Pulmonary Arterial Hypertension: A Review Article

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ARTICLE INFO	ABSTRACT

Pulmonary arterial hypertension (PAH) is characterized by the mean pulmonary artery pressure of more than 25 mmHg and pulmonary artery wedge pressure of less than 15 mmHg evidenced by right-heart catheterization. In the classification of PAH, some subgroups are defined as primary or secondary PAH based on the underlying etiologies of the disease. Early episodes of PAH have been reported to occur at younger ages and in women in idiopathic or familial forms with the survival rate of 1-3 years. According to recent registries, the affected patients are older and have better survival rates. Some of the key elements in the pathophysiology of PAH include intima and media proliferation, vascular remodeling, and blood coagulation, which could increase the defiance of pulmonary vascularity, so that the cellular and molecular pathways would be able to induce PAH through specific mechanisms. Although no pathognomonic signs and symptoms have been reported in the literature, the most prominent manifestations of PAH are associated with disorders such as heart failure. Currently, PAH is known as a severe and occasionally life-threatening multifactorial clinical condition. Considering endothelial dysfunction, vasoconstriction, inflammatory reactions, and platelet aggregation as the main pathophysiological arms of the disease, specific treatment approaches have been proposed to inhibit these manifestations. These methods result in the effective treatment response, as well as the proper early and late outcomes of PAH. Due to the high incidence of cardiovascular diseases and the associated progressive life-threatening conditions, such as heart failure and PAH in the Iranian population, identification of the etiological, pathophysiological, diagnostic, and novel therapeutic approaches for PAH is essential to the proper management of this clinical condition.

Introduction

Pulmonary arterial hypertension (PAH) is defined as the mean pulmonary artery pressure of more than 25 mmHg and pulmonary artery wedge pressure (PCWP) of less than 15 mmHg as measured by right-heart catheterization. In the classification of PAH, some subgroups have been defined as primary or secondary PAH based on the underlying etiologies of the disease. Early episodes of PAH have been reported to occur at younger ages and in women in idiopathic or familial forms with the survival rate of 1-3 years.

Currently, PAH is known to be a severe and occasionally life-threatening multifactorial clinical condition. Considering endothelial dysfunction, vasoconstriction, inflammatory reactions, and platelet aggregation as the main pathophysiological arms of PAH, specific treatment approaches have been proposed to inhibit these conditions. These methods result in the effective treatment response and proper early and late outcomes of the disease.

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Due to the high incidence of cardiovascular diseases and the associated progressive life-threatening conditions, such as heart failure and PAH, in the Iranian population, identification of the etiological, pathophysiological, diagnostic, and novel therapeutic approaches of PAH is essential to the proper management of this clinical condition.

Literature Search Strategy

The only inclusion criterion of the study was the articles that have been published in English. Literature search was conducted in databases such as PubMed, Medline, Medscape, and Web of Science by using medical subject headings (MeSH). In addition, the following terms were searched in the titles and abstracts of the eligible articles: "pulmonary arterial hypertension" or "pulmonary vascular disease" or "pulmonary artery hypertension" or "pulmonary hypertension" or "lung and heart disease" or "cardio-pulmonary disease" or "PAH".

1. Definition and Classification of PAH

Physiologically, the vasculature of normal pulmonary arteries adopts with less than 1:10 of the systemic vascular resistance to the blood flow. Alteration of this balance may lead to the development and progression of pulmonary arterial vasculopathies and increase arterial pressure and resistance. In this regard, PAH is defined as the mean pulmonary artery pressure of more than 25 mmHg and PCWP of less than 15 mmHg, which are measured by right-heart catheterization (1,2).

In the classification of PAH, some subgroups have been defined as primary or secondary PAH based on the underlying etiologies of the disease. The latest classification of PAH is as follow:

1) Familial or heritable PAH:

In the idiopathic or sporadic form, lack of an antecedent family report of PAH or a punctual risk factor is distinguished. This type of PAH mainly involves specific gene mutations, such as the polymorphisms on the bone morphogenetic protein receptor 2 (BMPR2) gene (11-40% of PAH patients) and the gene coding the transforming growth factor beta (TGF- ß), which could be detected in more than 70% of the patients. However, mutations in the genes coding the activin receptor-like kinase type 1 (ACVRL1 or ALK1) and endoglin are rare (3,4).

