Pulmonary artery hypertension: A review article

ABSTRACT

Pulmonary arterial hypertension (PAH) is characterized by mean pulmonary artery pressure of more than 25 mmHg along with a pulmonary artery wedge pressure (PCWP) of less than 15 mmHg evidenced by right heart catheterization. Respecting classification of PAH, some subgroups of disease were defined according to the underlying etiologies of disease as primary or secondary PAH. Earlier episodes of PAH have been appeared mostly in younger ages, in female, as well as in idiopathic or familial forms with a 1- to 3-year survival. According to recent registries, the affected patients have been older with better survey. The key points in PAH pathophysiology include intima and media proliferation, vascular remodeling and blood coagulation that have potency to increase defiance of pulmonary vascularity, both cellular and molecular pathways can induce PAH through especial mechanisms. No pathognomonic symptoms and signs have been pointed, but the prominent manifestations of PAH are related to associated disorders such as heart failure. Totally, PAH is now identified as a serious and occasionally life-threatening clinical condition with multifactorial etiologies. Due to discovering endothelial dysfunction, vasoconstriction, inflammation reactions, and platelet aggregation as main pathophysiological arms of disease, introduced specific treatment approaches are now based on inhibiting these conditions leading appropriate treatment response as well as proper early and late outcome.

Because of high incidence of cardiovascular disorders and related progressive life-threatening conditions such as heart failure and PAH among Iranians, the identification of all etiological, pathophysiological, diagnostic, and novel therapeutic approaches of PAH is essential to best management of this clinical condition.

Key words: Hypertension, Pulmonary artery, Arterial pressure

Literature search strategy:

Inclusion criteria includes articles published in English. Literature search conducted in the PubMed-Medline data base, using Medical subject heading (MeSH-term), Medscape, Web of Science. We searched following terms in titles and abstracts ("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").

Introduction

Pulmonary artery hypertension (PAH) is defined as a mean pulmonary artery pressure of over than 25 mmHg, parallel with a pulmonary artery wedge pressure (PCWP) of less than 15 mmHg, measured by right atrial catheterization. Respecting classification of PAH, some subgroups of disease were defined according to the underlying etiologies of disease as primary or secondary PAH. Earlier episodes of PAH have been appeared mostly in younger ages, in female, as well as in idiopathic or familial forms with a 1- to 3-year survival. Totally, PAH is now identified as a serious and occasionally life-threatening clinical condition with multifactorial etiologies. Due to discovering endothelial dysfunction, vasoconstriction, inflammation reactions, and platelet aggregation as main pathophysiological arms of disease, introduced specific treatment approaches are now based on inhibiting these conditions leading appropriate treatment response as well as proper early and late outcome.

Because of high incidence of cardiovascular disorders as well as related progressive life-threatening conditions such as heart failure and PAH among Iranians, the identification of all etiological, pathophysiological, diagnostic, and novel therapeutic approaches of PAH is essential to best management of this clinical condition.

Literature review

1. Definition and classification of PAH

Physiologically, the vasculature of normal pulmonary artery adopts with less than 1:10 of systemic vasculature resistance to flow. Any alteration in this balance can result in development and progression of pulmonary artery-related vasculopathies leading increase of both arterial pressure and resistance. In this regard, pulmonary arterial hypertension (PAH) is defined as a mean pressure in the pulmonary artery of more than 25 mmHg parallel with a less than 15 mmHg in wedge pressure of pulmonary artery (PCWP) which is measured by right atrial catheterization [1,2]. Respecting classification of PAH, some subgroups of disease were defined according to the underlying etiologies of disease as primary or secondary PAH. The last version of the PAH categorization is as follow: 1) Familial or heritable PAH: In idiopathic or sporadic form, the lack of a antecedent family report of PAH or an punctual risk factor is distinguished. This form is mainly based on some gene mutations such as the polymorphisms on bone morphogenetic protein receptor 2 (BMPR2) gene (in about 11 to 40% of patients with PAH) and the gene coding transforming growth factor beta (TGF- ß) that can be detected in more than 70% of affected patients and rarely the mutations in the genes which coded activin receptor like kinase type 1 (ACVRL1 or ALK1) or endoglin [3,4]; 2) Toxin and pharmaceutical-induced PAH: A number of drugs have been identified to be trigger for appearing PAH. In this context, Aminorex, Benfluorex, Fenfluramine formants and toxic Rapeseed Oil represent the only identified "documented" hazardous for PAH [5,6]. Recently, co-administration of Methamphetamines with Fenfluramine has been shown to enhance the risk for PAH [7,8]. 3) PAH associated with connective tissue diseases: systemic sclerosis has been revealed as a main risk profile in about 7 to 12% of patients with PAH [9,10]; 4) HIV infection: This infection is a rare cause for PAH can be detected in less than 0.5% of affected patients [11,12]; 5) Porto-pulmonary hypertension (POPH) that is

