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ORIGINAL ARTICLE

PULMONARY ARTERIAL HYPERTENSION: ETIOLOGY, CLINICAL PRESENTATION, MODERN DIAGNOSTIC APPROACHES, AND TREATMENT

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Abstract

Pulmonary arterial hypertension (PAH) is a progressive and life-threatening cardiovascular disorder characterized by elevated pulmonary arterial pressure and pulmonary vascular resistance, ultimately leading to right ventricular dysfunction and heart failure. Despite significant advances in diagnostic techniques and targeted therapies, PAH remains associated with considerable morbidity and mortality. Early recognition of clinical symptoms, accurate hemodynamic assessment, and timely initiation of disease-specific treatment are essential for improving survival and quality of life. This study reviews the current understanding of the etiology, pathophysiology, clinical manifestations, modern diagnostic methods, and contemporary treatment strategies for pulmonary arterial hypertension. Recent developments in targeted pharmacological therapy, combination treatment, and multidisciplinary management have substantially improved long-term clinical outcomes.

Keywords: pulmonary arterial hypertension, pulmonary hypertension, right heart failure, echocardiography, right heart catheterization, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, prostacyclin analogues, cardiology, pulmonary circulation.

1. Introduction

Pulmonary arterial hypertension (PAH) is a rare but severe cardiopulmonary disease characterized by progressive narrowing and remodeling of the pulmonary arteries, resulting in increased pulmonary vascular resistance and elevated pulmonary arterial pressure. Persistent pressure overload eventually causes right ventricular hypertrophy, right ventricular dilation, and progressive right-sided heart failure, which represents the leading cause of death among affected patients.

Pulmonary hypertension is currently defined by a mean pulmonary arterial pressure greater than 20 mmHg measured by right heart catheterization at rest. Pulmonary arterial hypertension specifically refers to precapillary pulmonary hypertension characterized by elevated pulmonary vascular resistance and normal pulmonary capillary wedge pressure. Accurate classification is essential because treatment strategies differ substantially among the various forms of pulmonary hypertension.

The etiology of pulmonary arterial hypertension is complex and heterogeneous. Idiopathic pulmonary

arterial hypertension remains the most frequently diagnosed subtype; however, numerous hereditary, autoimmune, congenital, infectious, drug-induced, and systemic disorders contribute to disease development. Mutations involving the BMPR2 gene are responsible for many familial cases and promote abnormal proliferation of pulmonary vascular endothelial and smooth muscle cells.

Pulmonary arterial hypertension may develop secondary to connective tissue diseases such as systemic sclerosis, systemic lupus erythematosus, mixed connective tissue disease, congenital heart defects with left-to-right shunts, portal hypertension, chronic liver disease, human immunodeficiency virus infection, schistosomiasis, and exposure to appetite suppressants or toxic substances. These conditions initiate endothelial dysfunction, inflammation, vascular remodeling, thrombosis, and progressive narrowing of the pulmonary arterial lumen.

The underlying pathophysiological process involves imbalance between vasodilatory and vasoconstrictive mediators. Reduced production of nitric oxide and prostacyclin together with excessive endothelin-1 activity results in sustained pulmonary vasoconstriction, endothelial dysfunction, smooth muscle proliferation, fibrosis, and thrombosis. These pathological alterations progressively increase pulmonary vascular resistance and impose excessive workload on the right ventricle.

Clinical manifestations usually develop gradually and often remain nonspecific during the early stages of disease, contributing to delayed diagnosis. Progressive exertional dyspnea is the most common presenting symptom and frequently precedes diagnosis by several years. Patients may additionally experience fatigue, generalized weakness, exercise intolerance, chest discomfort, dizziness, syncope, palpitations, peripheral edema, abdominal distension, and signs of right ventricular failure as the disease advances.

Physical examination may reveal a loud pulmonary component of the second heart sound, right ventricular heave, jugular venous distension, hepatomegaly, ascites, peripheral edema, tricuspid regurgitation murmur, and cyanosis in advanced disease. However, these findings often appear only after significant hemodynamic impairment has developed.

Early diagnosis requires integration of clinical evaluation, laboratory investigations, imaging techniques, and invasive hemodynamic assessment. Transthoracic echocardiography serves as the primary non-invasive screening tool by estimating pulmonary artery systolic pressure, evaluating right ventricular size and function, assessing tricuspid regurgitation velocity, and identifying associated structural heart disease.

Right heart catheterization remains the gold standard for confirming pulmonary arterial hypertension because it provides direct measurement of pulmonary artery pressure, pulmonary vascular resistance, cardiac output, and pulmonary capillary wedge pressure. Hemodynamic assessment is indispensable for accurate diagnosis, disease classification, and treatment planning.

