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

resource-limited countries and proper interpretation of hemodynamics might require specialized training. In addition, availability of catheterization laboratories may be limited to tertiary referral centers and, therefore, echocardiography may be the only method of diagnosis and monitoring disease progression.

CAUSES OF PULMONARY VASCULAR DISEASE IN RESOURCE-LIMITED SETTINGS

PVD can be caused by a variety of factors. PVD is often exaggerated in the resource-limited world due to causes such as endemic infectious diseases and environmental factors. Schistosomiasis, HIV/acquired immunodeficiency syndrome (AIDS), and tuberculosis are the predominant infectious diseases associated with PH [3]. A variety of hematologic disorders are prevalent in the resource-limited world [13]. Environmental factors such as HA and household air pollution exposure increase the likelihood of developing PH [14]. Cardiac diseases, including CHD and rheumatic heart disease, are much more common in the resource-limited world because limited access to health care leads to delayed diagnosis and treatment [15].

Infectious disease

Schistosomiasis. Schistosomiasis can cause PAH and is the third leading endemic parasitic disease in the world following malaria and amebiasis [16]. It has a higher prevalence than HIV/AIDS, given that up to 440 million people are infected with schistosomiasis and 600 million more are at risk for infection [17]. Schistosomiasis is endemic to eastern South America (Brazil), the Caribbean Islands, east Asia (China and the Middle East), and Sub-Saharan Africa. More than 85% of cases are from Sub-Saharan Africa [18]. An estimated 10 million individuals have hepatosplenic schistosomiasis and are at highest risk for the development of PAH. Given that 4.6% of such patients have PAH, schistosomiasis-associated PAH (Sch-PAH) affects over 450,000 individuals.

Schistosomiasis is caused by flatworms of many different species that are approximately 1-mm to 2-mm long. The 3 primary species of schistosomes that infect human beings are *Schistosoma haematobium*, *Schistosoma mansoni*, and *Schistosoma japonicum*.

Schistosoma infection can cause both acute and chronic pulmonary lesions in addition to liver, bladder, ureter, and kidney disease. Acute pulmonary schistosomiasis, also called Katayama fever, can present with nonspecific symptoms such as fever, cough, dyspnea, myalgia, headache, and abdominal tenderness 2 to 12 weeks after water contact. Migrating parasites and egg deposition lead to an inflammatory reaction marked by peripheral eosinophilia, and treatment with anthelmintic drugs including praziquantel and oxamniquine can lead to resolution of the disease without long-term sequelae [16]. PAH is more common in residents of endemic areas who have recurrent exposure, and there is a higher incidence of PVD among patients who had concomitant hepatic fibrosis [19].