characterized by the coexistence of PAH and pressure increment in the portal circulation that is found in 2 to 6% of affected patients with PAH [13,14]; 6) Congenital heart diseases (CHD): those patients with CHD in background of the systemic to pulmonary shunts affects concurrently by PAH especially when left untreated or by Eisenmenger's syndrome [15,16]; 7) Schistosomiasis: It seems that PAH in Schistosomiasis can be mediated by local vascular inflammation induced by the parasite as well as obstruction of vasculature bed by schistosoma eggs [17]; 8) Chronic hemolytic anemia: The appearance of PAH has been reported in background of some 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): this phenomenon Pulmonary veno-occlusive disease (PVOD) is a rare etiology of PAH caused by progressive blockage of the small veins in the lungs leading the increase PAP and thus heart failure mainly due to edematous or sclerotic fibrous tissue [24]; 10) Left-sided ventricular or valvular diseases: these situations covering systolic or diastolic dysfunction of left heart and its valvular diseases which can generate PAH by left atrial pressure increment, resulting in a pressure backward transmission and a so induce a passive increment in pulmonary arterial pressure. This process is due to pulmonary artery vasomotor tone increment and/or vascular remodeling in the lung[25]; 11) Lung disorders: PAH induced by lung diseases (such as chronic bronchiectasis, cystic fibrosis) is mainly caused by appearing alveolar hypoxia that its main mechanisms remains already unknown [26,27]; 12) Acute thromboembolic event: acute pulmonary embolism is the main cause of PAH in about 4% of affected patients [28]; 13) Hematologic disorders: chronic myeloproliferative disorders (polycythemia vera(PV), essential thrombocythemia (ET) and chronic myeloid leukemia(CML)) are other major etiologies of PAH mainly secondary to their influences on cardiopulmonary system as increasing cardiac output, obstruction of pulmonary arteries, and inducing congestive heart

failure [29]; 14) systemic disorders: Several systemic disorders have been reported as the secondary causes of PAH such as pulmonary Langerhans cell histiocytosis, sarcoidosis, lymphangioleiomyomatosis, neurofibromatosis or vasculitis. The mechanisms of PAH in these clinical conditions are mainly related to the Capillary vasculature demolition due to the chronic hypoxemia, fibrotic process, large arteries compression by enlargement of lymph nodes, and infiltration of the pulmonary bed, especially veins, by granulomatous tissue, that are generally categorized as the systemic vasculopathy [30,31]; 15) Metabolic disorders: Some metabolic disturbances leading glucose-6-phosphatase deficiency (such as type Ia glycogen storage disorders) have been shown to be related to PAH. The pathophysiology of this effect may be due to atrial septal defects, porto-caval shunts, thrombosis or restrictive pulmonary dysfunction[32]; 16) Miscellaneous conditions: Some rare conditions have been also found that lead to PAH including tumor-induced obstruction, fibrosing mediastinitis or chronic kidney disease or hemodialysis. In some conditions, pulmonary artery obstruction due to the thrombosis or tumor compression effect, microvasculature occlusion by emboli due to the metastatic tumor, as well as potential diastolic and systolic left heart dysfunctions (due to hemodialysis) are the main causes of PAH [33,34].