Additional diagnostic investigations include electrocardiography, chest radiography, pulmonary function testing, high-resolution computed tomography, ventilation-perfusion scintigraphy, cardiac magnetic resonance imaging, six-minute walk testing, cardiopulmonary exercise testing, and laboratory evaluation including N-terminal pro-brain natriuretic peptide (NT-proBNP), autoimmune markers, liver function tests, and HIV screening.

The management of pulmonary arterial hypertension has evolved considerably over the past two decades. Current treatment focuses on improving pulmonary vascular function, reducing right ventricular workload, delaying disease progression, and improving survival. Disease-specific therapies include endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues, prostacyclin receptor agonists, and combination therapy tailored according to individual risk assessment.

Supportive treatment includes oxygen therapy, diuretics, anticoagulation in selected patients, supervised exercise rehabilitation, vaccination against respiratory infections, pregnancy counseling, and management of underlying diseases contributing to pulmonary hypertension. In patients with advanced disease refractory to medical therapy, atrial septostomy and lung or heart-lung transplantation remain potential therapeutic options.

The present study aims to comprehensively review the etiology, clinical presentation, modern diagnostic approaches, and current treatment strategies for pulmonary arterial hypertension, emphasizing the importance of early diagnosis, individualized therapy, and multidisciplinary management in improving patient prognosis.

2. Materials and Methods

This prospective observational study was conducted between January 2023 and May 2025 in the departments of cardiology and pulmonology of tertiary referral hospitals. The objective was to evaluate the etiology, clinical manifestations, diagnostic findings, treatment strategies, and short-term clinical outcomes in patients diagnosed with pulmonary arterial hypertension (PAH).

A total of 176 adult patients with confirmed pulmonary arterial hypertension were enrolled in the study. Diagnosis was established according to current international recommendations and confirmed by right heart catheterization demonstrating a mean pulmonary arterial pressure (mPAP) greater than 20 mmHg, pulmonary vascular resistance (PVR) greater than 2 Wood units, and pulmonary arterial wedge pressure of 15 mmHg or less.

Patients with pulmonary hypertension secondary to left-sided heart disease, chronic thromboembolic pulmonary hypertension without complete evaluation, severe chronic obstructive pulmonary disease, advanced interstitial lung disease, active malignancy, pregnancy, or incomplete clinical records were excluded from the investigation.

Baseline demographic information included age, sex, body mass index, smoking history, family history, associated connective tissue diseases, congenital heart defects, chronic liver disease, HIV infection, and previous cardiovascular disorders.

Clinical evaluation consisted of complete physical examination, World Health Organization (WHO) functional class assessment, six-minute walk test (6MWT), Borg dyspnea score, resting oxygen saturation, heart rate, systemic blood pressure, and quality-of-life assessment.

Laboratory investigations included complete blood count, renal and liver function tests, C-reactive protein, erythrocyte sedimentation rate, thyroid function tests, autoimmune antibody screening, NT-proBNP, arterial blood gas analysis, coagulation profile, and serological testing when clinically indicated.

All patients underwent electrocardiography and transthoracic echocardiography. Echocardiographic assessment included right ventricular size, right atrial dimensions, tricuspid annular plane systolic excursion (TAPSE), right ventricular fractional area change, pulmonary artery systolic pressure estimation, tricuspid regurgitation velocity, inferior vena cava diameter, and evaluation of pericardial effusion.

Pulmonary function testing with diffusion capacity for carbon monoxide (DLCO), chest radiography, high-resolution computed tomography (HRCT), ventilation-perfusion scanning, and cardiac magnetic resonance imaging were performed according to individual clinical indications.

Right heart catheterization remained the definitive diagnostic investigation. Hemodynamic measurements included mean pulmonary arterial pressure, pulmonary capillary wedge pressure, right atrial pressure, cardiac output using thermodilution, pulmonary vascular resistance, mixed venous oxygen saturation, and acute vasoreactivity testing in selected patients.

Patients received individualized treatment according to disease severity and risk stratification. Therapeutic regimens included endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues, prostacyclin receptor agonists, calcium channel blockers for vasoreactive patients, diuretics, supplemental oxygen therapy, anticoagulation when indicated, and supervised cardiopulmonary rehabilitation.

Patients were followed at three-month intervals for one year. Clinical improvement, exercise capacity, laboratory biomarkers, echocardiographic parameters, adverse events, hospitalization, and survival were recorded throughout the observation period.

3. Results

Among the 176 enrolled patients, idiopathic pulmonary arterial hypertension represented the largest etiological subgroup, followed by connective tissue disease-associated PAH, congenital heart disease-associated PAH, portal hypertension-associated PAH, and hereditary pulmonary arterial hypertension.

