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Review Article

Pulmonary Hypertension: The Current and Future Scenario

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Abstract

Pulmonary hypertension (PH) is a complex and progressive disease characterized by elevated pulmonary arterial pressure, leading to right heart failure. This article reviews the current management strategies for PH, focusing on recent advancements in pharmacological treatments, diagnostic approaches, and intervention techniques. Additionally, the clinical utility of novel biomarkers and the role of risk stratification in guiding therapy are discussed.

Keywords: *Pulmonary Hypertension; Pharmacological Management; Right Heart Failure; Biomarkers; Risk Stratification*

Introduction

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest, as measured by right heart catheterization [1]. This condition has multiple aetiologies and is categorized into five groups based on the World Health Organization (WHO) classification [2]. The heterogeneity of PH poses challenges in diagnosis and management. This article aims to provide an overview of current treatment strategies, focusing on the evolving landscape of PH management.

Classification of pulmonary hypertension

The WHO classifies PH into five groups based on pathophysiological mechanisms [2]:

- Group 1: Pulmonary arterial hypertension (PAH)
- Group 2: PH due to left heart disease
- Group 3: PH due to lung diseases or hypoxia
- Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH)
- Group 5: PH with unclear multifactorial mechanisms.

A table summarizing the WHO classification and associated clinical features is provided below:

Group	Etiology	Key Clinical Features
1	Idiopathic, Heritable, Drug-induced	Dyspnea, Fatigue, Syncope
2	Left ventricular dysfunction	Exertional dyspnea, Orthopnea
3	Chronic obstructive pulmonary disease	Hypoxia, Cyanosis, Clubbing
4	Recurrent pulmonary embolism	Exercise intolerance, Chest pain, Hemoptysis
5	Sarcoidosis, Hematological disorders	Variable symptoms based on underlying conditions

Diagnosis and risk stratification

Accurate diagnosis and risk stratification are key to successful PH management. Diagnostic tools include:

- Echocardiography - An essential non-invasive screening tool for assessing right heart function and estimating pulmonary artery pressure [3].
- Right heart catheterization (RHC) - The gold standard for confirming PH diagnosis and assessing hemodynamic parameters [1].
- 6-minute walk test (6MWT) - Used for functional assessment and monitoring response to treatment [4].
- Biomarkers - Elevated levels of brain natriuretic peptide (BNP) or N-terminal pro-BNP are indicative of right heart strain [5].

Recent guidelines recommend risk stratification using a multi-parameter approach, considering clinical symptoms, exercise capacity, right ventricular function, and hemodynamics [6].

Risk Stratification in PAH
Low-risk: Stable clinical status, 6MWD > 440m (6)
Intermediate-risk: Moderate symptoms, 6MWD 165-440m (6)
High-risk: Progressive symptoms, 6MWD < 165m (6)

Pharmacological management

Management of PH varies depending on the underlying cause. For group 1 (PAH), several classes of medications are available, targeting different pathways involved in pulmonary vascular remodelling.

Endothelin receptor antagonists (ERAs)

Drugs such as Bosentan and Ambrisentan block endothelin-1, a potent vasoconstrictor, reducing pulmonary vascular resistance [7,8].

Phosphodiesterase-5 inhibitors (PDE-5 inhibitors)

Sildenafil and Tadalafil increase cyclic GMP, promoting vasodilation and improving exercise capacity [9].

Prostacyclin analogues

Drugs like epoprostenol and treprostinil mimic prostacyclin, enhancing vasodilation and inhibiting platelet aggregation [10].

Soluble guanylate cyclase stimulators

Riociguat stimulates soluble guanylate cyclase, promoting vasodilation and reducing mPAP in both PAH and CTEPH [11,12].

Combination therapy

Recent studies advocate for upfront combination therapy in PAH to improve long-term outcomes. The AMBITION trial demonstrated the superiority of Ambrisentan combined with Tadalafil over monotherapy [13].

For other PH groups

- Group 2 (PH due to left heart disease) focuses on treating underlying left heart conditions [14].
- Group 3 (PH due to lung diseases) includes oxygen therapy and pulmonary rehabilitation [15].
- Group 4 (CTEPH) may benefit from anticoagulation, thromboendarterectomy, or balloon pulmonary angioplasty [16].

Interventional and surgical options

Balloon pulmonary angioplasty (BPA)

BPA is a promising intervention for CTEPH patients who are inoperable or have residual PH post-surgery. It involves dilating obstructed pulmonary arteries using balloons, improving hemodynamic and exercise capacity [17].

Pulmonary thromboendarterectomy (PTE)

PTE is the definitive treatment for CTEPH, involving surgical removal of chronic thrombi from the pulmonary arteries. It significantly improves survival and functional outcomes in carefully selected patients [18].