2. Epidemiological aspects of PAH

The epidemiology of PAH has considerably altered during the recent decades. Earlier episodes of PAH have been appeared mostly in younger ages, in female, as well as in idiopathic or familial forms with a 1- to 3-year survival ranged 67% to 37% [35,36]. However, according to recent registries, the affected patients have been older with better survival rates [37,38]. The average of age at the time of diagnosis has been estimated to be 50 years with more delay in beginning of symptoms and diagnosis, less functional capacity, and more associated diseases in older group than in the younger [39]. Furthermore, older populations also suffer less severe PAH, but with poorer outcome [39].

3. Pathophysiology of PAH

The main fundament of PAH is arterial involvement due to vascular obstruction resulting in progressive increment in the vascular resistance. This change can elevate afterload of the right ventricular which leads to right ventricular failure. The key elements in pathophysiology of PAH include intima and media proliferation, vascular remodeling and thrombosis that all can increase pulmonary vascular resistance [40,41]. In total, both cellular and molecular pathways can induce PAH through their especial mechanisms. Regarding cellular mechanism, smooth muscular proliferation in the small peripheral pulmonary vascularity is the cornerstone. A combination of some processes including migration of fibroblasts of the adventitia to the media and intima layers, neovascularization of the adventitia, as well as thickening of the vascular walls provide a proper bed in occurring PAH [42,43]. All of these changes can be induced by various hypoxic, infectious, inflammatory, and genetic factors. It is assumed that inflammatory mechanisms such as auto-immune diseases or HIV infection has some impress in certain forms of PAH [44]. In this regard, production of some chemokines such as fractalkine and MCP-1 and inflammatory mediators such as Interleukin-1 (IL-1) and Interleukin-6 (IL-6), has been clearly demonstrated [45,46]. Besides, thrombosis and dysfunction of platelets can be important in the initiation of endothelial dysfunction and vascular obstruction in PAH. With respect to molecular factors, vasoconstriction is primitive occurrence in the process of PAH that associates with endothelial dysfunction leading decrease of vasodilators production and secretion and also increase of vasoconstrictors production [47]. Overall, the PAH pathophysiology is very complicated and multidimentional, that can be mediated by the triad of genetic, environmental, and idiopathic factors.

4. Clinical manifestation

No pathognomonic symptoms and signs have been pointed, but the prominent manifestations of PAH are related to associated 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 be prominent including venous jugular turgidity, hepato-jugular reflux, hepatomegaly, pain in the liver, lower extremity edema, ascites, and anasarca.

5. Diagnostic consideration

A series of diagnostic procedures such as electrocardiogram, rhenthogram,echocardiography, pulmonary function tests, arterial blood gases, high resolution computed tomography of lung (HRCT), ventilation/perfusion lung scan, exercise test, and pulmonary angiography are employed to diagnose PAH and its-related consequences. In electrocardiography assessment, the evidences of hypertrophy right ventricle and dilation of right atrium can be appeared. In chest radiography, abnormal changes such as central pulmonary arterial dilatation, right atrial and ventricular enlargement, can be manifested in about 90% of patients at diagnosis [48]. In pulmonary function test, a main pronounced finding is lower diffusing capacity of the lung for carbon monoxide (DLCO) especially in PVOD patients [49]. In blood gas analysis, mild to severe hypoxemia and hypo-capnia can be frequently revealed. In exercise testing, elevated pulmonary artery pressure due to blood flow increment may be impaired [50]. Doppler-echocardiography can accurately show an increased pulmonary artery systolic pressure, an enhanced velocity of pulmonary valve regurgitation and a short acceleration time of right ventricle ejection into the pulmonary artery, increased chambers dimensions in the right heart, hazard shape and dysfunction of the interventricular septum, increased wall thickness of right atrium, and pericardial effusion [51,52]. In high resolution computed tomography, the

probable underlying lung diseases such as pulmonary emphysema or interstitial lung disease can be detected. These conditions can be detected based on the appearance of pericardial effusions and pulmonary artery enlargement [53]. In pulmonary angiography assessment, the diagnosis of fibrosing mediastinitis, fully obstruction, and intimal irregularities can be feasible[54]. By using cardiac magnetic resonance imaging, all functional aspects of right ventricular and valvular components such as size, morphology and shape can be accurately assessed. Also, the assessment of blood flow related indices such as cardiac output, stroke volume, distensibility of pulmonary artery and right ventricular mass can be performed [55,56]. For detection of infections, serological blood tests can be applied. Finally, in right heart catheterization, the final diagnosis of PAH can be confirmed by demonstrating increased PAP higher than 25 mmHg along with a normal PCWP.