2) Toxin- and pharmaceutical-induced PAH:

Some drugs have been shown to trigger PAH. In this regard, aminorex, benfluorex, and fenfluramine formants and toxic rapeseed oil are the only documented hazardous agents for PAH (5,6). Recently, the co-administration of methamphet-

amines with fenfluramine has been reported to increase the risk of PAH (7,8).

3) PAH associated with connective tissue disorders:

Systemic sclerosis is considered to be a major risk factor in about 7-12% of the patients with PAH (9,10).

4) HIV infection:

HIV infection is a rare cause of PAH, which could be detected in less than 0.5% of PAH patients (11,12).

5) Portopulmonary hypertension (POPH):

POPH is characterized by the coexistence of PAH and increased pressure in the portal circulation, which is reported in 2-6% of the patients with PAH (13,14).

6) Congenital heart disease (CHD):

In background of the systemic to pulmonary shunts, CHD patients may be concurrently affected by PAH, especially when they are untreated or have the Eisenmenger's syndrome (15,16).

7) Schistosomiasis:

Evidence suggests that in the patients with schistosomiasis, PAH could be mediated by the local vascular inflammation induced by the parasite, as well as the obstruction of the vasculature bed by the schistosoma eggs (17).

8) Chronic hemolytic anemia:

PAH has been reported to occur along with some forms of hemolytic anemia, including sickle cell anemia (18,19), thalassemia (20), hereditary spherocytosis (21), stomatocytosis (22), and microangiopathic hemolytic anemia (23).

9) Pulmonary veno-occlusive disease (PVOD):

PVOD is considered to be a rare etiology of PAH, which is caused by the progressive blockage of the small veins in the lungs and increases the pulmonary artery pressure, thereby leading to heart failure mainly due to edematous or sclerotic fibrous tissues (24).

10) Left-sided ventricular and valvular diseases:

These conditions are associated with left-sided systolic or diastolic dysfunction and valvular diseases, which could give rise to PAH by increasing the left atrial pressure and lead to the backward transmission of the pressure, inducing a passive increment in the pulmonary artery pressure. This process occurs due to the increased pulmonary artery vasomotor tone and/or pulmonary vascu-

lar remodeling (25).

11) Pulmonary disorders:

PAH associated with lung diseases (e.g., chronic bronchiectasis and cystic fibrosis) is mainly caused by alveolar hypoxia, the main mechanisms of which remain unknown (26,27).

12) Acute thromboembolic events:

Acute pulmonary embolism has been reported to be the main cause of PAH in approximately 4% of the affected patients (28).

13) Hematologic disorders:

Chronic myeloproliferative disorders (e.g., polycythemia vera, essential thrombocythemia, and chronic myeloid leukemia) are among the other major etiologies of PAH, which are mainly secondary regarding their effects on the cardiopulmonary system, such as increased cardiac output, obstruction of the pulmonary arteries, and inducing congestive heart failure (29).

14) Systemic disorders:

Several systemic disorders have been considered to the secondary causes of PAH, including pulmonary Langerhans cell histiocytosis, sarcoidosis, lymphangioleiomyomatosis, neurofibromatosis, and vasculitis. PAH mechanisms in these clinical conditions are mainly associated with the capillary vasculature demolition due to chronic hypoxemia, fibrotic process, compression of large arteries by enlarged lymph nodes, and infiltration of the pulmonary bed (particularly the veins) by the granulomatous tissue. These conditions are generally categorized as systemic vasculopathies (30,31).

15) Metabolic disorders:

Some metabolic disturbances, which lead to glucose-6-phosphatase deficiency (e.g., type Ia glycogen storage disease), have been associated with PAH. Pathophysiology of this effect could be due to atrial septal defects, portocaval shunts, thrombosis or restrictive pulmonary dysfunction (32).

16) Miscellaneous conditions:

Some rare conditions have been shown to cause PAH, including tumor-induced obstruction, fibrosing mediastinitis, chronic kidney disease, and hemodialysis. Furthermore, some of the main causes of PAH in the other miscellaneous conditions include pulmonary artery obstruction due to thrombosis or tumor compression, embolic microvascular occlusion due to metastatic tumors, and potential left-sided systolic and diastolic dysfunctions due to hemodialysis (33,34).