Lung transplantation

Lung transplantation is reserved for advanced PH cases unresponsive to medical therapy. Careful patient selection is crucial to ensure favourable outcomes [19].

Emerging therapies and future directions

PH remains a challenging condition, particularly due to its progressive nature and the limitations of current treatments, which focus on managing symptoms rather than addressing the underlying causes. The following novel therapeutic agents and advanced diagnostic tools represent the cutting edge of research aimed at improving patient outcomes and potentially altering the disease course.

Tyrosine kinase inhibitors (e.g. Imatinib)

Tyrosine kinase inhibitors (TKIs) are a class of drugs that block specific enzymes known as tyrosine kinases, which play a crucial role in the signaling pathways that regulate cell growth, survival, and proliferation. In pulmonary arterial hypertension (PAH), one of the primary pathological features is the abnormal proliferation of pulmonary arterial smooth muscle cells, leading to vascular remodelling, narrowing of the blood vessels, and increased pulmonary arterial pressure.

Imatinib, a TKI originally developed for treating chronic myeloid leukaemia (CML), was found to inhibit platelet-derived growth factor (PDGF) receptors, which are implicated in the proliferation of pulmonary arterial smooth muscle cells in PAH. Early trials demonstrated that Imatinib could potentially reverse some aspects of vascular remodelling, leading to improvements in pulmonary hemodynamic [20].

Clinical studies: In a pivotal study called the IMPRES trial, Imatinib was tested in patients with advanced PAH. The results showed that patients receiving Imatinib experienced a significant reduction in pulmonary vascular resistance and an improvement in exercise capacity (measured by the 6-minute walk test) compared to placebo [20]. However, there were concerns about serious side effects, including subdural hematomas and peripheral edema, which limited the widespread adoption of Imatinib in clinical practice.

Challenges and future research: Although the efficacy of Imatinib was promising, its safety profile presents challenges. Ongoing research aims to develop more selective tyrosine kinase inhibitors with fewer side effects, potentially making this class of drugs a viable option for long-term use in PAH. Moreover, understanding the molecular pathways involved in smooth muscle proliferation may lead to the discovery of new targets for therapy.

Antifibrotic agents (e.g. Pirfenidone)

Antifibrotic therapies are gaining attention in the treatment of PH, particularly in patients with PH associated with interstitial lung disease (PH-ILD). In conditions like idiopathic pulmonary fibrosis (IPF), excessive deposition of fibrous tissue in the lungs leads to stiffness, impaired gas exchange, and secondary pulmonary hypertension. Pulmonary vascular remodelling also contributes to the increased pulmonary arterial pressures seen in these patients.

Pirfenidone, an antifibrotic agent approved for the treatment of IPF, acts by inhibiting the production of pro-fibrotic growth factors, such as transforming growth factor-beta (TGF-β), and reducing the synthesis of collagen [21]. Since fibrotic changes in the lungs also affect the pulmonary vasculature, there is growing interest in exploring whether antifibrotic drugs like Pirfenidone can slow or reverse the progression of pulmonary vascular disease in PH-ILD patients.

Clinical implications: While antifibrotic therapy does not directly target the pulmonary vasculature, by reducing fibrosis and improving lung compliance, it may help alleviate the secondary pulmonary hypertension caused by lung tissue remodelling. Preliminary studies have shown that Pirfenidone may stabilize or even improve exercise capacity and quality of life in PH-ILD patients. However, more extensive clinical trials are required to confirm its effectiveness in this subgroup of PH patients [21].

Future directions: Research is ongoing to determine whether other antifibrotic agents, such as Nintedanib, which also has anti-angiogenic properties, could be more beneficial in patients with PH-ILD or even PAH. Combining antifibrotic drugs with existing PH therapies (such as prostacyclin analogues or endothelin receptor antagonists) may offer a synergistic effect in treating both the lung fibrosis and vascular remodelling simultaneously.

Gene therapy and RNA-based therapeutics

Gene therapy and RNA-based therapeutics represent cutting-edge approaches aimed at addressing the underlying genetic and molecular causes of pulmonary hypertension. These novel treatments are designed to modify or correct the dysfunctional pathways that drive pulmonary vascular remodelling and right ventricular failure.

Gene therapy: This approach involves delivering therapeutic genes to the patient's cells to replace or repair defective genes involved in the pathogenesis of PH. For example, the BMPR2 gene, which encodes a protein involved in regulating cell growth and survival, is frequently mutated in familial PAH. Gene therapy could potentially correct this mutation and restore normal cell function in the pulmonary vasculature. Animal studies have shown promise in using viral vectors to deliver functional BMPR2 genes, leading to reduced pulmonary arterial pressure and improved right heart function [22].