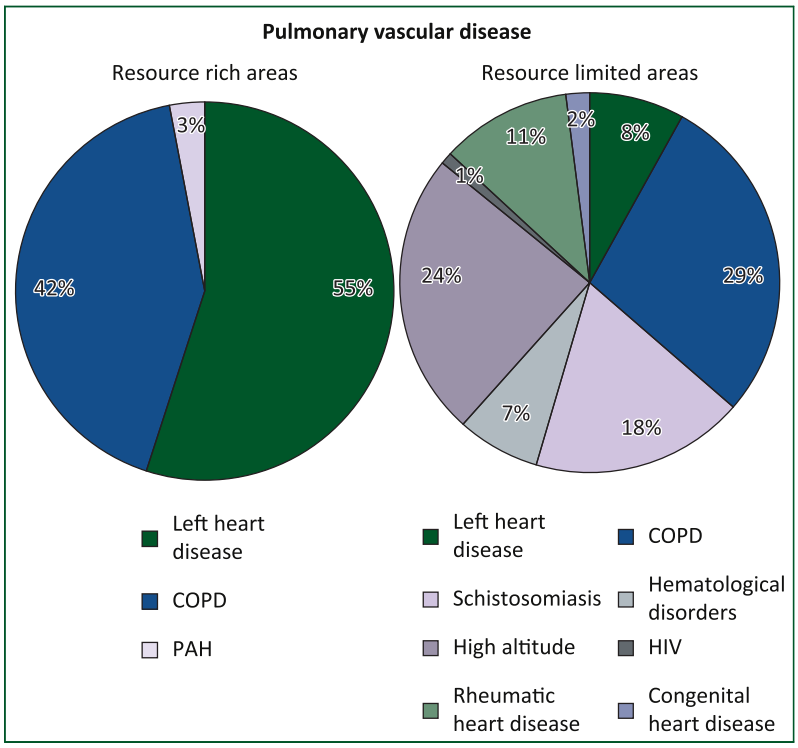

FIGURE 1. The burden of pulmonary vascular disease in resource-rich versus resource-limited settings. COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension.

Acute pulmonary schistosomiasis is marked by a T-helper 1 response. Chronic disease is predominated by a T-helper 2 response and results from a hypersensitive reaction to eggs leading to the development of granulomatous disease, which is mediated via a complex cytokine interaction that includes interleukin-4, interleukin-6, interleukin-13, interferon-gamma, and tumor necrosis factor [20–24]. This inflammatory milieu leads to endothelial dysfunction, smooth muscle cell proliferation, thrombosis, and vasoconstriction that result in PVD (Fig. 3) [25].

Several studies from Brazil indicate that approximately 7% to 20% of people infected with schistosomiasis develop PAH [26,27]. However, this only reflects the PAH development rate of a population that is highly controlled; other less-regulated regions may have much higher rates. In endemic regions, schistosomiasis is the cause of approximately 30% of PAH cases [26]. In a study from Sao Paulo by Lapa et al. [28], all patients with hepatosplenic schistosomiasis underwent echocardiographic evaluation for PH. The prevalence of PH was 18.5% and invasive hemodynamics confirmed PH in 7.7% of cases with 4.6% meeting criteria for PAH [28]. A subsequent study compared patients with Sch-PAH to idiopathic PAH and found that Sch-PAH had less severe PH with lower pulmonary vascular resistance, higher cardiac outputs and

