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Review Article

An Ephemeral Review on Pulmonary Arterial Hypertension

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Abstract: Pulmonary arterial hypertension [PAH] is a rare and potentially fatal disease whose management is usually restricted to a few specialized centers. The crucial vascular modifications in pulmonary arterial hypertension are endothelial-cell proliferation, vasoconstriction, thrombosis and smooth-muscle cell. As patients don't essentially board in the neighborhood to those centers, daily care and emergencies ought to be delegated to the primary and second lines. Reduced contractility of mycardium, decreased venous return and abnormal rate of exchange of gases leads to deprivation of oxygen to cell and death. Diagnosing and management of pulmonary arterial hypertension is critical. There is no cure for PAH. Modern developments regarding cell biology, molecular genetics and of idiopathic pulmonary arterial hypertension create new insights and therapeutic targets in the management. However, there are several treatment options that aim to reduce symptoms, improve the quality of life, and slow disease progression. This short review provides an outline of our therapeutic protocols supported out there information. Based on the analysis of the reasons for death in the PAH population, a review of the main emergencies is provided. Drugs include vasodilators, anticoagulants, antiplatelet agents, antiinflammatory therapies, and vascular-remodeling therapies. Most of the drugs have pleiotropic effects.

Keywords: Pulmonary Arterial Hypertension, Nitric Oxide, Hypoxemia, Thromboembolism, Vasopressors

1. Introduction

Pulmonary high blood pressure [PH] consists of a bunch of diseases with a resting mean pulmonic artery pressure [mPAP] 25 mmHg as measured with a right heart catheterization [1]. PH is considered a rare disease [2]. In PAH, the pre-capillary arterioles are affected by an angioproliferative vasculopathy that increases the pulmonary vascular resistance, thereby increasing the right ventricular afterload with the resulting right heart failure being the ultimate cause of mortality. Patients exhibit pathological changes which include enhanced pulmonary arteriole contractility, endothelial dysfunction, remodeling and proliferation of both endothelial and smooth muscle cells [3].

2. Pathogenesis of Pulmonary Arterial Hypertension

2.1. Nitric Oxide Pathway

Inhaled nitric oxide gas can alleviate vasoconstriction and may modulate cellular proliferative responses. [4] Nitric oxide is produced in endothelial cells by eNOS, which, in the presence of oxygen. NADPH and other cofactors catalyze the oxidation of L-arginine to L-citrulline. Nitric Oxide diffuses into the underlying pulmonary vascular smooth muscle cells [PVSMC] and binds to soluble guanylate cyclase [sGC], which in turn, converts guanosine triphosphate [GTP] to cyclic guanosine monophosphate [cGMP]. The subsequent activation of downstream cGMP-dependent protein kinases [PKG] results in pulmonary vasodilatation. Additionally, NO

inhibits PVSMC proliferation, platelet aggregation, and thrombosis, maintaining normal healthy pulmonary vasculature [5, 6].

2.2. Prostacyclin - Thromboxane A_2 Pathway

This pathway is activated once PGI_2 stimulates the IP receptor, resulting in increased cyclic adenosine monophosphate and leading to vasodilatory and antiproliferative effects [7]. An increase in the release of the vasoconstrictor thromboxane A_2 leads to the activation of platelets in both primary and secondary forms of pulmonary hypertension [8].

2.3. Endothelin-1 Pathway

ET-1 is a peptide that acts as a potent vasoconstrictor. [9] It has two types of receptors ET_A and ET_B. ET_A is present in smooth muscle cells and ET_B are localized in both endothelial and smooth muscle cells. Activation of ET_A and ET_B receptors on smooth muscle cells mediates the vasoconstrictive and mitogenic effects of ET-1. Stimulation of endothelial ET_B receptor promotes ET-1 clearance and activation of prostacyclin release [10].

