

Physical examination findings are usually subtle. A pronounced pulmonary

component of the second heart sound,a murmur of tricuspid regurgitation, or exertionalcyanosis may be present. Vital signs are often within normal limits.

Given the low specificity of symptoms, screening investigations play an important role, including electrocardiography (ECG), measurement of BNP/NT-proBNP levels, and echocardiography [7; 12].

Advanced Symptoms

In advanced stages of pulmonary hypertension,manifestations of right ventricularfailure and systemic hemodynamic compromise predominate. Dyspnea may occur even at rest, and exercise tolerance is markedly reduced, accompanied by pronounced fatigue and weakness [11; 12]. Episodes ofpresyncope and syncope become more frequent and are associated with a poorer prognosis [5].

On physical examination, signs of systemic venous congestion are evident, including jugular venous distension, peripheral edema, ascites, and hepatomegaly. Additional

characteristic findings include an accentuated pulmonary component of the second heart

sound (P2) and a murmur of tricuspid regurgitation [11; 14]. Progressive right ventricular

failure leads to reduced cardiac output, hypotension, and signs of hypoperfusion, such as cool extremities and oliguria [14]. Cardiac arrhythmias, particularly atrial fibrillation and atrial

flutter, are commonly observed and may further worsen the clinical course [15].

Diagnosis of Pulmonary Hypertension

The diagnosis of pulmonary hypertension (PH) requires a comprehensive approach,incorporating both non-invasive and invasive methods. The objective is not only to confirm the diagnosis but also to determine the underlying etiology, assess disease severity, and

evaluate prognosis.

Initial Evaluation

Transthoracic Echocardiography

Transthoracic echocardiography (TTE) is the primary non-invasive modality for the initial evaluation of pulmonary hypertension (PH).It enables estimation of systolic

pulmonary arterial pressure (sPAP) based on the peak tricuspid regurgitation velocity (TRV), as well as assessment of right heart structure and function [11; 14].

Additional echocardiographic findings suggestive of PH include right ventricular andright atrial enlargement, right ventricular wall hypertrophy, flattening of the interventricularseptum, and dilation of the pulmonary artery. Even when Doppler measurements are

inconclusive,the presence of these features increases the likelihood of PH.

TTE is primarily used to estimate the probability of PH and to guide referral forfurther invasive diagnostic evaluation. It also allows identification of potential underlying causes, such as left heart disease or congenital heart disease. However, its diagnostic

accuracy is limited, and definitive diagnosis requires confirmation with invasive testing.

Functional Testing

The six-minute walk test (6MWT) is the most commonly used method for assessing exercise capacity, based on the distance walked.The test result correlates with disease

severity and prognosis, with a distance <330 m associated with poorer outcomes. During the test, dyspnea is also evaluated(e.g., using the Borg scale), along with oxygen saturation. A decrease in oxygen saturation of >10% suggests more advanced disease [11; 14].

Cardiopulmonary exercise testing (CPET) provides more detailed information on gas exchange and the mechanisms underlying exercise limitation. Parameters such as peak

oxygen uptake (VO2peak) and the ventilatory equivalent for carbon dioxide (VE/VCO2) have significant prognostic value and may aid in differentiating the underlying causes of PH.

Imaging Studies

Computed Tomography

Computed tomography (CT) plays an important role in the diagnostic evaluation of pulmonary hypertension (PH), enabling assessment of both etiology and structural changes in the lungs and pulmonary vasculature.

High-resolution CT (HRCT) is particularly useful for identifying interstitial lung diseases, emphysema, and rare forms of PH, such as pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH). Typical findings include

ground-glass opacities, interlobular septal thickening, andenlarged lymph nodes.

CT pulmonary angiography (CTPA) is essential in the diagnosis of chronic

thromboembolic pulmonary hypertension (CTEPH),allowing detection of vascular stenoses, occlusions,and evaluation of collateral circulation.

CT also enables assessment of pulmonary artery size and identification of other

potential causes of PH, such as congenital heart disease. The presence of a mosaic attenuationpattern may suggest perfusion abnormalities, particularly in CTEPH.