2. Epidemiology of PAH

In recent decades, the epidemiology of PAH has altered noticeably. Early episodes of PAH have been mostly reported at younger ages and in women in the idiopathic or familial forms, with the survival rate of 1-3 years (range: 37-67%) (35,36). However, according to recent registries, the patients affected by PAH are older and have better survival rates (37,38). Mean age at the diagnosis of PAH has been estimated to be 50 years, with more delay at the onset of the symptoms and diagnosis, less functional capacity, and higher rate of the associated disorders in the elderly compared to the young populations (39). Moreover, the elderly patients have been reported to be affected by the less severe forms of PAH, while they also have poorer outcomes compared to the younger patients (39).

3. Pathophysiology of PAH

PAH is basically developed in the presence of arterial involvement due to vascular obstruction, which results in the progressive increment of the vascular resistance. This alteration could elevate the right ventricular afterload and lead to right ventricular failure. The key elements in the pathophysiology of PAH include intima and media proliferation, vascular remodeling, and thrombosis, all of which could increase the pulmonary vascular resistance (40,41).

In general, both the cellular and molecular pathways could induce PAH through specific mechanisms. Regarding the cellular mechanism, smooth muscular proliferation in the small peripheral pulmonary vascularity is the cornerstone of the disease. In addition, a combination of some processes may be involved in the development of PAH, including the migration of the adventitial fibroblasts to the intima and media layers, neovascularization of the adventitia, and thickening of the vascular walls (42,43). These changes may be induced by various hypoxic, infectious, inflammatory, and genetic factors. It is assumed that inflammatory mechanisms (e.g., autoimmune diseases, HIV infection) might variably affect different forms of PAH (44).

In this regard, production of some chemokines (fractalkine and MCP-1) and inflammatory mediators (interleukin-1 and interleukin-6) has been clearly demonstrated (45,46). Furthermore, thrombosis and platelet dysfunction could play a role in the initiation of endothelial dysfunction and vascular obstruction in PAH. With respect to molecular factors, vasoconstriction is considered to be the primitive occurrence in the process of PAH, which is associated with endothelial dysfunction and leads to the reduction of vasodilator production and secretion, as well as increased vasoconstrictor production (47). Overall, the pathophysi-

ology of PAH is complicated and multidimentional and could be mediated by the triad of genetic, environmental, and idiopathic factors.

4. Clinical Manifestations

Although no pathognomonic signs and symptoms have been reported for the disease, the most prominent manifestations of PAH are associated with disorders such as heart failure. These manifestations include persistent exertion dyspnea, hemodynamic instability, reduced functional capacity, chest pain, light-headedness, palpitation, fatigue, weakness, hemoptysis, and hoarseness of the voice. In severe conditions, the signs of heart failure may also appear, such as venous jugular turgidity, hepatojugular reflux, hepatomegaly, liver pain, lower-extremity edema, ascites, and anasarca.

5. Diagnostic Considerations

A series of diagnostic procedures are employed in the diagnosis of PAH and its outcomes, including electrocardiogram, rhenthogram, echocardiography, pulmonary function test, arterial blood gas, high-resolution computed tomography (HRCT) of the lungs, ventilation/perfusion lung scan, exercise test, and pulmonary angiography.

In electrocardiography, the evidence of right ventricular hypertrophy and right atrial dilation may appear. In chest radiography, abnormal changes (e.g., central pulmonary arterial dilatation, right atrial and ventricular enlargement) may present in approximately 90% of the patients upon diagnosis (48). In the pulmonary function test, a major finding is the lower diffusing capacity of the lung for carbon monoxide, especially in the patients with PVOD (49). In the arterial blood gas analysis, mild-to-severe hypoxemia and hypocapnia are frequently detected. In the exercise test, elevated pulmonary artery pressure may be impaired due to the increased blood flow (50).

Doppler echocardiography is an accurate modality to show the increased pulmonary artery systolic pressure, enhanced velocity of the pulmonary valve regurgitation and short acceleration time of the right ventricular ejection into the pulmonary artery, increased right-heart chamber dimensions, hazardous shape and dysfunction of the interventricular septum, increased wall thickness of the right atrium, and pericardial effusion (51,52).

HRCT could detect possible underlying lung diseases, such as pulmonary emphysema and interstitial lung disease. These conditions could be identified based on the presence of pericardial effusions and pulmonary artery enlargement (53). Pulmonary angiography facilitates the diagnosis of fibrosing mediastinitis, full obstruction, and intimal irregularities (54).

