The Burden of Pulmonary Hypertension in Resource-Limited Settings

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ABSTRACT

Pulmonary vascular disease (PVD) is a significant global health problem and accounts for a substantial portion of cardiovascular disease in the developing world. Although there have been considerable advances in therapeutics for pulmonary arterial hypertension, over 97% of the disease burden lies within the developing world where there is limited access to health care and pharmaceuticals. The causes of pulmonary arterial hypertension differ between industrialized and developing nations. Infectious diseases—including schistosomiasis human immunodeficiency virus, and rheumatic fever—are common causes of PVD, as are hemoglobinopathies, and untreated congenital heart disease. High altitude and exposure to household air pollutants also contribute to a significant portion of PVD cases. Although diagnosis of pulmonary arterial hypertension requires the use of imaging and invasive hemodynamics, access to equipment may be limited. PVD therapies may be prohibitively expensive and limited to a select few. Prevention is therefore important in limiting the global PVD burden.

Cardiovascular disease accounts for roughly 30% of deaths worldwide and is the leading cause of death globally [1]. Pulmonary vascular disease (PVD) accounts for a substantial burden of cardiovascular disease in resource-limited settings. PVD broadly refers to any disorder that may affect the pulmonary blood circulation. The *sine qua non* of PVD is elevations in pulmonary vascular pressure and, therefore, PVD and pulmonary hypertension (PH) can be used interchangeably. PH is defined by a mean pulmonary artery (PA) pressure >25 mm Hg by invasive catheterization [2]. PVD can result from pulmonary arterial hypertension (PAH), pulmonary venous hypertension with or without associated pulmonary edema, hypoxic pulmonary vascular constriction secondary to chronic respiratory disease and high altitudes (HA), acute and chronic thromboembolic disease, and arteriovenous malformations that can occur in association with inherited systemic diseases or congenital heart disease (CHD).

Approximately 98% of the global PVD burden occurs in the resource-limited world with an estimated prevalence of 20 to 25 million people with up to 64 million at risk but who are undiagnosed [3,4]. Given this strikingly high statistic, and considering the associated morbidity and mortality, the recognition, treatment, and prevention of PVD in resource-limited areas is a medical priority. This review will focus on the diagnosis and major causes of PVD in resource-limited settings with a key focus on etiologies, diagnosis, and treatment of PAH.

DEFINITION OF PULMONARY HYPERTENSION

The 2013 Nice Classification of PH includes 5 subgroups: PAH (group 1); PH secondary to left heart disease (group 2); PH secondary to pulmonary disease (group 3); chronic thromboembolic PH (group 4); and PH from multifactorial etiologies (group 5) [5] (Table 1). PAH represents a subset of PVD that is characterized by pre-capillary PVD. The hemodynamic definition of PAH is a mean PA pressure >25 mm Hg, a pulmonary capillary wedge pressure <15 mm Hg, and a pulmonary vascular resistance >3 Woods units [2]. PAH is a relatively rare disease affecting 1 in 1 million people in resource-rich areas of the world and, therefore, is an "orphan" disease [6]. However, in resource-limited areas, the prevalence of PAH may be 1 in 10,000 people [7]. As opposed to other forms of PVD, PAH carries an estimated survival rate of 2.8 years if left untreated [8].

The disparity in the epidemiology of PVD between industrialized and resource-limited nations is significant. In resource-rich settings around the world, PH is due to heart failure in 55% of cases, chronic obstructive pulmonary disease (COPD) in 42%, and PAH in only 3%. In resource-limited areas, heart failure accounts for 8% and COPD (and associated lung disorders) for 28% of PVD. Schistosomiasis (18%), hematological disorders (7%), HA (24%), rheumatic heart disease ([RHD] 11%), CHD (2%), and human immunodeficiency virus (HIV) (1%) compose the other etiologies of PVD [3] (Fig. 1).

DIAGNOSIS

Diagnosis of PH requires the following progressive steps: a thorough history and physical examination; echocardiogram; right catheterization; and vasoreactivity testing (Fig. 2).

It is critical for physicians in resource-limited countries to be aware of the main signs, symptoms, and causes of

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TABLE 1. Classification of pulmonary hypertension as determined at the Fifth World Symposium of Pulmonary Hypertension, Nice 2013

1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 *ALK-1, ENG, SMAD9, CAV1, KCNK3*
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″ Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

BMPR2, bone morphogenetic protein receptor-2; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

PH. Any patient that has unexplained dyspnea, syncope, angina, or other signs of right ventricular dysfunction should be suspected to have PH. According to the REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) registry, 21% of patients had symptoms for >2 years before diagnosis [9,10].

The most helpful screening method for PH is an echocardiogram [11]. An estimate of PA systolic pressure can be derived using the tricuspid regurgitant jet velocity, and the right ventricular size, thickness, and function can be evaluated. With significant PH and right ventricular pressure overload, bulging of the septum into the left ventricle and right ventricular hypertrophy occur. Progressive right ventricular failure leads to right atrial dilation, tricuspid regurgitation, and hepatic congestion manifested by inferior vena cava dilation and systolic reversal of hepatic vein flow. Diminished movement at the base of the right ventricle, reflected by a tricuspid annular plane systolic excursion <1.8 cm, has been associated with increased mortality [11].

A right heart catheterization is the gold standard and the only test that can definitively confirm PAH. A mean pulmonary artery pressure (PAPm) of ≥25 mm Hg is considered to be PH, although high-risk patients with PAPm values between 21 and 24 mm Hg should be closely monitored. In patients with idiopathic PAH, pulmonary vasoreactivity testing using nitric oxide, epoprostenol, or adenosine can be performed to identify patients who may respond to calcium channel blockers. Vasoreactivity is defined by a 10−mm Hg decrease in PAPm to <40 mm Hg [12]. A right heart catheterization, with or without vasoreactivity testing, however, may be difficult to conduct in