In addition, CT findings may have prognostic significance; for example, loss of distal pulmonary vessels ("vascular pruning")has been associated with an increased risk of

mortality.

Magnetic Resonance Imaging

Cardiac magnetic resonance (CMR) is the reference standard for the assessment of right ventricular structure and function. It enables accurate and reproducible evaluation of right ventricular volumes, mass, and both systolic and diastolic function, as well as

hemodynamic parameters such as stroke volume (SV) and cardiac output (CO) [4; 14].

This modality is of particular importance in patients with suspected congenital heartdisease or when echocardiographic assessment is inconclusive. Magnetic resonance

angiography (MRA) also allows evaluation of the pulmonary vasculature and may serve as an alternative to CT in patients with contraindications to iodinated contrast agents (e.g., young patients or pregnant women) [19].

CMR also provides prognostic information. Parameters such as right ventricular

enlargement, reduced ejection fraction (<35%), increased right ventricular mass, and

decreased pulmonary artery compliance are associated with worse outcomes. The presence of late gadolinium enhancement (LGE) indicates right ventricular remodeling and overload [3].

Advanced techniques, including T1 mapping and strain imaging, enable assessment of myocardial fibrosis and right ventricular function, while flow analysis allows evaluation of pulmonary hemodynamics.

Treatment Strategies

The management of pulmonary hypertension (PH) depends on its underlying etiologyand disease severity and should be conducted in specialized centers. Accurate classification of patients into the appropriate PH group is essential, as therapeutic strategies differ

substantially according to the underlying pathophysiological mechanism.

Pharmacotherapy

Pulmonary Vasodilator Therapy

Pulmonary vasodilator therapies constitute the cornerstone of treatment for pulmonaryarterial hypertension (PAH) [2; 12]. Their effects target three key pathophysiological

pathways: the prostacyclin, nitric oxide (NO), and endothelin pathways, which regulate vascular tone and smooth muscle cell proliferation.

Within the prostacyclin pathway, prostacyclin (PGI2) analogues (epoprostenol,

iloprost, treprostinil) and the prostacyclin receptor (IP) agonist selexipag are used. These

agents increase cyclic adenosine monophosphate (cAMP) levels, resulting in vasodilation and antiproliferative effects. Epoprostenol is the only agent shown to improve survival, although

its administration requires continuous intravenous infusion [2; 18]. Inhaled iloprost improves exercise capacity but requires frequent dosing, whereas treprostinil (available via multiple

routes of administration) may beassociated with infusion-site pain [20; 17]. Selexipag,

administered orally, exerts vasodilatory and antiproliferative effects via the IP receptor [20].

The nitric oxide pathway includes phosphodiesterase type 5 (PDE5) inhibitors

(sildenafil, tadalafil) and soluble guanylate cyclase stimulators (riociguat), which increase

cyclic guanosine monophosphate (cGMP) levels, leading to vasodilation. Sildenafil improves exercise capacity and hemodynamics, tadalafil has a longer duration of action, and riociguat is also used in chronic thromboembolic pulmonary hypertension (CTEPH) [12; 2].

The endothelin pathway is targeted by endothelin receptor antagonists (ERAs).

Bosentan improves exercise tolerance and hemodynamics but requires monitoring of liverfunction [17; 12]. Ambrisentan selectively targets the ETA receptor, while macitentan

demonstrates improved tissue penetration and reduces the risk of disease progression [12].

Treatment strategies may involve monotherapy or combination therapy. In patients at higher risk, early initiation of combination therapy is recommended, while in advanced

disease, parenteral treatment (e.g., epoprostenol) should be considered [19]. A small subset of patients who demonstrate a positive vasoreactivity test may benefit from calcium channel

blocker therapy [20].

Assessment of treatment efficacy is based on clinical parameters,including

six-minute walk distance (6MWD), BNP/NT-proBNP levels, and echocardiographic findings [19]. In the absence of adequate response, interventional therapies or transplantation should be considered.

Supportive Management

Oxygen Therapy

Oxygen therapy is an important component of supportive management in pulmonaryhypertension, particularly in patients with hypoxemia. Its primary aim is to improve arterial oxygenation and to mitigate hypoxia-induced pulmonary vasoconstriction.