6. Management and treatment of PAH

Both non-therapeutic and therapeutic approaches should be considered for proper management of PAH in different degrees.

A) Conservative approach: 1) Because of lower functional capacity, extreme physical activity can be advised. Instead, physical rehabilitation is recommended to improve functional capacity of course in especial conditions and considering patients' physical and hemodynamic status. 2) Because hypoxia is a major component of PAH, oxygenation and removing hypoxia is warranted in the affected patients. 3) Some prescribed medications including vasoconstrictors and beta-blockers should be avoided.

B) Nonspecific medication approach: some drugs that reduce heart failure signs (fluid retention, hepatic congestion, ascites and anasarca) can be very helpful in improving disease manifestations such as diuretics [57]. Also, to reduce risk for thrombosis, anticoagulation treatment should be considered to maintain International Normalized Ratio (INR) in the range of 1.5 to 2.5 [58,59]. In terms of atrial tachyarrhythmia, digitalis should be administered.

Also, calcium channel blockers are recommended in patients with a positive vasodilatation challenge test after inhaled Nitric Oxide [60].

C) Specific medication approach: Many specific pharmaceutic agents were prescribed for the medical management of PAH including prostanoids, endothelin receptor antagonists and phosphodiesterase-5 inhibitors. 1) Prostacyclin and its agonists (intravenous Epoprostenol and subcutaneous Treprostinilis) are powerful systemic and pulmonary vasodilators and inhibitors of platelet aggregation that act as anti-proliferative, anti-thrombotic, anti-mitogenic and immunomodulatory agents that their use has led to increase in lung capacity, improvement in patients quality of life, pulmonary hemodynamics, clinical symptoms and so, long-term survival [61-65]. 2) Endothelin receptors antagonists (Bosentan, Ambrisentan) can inhibit Endothelin-1 as a potent vasoconstrictor and proliferator as main arms of PAH [66-72]. 3) Phosphodiesterase type-5 inhibitors (Sildenafil, Tadalafil) have a big legend in remodeling of vasculature and also, vasodilatation [73-75].

D) In cases with resistance to medical treatments, some non-medical and invasive approaches should be applied to achieve an appropriate hemodynamic stability. 1) Balloon atrial septostomy: Putting the right-left shunt by a heart surgery, diminishes right auricular pressure and increases systemic blood flow; also, reduces right ventricular wall tension, totally leads to the symptoms regression and functional capacity increment[76]. 2) Lung transplantation: although this surgical approach has remained as the first choice treatment in those with severe PAH, this procedure is very heavy with a partially low long-term survival. However, it can be considered in those patients with very severe PAH and in live with disappointed previous approaches [77,78]. In the study was done by Buys et al ,showed that exercise training beneficial for PAH patients,but this idea is new.It seems that rehabilitation can improve quality of life.[79].Ehlken believed that exercise has good effect on peak oxygen consumption and patients hemodynamic[80].Magdalena et al suggested that statins can not

improve pulmonary arterial pressure ,cardiac index and resistance pulmonary vasculature of significantly[81].

Conclusion

In total, PAH is now identified as a serious and occasionally life-threatening clinical condition with multifactorial etiologies. Due to discovering endothelial dysfunction, vasoconstriction, inflammation reactions, and platelet aggregation as the main pathophysiological arms of disease, the introduced specific treatment approaches are now based on inhibiting these conditions leading appropriate treatment response as well as proper early and late outcome. Because of high incidence of cardiovascular disorders as well as related progressive life-threatening conditions such as heart failure and PAH among Iranians, the identification of all etiological, pathophysiological, diagnostic, and novel therapeutic approaches of PAH is essential to best management of this clinical condition.

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