By using the cardiac magnetic resonance imaging, all the functional aspects of the right ventricular and valvular components (e.g., size, morphology, and shape) could be assessed accurately. Moreover, this method could be employed to evaluate the indices associated with the blood flow, such as the cardiac output, stroke volume, pulmonary artery distensibility, and right ventricular mass (55,56). Serological blood tests are normally performed to detect infections. Finally, right-heart catheterization provides the definite diagnosis of PAH by demonstrating the increased pulmonary artery pressure (>25 mmHg) along with normal PCWP.

6. Management and Treatment of PAH

Non-therapeutic and therapeutic approaches should be considered for the proper management of PAH of various degrees. Some of the most common methods in this regard are as follows:

A) Conservative approach:

Due to the lower functional capacity, extreme physical activity may be advised. Instead, physical rehabilitation is recommended to improve the functional capacity under particular circumstances based on the physical and hemodynamic status of the patients. On the other hand, since hypoxia is considered a major component of PAH, oxygenation and removal of hypoxia are warranted in the affected patients. Prescribed medications in this approach may include vasoconstrictors, and beta-blockers should be avoided.

B) Nonspecific medications:

Some medications that alleviate the signs of heart failure (fluid retention, hepatic congestion, ascites, and anasarca) could be effective in improving the manifestations of PAH; for instance, diuretics are considered a proper choice for this purpose (57). Additionally, anticoagulation treatment should be considered to maintain the International Normalized Ratio (INR) within the range of 1.5-2.5 in order to reduce the risk of thrombosis (58,59). Of note, digitalis should be administered in the case of atrial tachyarrhythmia. Calcium channel blockers are also recommended for the patients with a positive vasodilatation challenge test after nitric oxide inhalation (60).

C) Specific medications:

Several specific pharmaceutical agents are prescribed for the medical management of PAH, including prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors. Prostacyclin and its agonists (intravenous epopro-

stenol and subcutaneous treprostinil) are potent systemic and pulmonary vasodilators and inhibitors of platelet aggregation, which have antiproliferative, antithrombotic, antimitogenic, and immunomodulatory properties. These agents increase the lung capacity and survival and improve the quality of life, pulmonary hemodynamics, and clinical symptoms of the patients (61-65).

As potent vasoconstrictors and proliferators, endothelin receptor antagonists (e.g., bosentan and ambrisentan) inhibit endothelin-1 as the main arm of PAH (66-72). Moreover, phosphodiesterase type 5 inhibitors (e.g., sildenafil and tadalafil) are among the most effective agents in vascular remodeling and vasodilatation (73-75).

In the cases with resistance to medical treatments, non-pharmaceutical and invasive approaches should be applied to achieve the appropriate hemodynamic stability. Some of the examples in this regard are as follows:

1) Balloon atrial septostomy:

Placement of the right-left shunt through heart surgery diminishes the right auricular pressure and increases the systemic blood flow, while also reducing the right ventricular wall tension. Eventually, the process leads to the regression of the PAH symptoms and increased functional capacity (76).

2) Lung transplantation:

Although this surgical approach remains the first-line treatment for the patients with severe PAH, it is largely invasive and is associated with a relatively low long-term survival rate. However, this approach could be considered in the patients with very severe PAH, in whom the previously mentioned methods have failed (77,78).

In a study by Buys et al., exercise training was reported to be beneficial for PAH patients; however, this is a relatively novel approach and must be further investigated. Evidence suggests that rehabilitation could improve the quality of life of PAH patients (79). In this regard, Ehlken believes that exercise positively affects the peak oxygen consumption and hemodynamics of PAH patients (80). In another research, Magdalena et al. claimed that statins could not improve the pulmonary artery pressure, cardiac indices, and pulmonary vascular resistance significantly (81).

Conclusion

Currently, PAH is known to be a severe and occasionally life-threatening clinical condition with multifactorial etiologies. Due to the associated endothelial dysfunction, vasoconstriction, inflammatory reactions, and platelet aggregation as the main pathophysiological arms of the disease, the specific treatment approaches for PAH are mainly based on inhibiting these conditions to achieve an effective treatment response and proper early and late outcomes in the patients. Considering the high incidence of cardiovascular diseases and the related progressive life-threatening conditions (e.g., heart failure and PAH) in the Iranian population, identification of all the etiological, pathophysiological, diagnostic, and novel therapeutic approaches for PAH is essential to the effective management of this clinical condition.

Conflict of Interest
The authors declare no conflict of interest.

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