It is of greatest relevance in PH associated with lung diseases (Group 3), where

long-term oxygen therapy has been shown to improve outcomes. According to current

guidelines, oxygen therapy should be initiated when arterial oxygen tension (PaO2) is <60 mmHg [7], including in cases of nocturnal or exertional hypoxemia.

Oxygen acts as a pulmonary vasodilator, transiently reducing pulmonary vascular

resistance and pulmonary arterial pressure. It also improves exercise tolerance and quality of life [17].

Oxygen may be administered continuously or intermittently (e.g., during exertion or sleep), depending on the patient's clinical status. In patients with idiopathic or heritable PAH (IPAH/HPAH), oxygen therapy should be considered in NYHA/WHO functional class III–IV when PaO2 is <60 mmHg, particularly during air travel. In pediatric patients, indications

include PaO2 <60 mmHg or oxygensaturation <92% [3].

Diuretic Therapy

Diuretics are an important component of supportive management in pulmonary

hypertension, particularly in patients with fluid overload and right ventricular failure. Their primary goal is to reduce fluid retention, alleviate venous congestion, and decrease cardiac volume load, thereby improving patient comfort. Their use leads to a reduction in peripheral edema, hepatomegaly, pleural effusions, and ascites.

They are most commonly used in patients with pulmonary arterial hypertension (PAH) and right ventricular decompensation. By reducing circulating blood volume and ventricular filling pressures, diuretics contribute to improved hemodynamic status.

Loop diuretics (e.g., furosemide, torasemide) are most frequently prescribed, often in combination with aldosterone antagonists.Therapy requires careful monitoring of renal

function and electrolyte balance due to the risk of hypokalemia and renal impairment. In pediatric patients, diuretics should be used with caution to avoid compromising cardiac output.

Rehabilitation and Lifestyle Modification

Exercise Training Programs

Exercise-based rehabilitation aims to improve physical capacity and quality of life;however, it requires individualized adjustment and careful attention to safety. Physical

activity should be performed within symptom tolerance—mild dyspnea may be acceptable, but strenuous exertionand severe symptoms should be avoided.

Clinical studies have demonstrated that structured exercise training improves

six-minute walk distance, overall physical activity, and reduces fatigue. Training programs should be conducted in specialized centers and include moderate-intensity aerobic exercise combined with resistance training. Exercise intensity should be tailored individually, as

standardized protocols are not well established [14; 15].

Excessive exertion may lead to adverse events, including syncope and arrhythmias; therefore, risk assessment prior to initiation of training is essential. In clinically stable

patients, supervised exercise with monitoring of heart rate, oxygen saturation, and bloodpressure is recommended, incorporating rest periods and gradual progression.

Such programs may also be implemented in pediatric patients, although they require particular caution. Their effectiveness is assessed, among others, using six-minute walk

distance and NT-proBNP levels.

Risk Factor Control

Risk factor control in pulmonary hypertension encompasses reduction of

environmental exposures,management of comorbid conditions,and implementation of

preventive measures. Particular importance is placed on optimal treatment of left heart andlung diseases, as well as the prevention of chronic hypoxia [15].

Reducing exposure to air pollution and tobacco smoke is essential. At the individual level, recommended measures include dietary modification (e.g., reduced intake of salt and

trans fats) and control of systemic blood pressure and cholesterol levels. In low-income countries, prevention of infections such as schistosomiasis, tuberculosis, and HIV is also crucial, as these conditions increase the risk of PH [6].

In selected cases, avoidance of toxic substances (e.g., methamphetamine) is

important, along with improving access to specialized care. In pediatric patients, careful

management of hypoxia and early treatment of congenital heart defects are key componentsof prevention and care.

Future Perspectives and Research Directions

Emerging Therapeutic Targets

Despite significant advances in the treatment of pulmonary arterial hypertension

(PAH), current therapies primarily improve exercise capacity and quality of life but do not reverse pulmonary vascular remodeling. Consequently, there is growing interest in the

development of novel therapeutic strategies targeting the molecular mechanisms underlyingthe disease.

A key area of research involves modulation ofthe TGF-β/BMP axis,particularly

BMPR2signaling.Dysregulation of this pathway plays a central role in the pathogenesis ofPAH by promoting vascular cell proliferation and remodeling [2].