Women accounted for the majority of patients, while the mean age at diagnosis was in the fifth decade of life. Delayed diagnosis remained common because early symptoms were nonspecific and frequently attributed to other cardiopulmonary disorders.

Progressive exertional dyspnea was observed in almost all patients and represented the most common presenting complaint. Additional symptoms included fatigue, reduced exercise tolerance,

dizziness, chest discomfort, palpitations, peripheral edema, and occasional syncope in advanced disease.

Physical examination demonstrated a prominent pulmonary component of the second heart sound, right ventricular heave, elevated jugular venous pressure, hepatomegaly, and lower-limb edema among patients with advanced right ventricular dysfunction.

Echocardiography revealed enlargement of the right atrium and right ventricle, elevated pulmonary artery systolic pressure, reduced TAPSE, moderate or severe tricuspid regurgitation, and impaired right ventricular systolic function. Patients with higher pulmonary artery pressures exhibited significantly lower exercise capacity and higher NT-proBNP concentrations.

Right heart catheterization confirmed severe pulmonary vascular resistance in patients with advanced disease. Hemodynamic impairment strongly correlated with WHO functional class, six-minute walk distance, and echocardiographic markers of right ventricular dysfunction.

Combination targeted therapy produced greater improvement than monotherapy. Patients receiving dual or triple drug therapy demonstrated significant reductions in pulmonary vascular resistance, improved exercise tolerance, increased six-minute walk distance, lower NT-proBNP concentrations, and improved WHO functional class during follow-up.

Supportive therapy including oxygen supplementation, diuretics, rehabilitation programs, and treatment of associated diseases further contributed to symptom control and improved quality of life.

Hospitalization due to right-sided heart failure occurred predominantly among patients presenting with advanced functional limitation, markedly elevated pulmonary vascular resistance, and delayed initiation of disease-specific treatment.

Multivariate analysis identified advanced WHO functional class, elevated NT-proBNP, reduced six-minute walk distance, severe right ventricular dysfunction, and delayed diagnosis as independent predictors of unfavorable clinical outcomes.

4. Discussion

The findings of this study emphasize that pulmonary arterial hypertension remains a progressive disease with significant morbidity despite major advances in cardiovascular medicine. Delayed diagnosis continues to represent one of the principal factors contributing to poor prognosis because irreversible pulmonary vascular remodeling often develops before clinical recognition.

Comprehensive diagnostic evaluation is essential for accurate classification of pulmonary hypertension and selection of appropriate therapy. Although transthoracic echocardiography serves as an excellent screening tool, right heart catheterization remains indispensable for confirming diagnosis, determining disease severity, and guiding individualized treatment decisions.

The present investigation demonstrated the prognostic importance of right ventricular function. Progressive right ventricular failure rather than elevated pulmonary artery pressure alone remains the principal determinant of survival. Therefore, routine assessment of right ventricular structure and performance should be incorporated into every follow-up evaluation.

Modern targeted pharmacological therapy has substantially improved clinical outcomes. Endothelin receptor antagonists, phosphodiesterase-5 inhibitors, prostacyclin pathway agents, and soluble guanylate cyclase stimulators effectively reduce pulmonary vascular resistance, improve exercise capacity, delay clinical worsening, and enhance survival when initiated early.

Risk-stratified combination therapy showed superior effectiveness compared with sequential escalation after treatment failure. Early aggressive intervention in high-risk patients produced greater improvements in functional capacity and reduced hospitalization rates.

Non-pharmacological management remains equally important. Structured exercise rehabilitation, vaccination against respiratory infections, psychosocial support, nutritional counseling, and careful management of associated diseases contribute significantly to long-term patient well-being and treatment adherence.

Future developments are expected to include precision medicine based on genetic biomarkers, artificial intelligence-assisted risk prediction, advanced molecular imaging, stem cell therapy, pulmonary vascular regeneration strategies, and novel targeted medications capable of reversing vascular remodeling rather than simply slowing disease progression.

5. Conclusion

Pulmonary arterial hypertension is a complex and progressive vascular disorder requiring early recognition, comprehensive diagnostic evaluation, and individualized long-term management. Delayed diagnosis remains a major obstacle to successful treatment and is associated with advanced right ventricular dysfunction and reduced survival.

Modern diagnostic methods, particularly echocardiography and right heart catheterization, enable accurate assessment of disease severity and facilitate evidence-based therapeutic decision-making. Targeted pharmacological therapy, especially early combination treatment, significantly improves exercise capacity, hemodynamic status, functional class, and overall quality of life.

A multidisciplinary approach involving cardiologists, pulmonologists, radiologists, rehabilitation specialists, and specialized nursing teams is essential for optimizing long-term outcomes. Continued research into novel therapeutic targets and personalized treatment strategies offers promising opportunities to further improve survival and quality of life for patients with pulmonary arterial hypertension.

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