3. Risk Factors

It is a rare disease, which can be sporadic or clustered in families. Genetic studies identified mutations in the bone morphogenetic protein-2 [BMPR-2] gene, a receptor member of the transforming growth factor-β family, i9n most familial cases of PAH. Other vascular processes included are a vasoconstrictor-vasodilator imbalance, thrombosis, misguided angiogenesis, and inflammation. Drugs, chemical products, diseases, obesity, altitude, age, gender may also be associated with the risk factor [12]. Complications include Right heart enlargement, Blood clots, Irregular heartbeats, Coughing up blood [13].

Table 1. *Revised WHO Groups for Pulmonary Hypertension [11].*

Group	Examples
Group 1: Pulmonary Arterial Hypertension	Familial, idiopathic PAH, HIV, drug induced, congenital heart Disease Must exclude other secondary causes of PH to diagnose PAH
Group 2: Pulmonary Hypertension caused by left-sided heart disease	Chronic LV failure, severe mitral valve disease, severe aortic valve disease
Group 3: Pulmonary Hypertension caused by lung disease or hypoxemia	COPD, OSA, obesity hypoventilation Syndrome
Group 4: Pulmonary Hypertension from chronic thromboembolic or embolic disease	Previous PE, especially recurrent PEs, large PEs, extremes of age, or PH at diagnosis of PE Up to 30% of patients may not have had a previous PE
Group 5: Miscellaneous	Mediastinal tumors or adenopathy, sarcoidosis, hemodialysis, thyroid disorders, vasculitis

COPD-chronic obstructive pulmonary disease, LV- left ventricular, PE- pulmonary embolus, PAH-Pulmonary Arterial Hypertension, OSA- obstructive sleep apnea, PH- Pulmonary Hypertension.

4. Clinical Presentation

Symptoms are unspecific, so there is often delay of many months or even years between the onset of symptoms and diagnosis. With the progression of a disease, the symptoms become worse and new symptoms occur. Dyspnea on bending down, Syncope even on slight exertion, Fatigue, Weakness, Decreased exercise tolerance, Dizziness, low blood pressure, fast heart rate, chest pressure, swollen legs [14].

5. Treatment and Management

Two decades past, patients with idiopathic PAH had a dismal median survival rate from diagnosis of, < 3 yrs, despite available supportive treatment. There is no cure for PAH; however, there are several treatment options that aim to reduce symptoms, improve the quality of life, and slow disease progression [15]. Eight drugs belonging to three pharmacological classes [endothelin receptor antagonists, phosphodiesterase type-5 inhibitors and prostanoids] are approved which are administered by subcutaneous, intravenous inhaled, andoral. None of these therapies is curative, but they contributed to allowing PAH to evolve from a uniformly fatal condition to chronic disease in some cases [16].

Table 2. *Management considerations [17].*

PH	ED Management
RV failure in PAH [group 1]	Continue/resume pulmonary vasodilator regimen, especially in cases of pump malfunction. Early consultation with PH specialist. Consider pulmonary or cardiology or emergency consultation if PH specialist is unavailable. Consider early transfer for mechanical support, including RVAD or ECMO. Consider volume overload, as indicated provide hemodynamic support with vasopressors, pulmonary vasodilators, and inotropes.
RV failure in other types of PH [groups 2–5]	Aggressively treat the underlying condition, such as diuresis for PH from left-sided heart failure Treat respiratory acidosis and hypoxemia, consider bronchodilators for COPD in PAH. Consider first-line agent norepinephrine. Early consultation with cardiologist, pulmonologist, or PH specialist. Consider mechanical support early with RVAD or ECMO For CTEPH patients, consider pulmonary endarterectomy in an emergency.

PAH-Pulmonary arterial hypertension; RVAD- right ventricular assist device; ECMO- extracorporeal membrane oxygenation; CTEPH- Chronic Thrombo Embolism Pulmonary Hypertension.