Promising results have been reported for sotatercept, which acts as a ligand trap for members ofthe TGF-βsuperfamily and has demonstrated improvements in hemodynamicparameters and exercise capacity in clinical trials. Other approaches include restoration of BMPR2 function (e.g., using 4-phenylbutyrate) and modulation of BMP9 and BMP10

ligands, although their clinical relevance remains under investigation [5; 8].

Emerging strategies also target metabolic disturbances (including enhanced glycolysis and glutaminolysis), epigenetic mechanisms, oxidative stress, and fibrosis [2]. Increasing

attention is being paid to the role of inflammatory responses and the influence of sexhormones on disease progression.

Prognostic Biomarkers

Prognostic assessment in pulmonary hypertension (PH), particularly in pulmonary arterial hypertension (PAH), relies on an integrated evaluation of clinical, hemodynamic, imaging, and circulating biomarker parameters.

Natriuretic peptides—BNP and NT-proBNP—have the most well-established role, with levels correlating closely with disease severity and rightventricular function. Elevated concentrations are associated with poorer outcomes, whereas low or decreasing levels

indicate clinical improvement [15; 14]. NT-proBNP values <1800 pg/mL during follow-up are associated with a more favorable disease course [4]. These biomarkers are widely

available and recommended for risk stratification and treatment monitoring; however, no single biomarker is sufficient for prognostic assessment [14].

Additional markers under investigation include troponin T, uric acid, C-reactive

protein (CRP), and arterial carbon dioxide tension (PaCO2), although their clinical utility is

less well established. Increasing attention is also being paid to longitudinal changes in biomarker levels, which may reflect treatment response [4].

Prognostic evaluation should be multiparametric and include classification of patientsinto risk categories (low, intermediate, high), enabling optimization of therapeutic strategies.

In the future,the development of novel biomarkers and the application of advanced dataanalysis methods may further improve prognostic precision [2]. At present, BNP and

NT-proBNP remain the most validated prognostic indicators, particularly when regularly monitored and interpreted in conjunction with other clinical findings [14].

Conclusion

Pulmonary hypertension represents a complex and heterogeneous group of disorderswith diverse etiologies and pathophysiological mechanisms, unified by a progressive increase in pulmonary vascular resistance and the development of right ventricular failure.Despite

substantial advances in diagnostics and therapy, the condition remains associated with a poor prognosis, largely due to nonspecific early symptoms and delays in diagnosis.

Early identification of patients and accurate classification of pulmonary hypertensionare essential for optimal clinical management, enabling the implementation of appropriate therapeutic strategies. Advances in diagnostic modalities, including imagingtechniques and circulating biomarkers,have improved the assessment of disease severity and risk

stratification.

The introduction of targeted therapies acting on the prostacyclin, nitric oxide, and

endothelin pathways has significantly improved outcomes in patients with pulmonary arterial hypertension;however,these treatments do not halt the underlying process of pulmonary

vascular remodeling. Consequently, emerging research focuseson molecular mechanisms,

including dysregulation of BMPR2/TGF-β signaling, metabolic alterations, and inflammatorypathways.

Future therapeutic approaches in pulmonary hypertension are likely to shift toward targeting the underlying causes of the disease rather than solely its hemodynamic

consequences, potentially enabling more effective control of disease progression and

improved patient outcomes. At the same time, continued development of biomarkers andprognostic models may facilitate a more personalized approach to treatment.

Disclosure

Author's contribution

Conceptualization, A. Jakimowicz; methodology, M. Mrozek and M. Blecharczyk; software, A. Zielińska; check, I. Zydlewski, and Z. Kamińska; formal analysis, A. Malcher and I.
Zydlewski; investigation, M. Blecharczyk; resources, I. Zydlewski; data curation, M.
Pacanowska - Trawnicka; writing - rough preparation, M. Pacanowska - Trawnicka; writing - review and editing, M. Blecharczyk; visualization, A. Malcher; supervision, A. Jakimowicz; project administration, A. Jakimowicz
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Conflict of interest

The authors deny any conflict of interest.

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