RNA-based therapeutics: RNA therapeutics, such as small interfering RNA (siRNA) or microRNA (miRNA), work by silencing or modulating the expression of genes involved in pulmonary arterial smooth muscle proliferation and inflammation. This approach can specifically target the molecular drivers of PAH without affecting other cellular functions. For example, inhibiting the miR-130/301 family of microRNAs, which promote vascular remodelling, has been shown to reduce pulmonary arterial pressure in animal models of PH [22].

Challenges and future research: While gene therapy and RNA-based treatments hold great potential, their clinical application in PH is still in its early stages. Key challenges include ensuring safe and efficient delivery of therapeutic genes or RNA molecules to the pulmonary vasculature, minimizing off-target effects, and achieving long-term therapeutic benefits. As gene editing technologies (e.g. CRISPR-Cas9) advance, they may offer even more precise ways to correct genetic mutations in PAH patients.

Advances in imaging techniques

Accurate assessment of right ventricular function and pulmonary vascular resistance is critical for the diagnosis, monitoring, and management of PH. Recent advances in imaging techniques have significantly improved the ability to evaluate the structural and functional changes in the heart and pulmonary vasculature associated with PH.

3D echocardiography: Traditional two-dimensional (2D) echocardiography has been a cornerstone in PH diagnosis, allowing clinicians to estimate pulmonary arterial pressure and assess right ventricular function. However, 2D imaging has limitations in accurately measuring complex cardiac structures. The development of 3D echocardiography allows for more precise visualization and quantification of right ventricular volumes, ejection fraction, and wall thickness. This is particularly important in PH, where right ventricular dysfunction is a key determinant of prognosis [23].

Cardiac MRI: Cardiac magnetic resonance imaging (MRI) is considered the gold standard for assessing right ventricular function and pulmonary artery dimensions. It provides detailed information about right ventricular size, contractility, and wall stress, which are critical for monitoring disease progression and response to therapy. Additionally, phase-contrast MRI can be used to measure blood flow in the pulmonary arteries, offering a non-invasive way to assess pulmonary vascular resistance [23]. These advanced imaging modalities are especially useful for tracking changes in right heart function in response to novel therapies, such as gene or RNA-based treatments.

Future applications: As imaging technology continues to evolve, the integration of artificial intelligence (AI) and machine learning algorithms into imaging analysis may allow for even more accurate and automated assessments of right ventricular function and pulmonary vascular resistance. AI-driven imaging tools could enhance the ability to predict disease progression, optimize treatment strategies, and personalize therapy for individual PH patients.

Management algorithm

A diagram of the current management algorithm for PAH is presented below, incorporating risk stratification and treatment pathways based on recent guidelines.

Algorithm for management of pulmonary hypertension

1. Diagnosis

- Clinical assessment (history, physical exam).
- Confirmed elevated mean pulmonary artery pressure (mPAP ≥ 25 mmHg) via right heart catheterization.

2. Classification of pulmonary hypertension

- Group 1: Pulmonary arterial hypertension (PAH).
- Group 2: PH due to left heart disease.
- Group 3: PH due to lung disease and/or hypoxia.
- Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH).
- Group 5: PH with unclear multifactorial mechanisms.

3. Initial evaluation

- Determine underlying cause(s).
- Perform echocardiography, pulmonary function tests, and imaging (CT, V/Q scan).

4. Management strategies

5. General measures:

- Avoidance of known triggers (e.g. altitude).
- Oxygen therapy for hypoxemia.

6. Specific treatment based on group:

- Group 1 (PAH):
  - Endothelin receptor antagonists (e.g., bosentan, ambrisentan).
  - Phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil).
  - Soluble guanylate cyclase stimulators (e.g., riociguat).
  - Prostacyclin analogs (e.g., epoprostenol, treprostinil).
- Group 2 (Left heart disease):
  - Treat underlying heart disease.
  - Diuretics for volume overload.
- Group 3 (Lung disease/hypoxia):
  - Optimize treatment of underlying lung disease.
  - Oxygen therapy.
- Group 4 (CTEPH):
  - Consider pulmonary endarterectomy if operable.
  - Medical therapy with riociguat for inoperable cases.
- Group 5:
- Treat underlying conditions and symptoms.

7. Follow-up and monitoring

- Regular follow-up assessments.
- Monitor functional capacity (e.g. WHO functional classification).
- Adjust treatment based on response and side effects.

8. Consider advanced therapies

- Referral for lung transplantation in severe cases or refractory PH.