a) Pulmonary hypertension should be considered in any ED patient with unexplained dyspnea exertion, syncope, or signs of right ventricular dysfunction. Patients with a history of pneumonic emboli who present with dyspnea and no explanation on ED testing should be considered at risk for chronic thromboembolism pulmonary hypertension. [18]
b) Chest computed tomography [CT] may demonstrate evidence of pulmonary hypertension [19]. Pulmonary artery dilatation on CT correlates well with pulmonary artery pressure and CT scans can evaluate the right ventricular size and detect interventricular septal bowing. Enlargement of the right ventricle to greater than nine-tenths of the size of the LV by CT scan correlates with an increased risk of adverse events and death in patients with acute pulmonary emboli [20-24].
c) Systemic hypotension should be avoided. The cardiac output in most patients with advanced pneumonic high blood pressure cannot be increased due to "fixed" pneumonic tube resistance. Therefore, any reduction in systemic vascular resistance [SVR] will not be followed by a compensatory increase in cardiac output, thus magnifying the degree of hypotension. In addition, as described above, as the right ventricular pressures approach systemic arterial pressures, right coronary perfusion will decrease [25].
d) Norepinephrine offers several advantages in the emergency care of these patients. It is of proven benefit in several types of shock, especially septic shock. It helps maintain coronary perfusion pressure and slightly augment inotropy [26-28].
e) On balance, especially if a component of distributive shock is suspected, norepinephrine is an appropriate first-line vasopressor despite potential increases in pulmonary vascular resistance from a stimulation.
f) Phenylephrine should be avoided in patients with pulmonary hypertension because of increases of the pulmonary vascular resistance, whereas vasopressin may actually decrease pulmonary vascular resistance through a nitric oxide-based mechanism [29-32]. Although dobutamine increases cardiac output, it has 2 major disadvantages of increased tachycardia [33] and decreased SVR, limiting its use as a single agent because of the risk of systemic hypotension [31].

Table 3. *Pulmonary Vasodilators And Emergency Considerations [34-36].*

Class of Medication	Delivery	Mechanism of action	Emergency considerations
iNO	Inhalation	Relaxes vascular smooth muscle Inhibits platelet aggregation	Not used as long-term therapy in PAH May be employed in severe RV failure, massive pulmonary embolism Will decrease PVR; minimal effects on SVR Will improve V/Q mismatch
Prostacyclins. Epoprostenol [Flolan, Veletr] Treprostinil Iloprost	Intravenous, inhalation. Intravenous, inhaled, subcutaneous. Inhaled	Relaxes vascular smooth muscle	Intravenous formulations may be used as long-term therapy in PAH. Sudden withdrawal can lead to rebound PH May be used rather than iNO for severe RV failure Will decrease each SVR and PVR if given intravenously Will decrease solely PVR if inhaled can worsen V/Q twin if given intravenously; will improve V/Q mismatch if inhaled
Endothelin receptor antagonists-Bosentan Macitentan Ambrisentan	oral	Inhibits the vasoconstrictive properties of endothelin	Used as long-term therapy in PAH Minimal emergency use Patients ought to still receive this medication unless changes prescribed by PH specialist
PDE-5 inhibitors, sildenafil, tadalafil	Oral, intravenous	Block degradation of cyclic guanosine monophosphate to allow vascular smooth muscle relaxation	Used as long-term therapy in PAH Minimal emergency usePatients should continue to receive this medication unless changes prescribed by hydrogen ion concentration specialist

iNO, Inhaled nitric oxide; V/Q, ventilation-perfusion; PDE, phosphodiesterase.

Continuous positive airway pressure is a well-established treatment for patients with obstructive sleep apnea and pulmonary hypertension, and bilevel positive airway pressure has demonstrated excellent outcomes in chronic obstructive pulmonary disease and congestive heart failure [37].

If intubation and mechanical ventilation are unavoidable, hypotension and loss of right ventricular contractility must be prevented [38].

6. Conclusion

The emergency care of unstable PAH patient requires immediate and closed collaboration between critical care experts and PAH experts. Substantial advancements in the understanding and management of PAH have been made. The current understanding of PAH etiology includes nitric oxide, prostacyclin-thromboxane, and endothelin-1 pathways. There are five classes of drugs that target specifically phosphodiesterase-5 inhibitors, endothelin receptor antagonists, prostacyclin receptor agonists, prostacyclin analogs and soluble guanylate cyclase inhibitors. Recent long-term trials have shown evidence of progression-free survival with an initial, or early, the addition of these drugs, either in isolation or in combination with other drug classes.

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