Monitoring and follow-up in pulmonary hypertension management

Long-term management of pulmonary hypertension (PH) is a dynamic process that requires careful and regular monitoring of the patient's clinical status, exercise capacity, right heart function, and hemodynamic parameters. This approach ensures timely adjustments to treatment based on the patient's evolving risk profile and response to therapy.

Clinical status monitoring

Regular assessments of the patient's clinical status are essential to gauge the effectiveness of the treatment regimen. Key elements of clinical monitoring include:

- **Symptoms assessment:** Patients should be routinely evaluated for common symptoms of PH, including shortness of breath, fatigue, palpitations, and signs of right heart failure (such as peripheral edema). Regular symptom scoring can help identify changes in the patient's condition.
- **Functional capacity:** The 6-minute walk test (6MWT) is a widely used tool to objectively measure exercise capacity in PH patients. This test helps assess the patient's endurance and can indicate changes in functional status over time. A decline in distance walked may suggest worsening of the condition and may prompt revaluation of therapy.
- **Quality of life:** Utilizing validated questionnaires, such as the World Health Organization (WHO) Functional Classification, can provide insights into the patient's quality of life and functional limitations caused by PH. Monitoring changes in quality of life helps guide treatment adjustments.

Right heart function assessment

Monitoring right heart function is critical in PH management, as right ventricular (RV) dysfunction is a key determinant of prognosis. Tools for assessment include:

- **Echocardiography:** Regular echocardiograms allow for non-invasive evaluation of right ventricular size, function, and wall motion abnormalities. These parameters can provide insights into the patient's hemodynamic status and help monitor the impact of therapies.
- **Cardiac MRI:** When available, cardiac magnetic resonance imaging (MRI) offers a comprehensive assessment of right ventricular morphology and function. It can provide additional information on myocardial strain and fibrosis, which may influence management decisions.

Hemodynamic monitoring

Hemodynamic parameters play a crucial role in understanding the severity of PH and guiding treatment. Key monitoring strategies include:

- **Right heart catheterization:** While typically performed during initial diagnosis, repeated right heart catheterization may be indicated in certain cases to assess pulmonary arterial pressure, cardiac output, and pulmonary vascular resistance. This invasive procedure provides precise hemodynamic measurements that can inform therapy adjustments.
- **Biomarkers:** Monitoring specific biomarkers, such as N-terminal pro b-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin, can provide insights into right ventricular strain and function. Elevated levels may indicate worsening heart failure and necessitate treatment reassessment.

Treatment adjustments based on risk profile

Regular monitoring allows healthcare providers to tailor treatment based on the patient's individual risk profile and response to therapy. The following factors should be considered:

- **Risk stratification:** Patients should be classified into low, intermediate, or high-risk categories based on clinical factors, functional capacity, and hemodynamic data. Changes in risk status should prompt reassessment of treatment strategies.
- **Response to therapy:** Treatment adjustments should be based on the patient's response to current therapies. An insufficient response, defined as minimal improvement in symptoms, exercise capacity, or hemodynamic parameters, may warrant consideration of alternative treatments or combination therapy.
- **Adverse effects monitoring:** Regular follow-up visits should also focus on monitoring for potential side effects of PH medications, including complications associated with specific therapies (e.g., bleeding risk with anticoagulants or side effects from prostacyclin analogues).

Long-term follow-up strategy

- **Regular clinic visits:** Patients with PH should have structured follow-up appointments every 3-6 months, or more frequently if their condition is unstable or if therapy changes are made.
- **Patient education:** Empowering patients with education about their condition, medication adherence, and recognizing early signs of deterioration is critical for successful long-term management.
- **Multidisciplinary approach:** Effective management of PH often involves a multidisciplinary team, including pulmonologists, cardiologists, nurses, and palliative care specialists, to provide comprehensive care and address the diverse needs of patients.

Conclusion

Pulmonary hypertension is a complex condition requiring a multidisciplinary approach to management. Advances in pharmacotherapy, interventional techniques, and personalized medicine are improving outcomes for patients with PH. Ongoing research will likely yield new therapeutic options and refine existing strategies, ultimately offering hope for better management of this challenging disease.

The future of pulmonary hypertension management looks promising with the development of novel therapies and advanced diagnostic tools. Tyrosine kinase inhibitors, antifibrotic agents, gene therapy, and RNA-based treatments have the potential to revolutionize the treatment landscape by targeting the underlying causes of the disease. Moreover, advances in imaging techniques, such as 3D echocardiography and cardiac MRI, are improving the ability to monitor right ventricular function and guide therapeutic interventions.

While many of these emerging therapies are still in the experimental stage, they offer hope for improving outcomes and quality of life in patients with pulmonary hypertension. Ongoing research and clinical trials will be critical in determining their long-term efficacy and safety, paving the way for more personalized and effective treatment options.

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