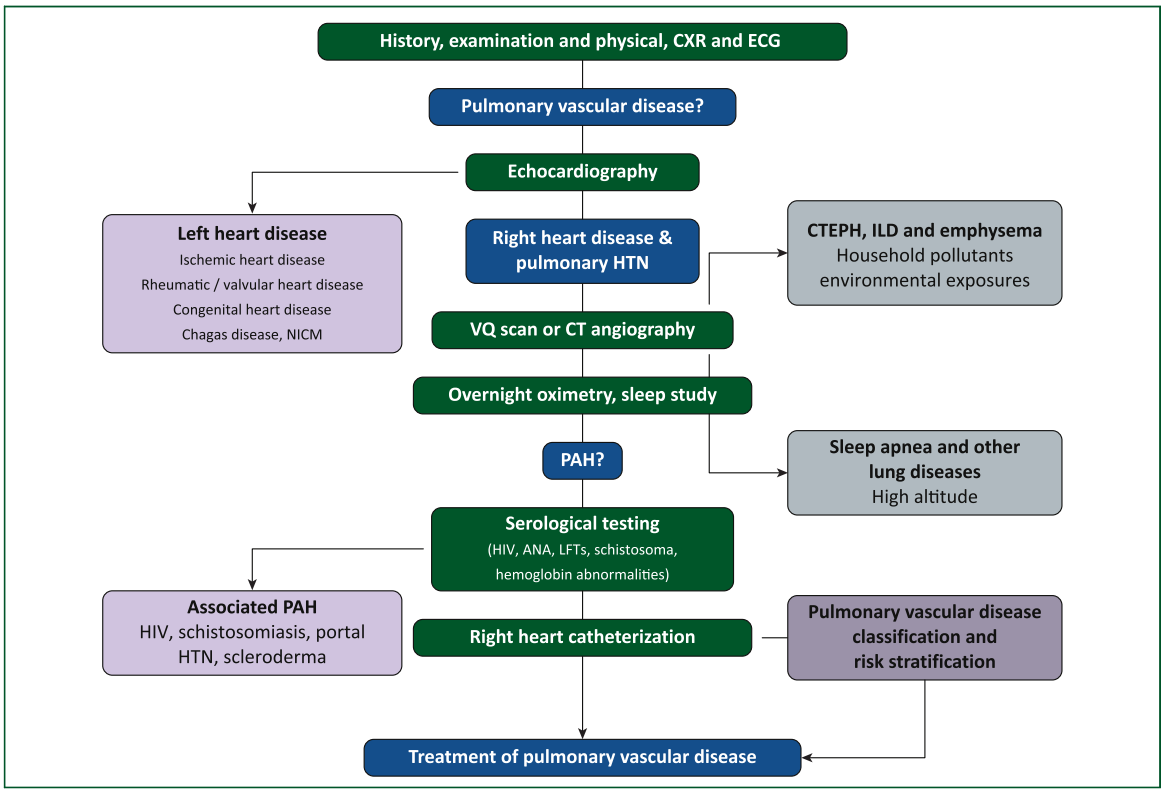

FIGURE 2. Diagnostic algorithm for pulmonary vascular disease. History, physical examination, chest X-ray (CXR), and electrocardiogram (ECG) will lead to the diagnosis of pulmonary vascular disease (PVD). This should be confirmed via an echocardiogram. If left heart disease is present, appropriate therapies for congestive heart failure, congenital heart disease, and valvular heart disease should be considered. If there is right heart disease and pulmonary hypertension (HTN), additional evaluation by ventilation-perfusion (VQ) scan or computed tomography (CT) angiography may yield a diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH), interstitial lung disease (ILD), or COPD/emphysema. In resource-limited areas, household air pollutants may lead to COPD. Overnight oximetry and sleep studies may diagnose sleep apnea. High-altitude PVD should be considered in patients at risk. Serological testing for associated causes of PAH and hemolytic anemias should be performed followed by right heart catheterization in all patients suspected of having PAH. ANA, antinuclear antibody; LFT, liver function test; other abbreviations as in Figure 1.

lower PAPm. The Sch-PAH patients had similar survival rates to idiopathic PAH patients at 1, 2, and 3 years (95.1%, 95.1%, and 85.9%, respectively) [29].

HIV. PVD from HIV can result from HIV-associated cardiomyopathy or PAH. The prevalence of left ventricular systolic dysfunction in HIV-1–infected individuals is >8% and diastolic dysfunction >43% [30]. The pathophysiology of HIV-associated cardiomyopathy is likely multifactorial and readers are referred to more comprehensive reviews on the subject [31].

The incidence of PAH is approximately 1,000× higher in HIV-infected patients than in the general population. According to the 2013 AIDS epidemic report, approximately 39 million people are living with HIV and the majority of these cases are in Africa [32]. The prevalence of PAH in patients with HIV is estimated to be 0.5% [33]. Using these estimates, approximately 1.7 million individuals may have HIV-associated PAH.

The exact pathogenesis of PAH in HIV patients is unclear. On pathological examination, complex plexiform lesions characterized by luminal obstruction, intimal disruption, medial hypertrophy, and thrombosis have been observed [34]. HIV proteins implicated in the disease include glycoprotein 120, HIV-1 transactivator of transcription (Tat), and negative factor antigen (Nef) [35–38]. Exposure of glycoprotein 120 to primary human lung endothelial cells can induce apoptosis and significantly increase secretion of endothelin-1 (ET1), a potent vasoconstrictor [35]. HIV-1 Tat has also been implicated in PAH through its interactions with bone morphogenetic protein receptor-2 (BMPR2) [37,39]. BMPR2 regulates ET growth in response to injury, and mutations in the BMPR2 gene are associated with hereditary primary PH [40,41]. In vitro models have demonstrated dose-dependent repression of BMPR2 promoter activity in the presence of Tat [37]. HIV Nef has been found in vascular cells of HIV patients with PAH, and primates infected with chimeric

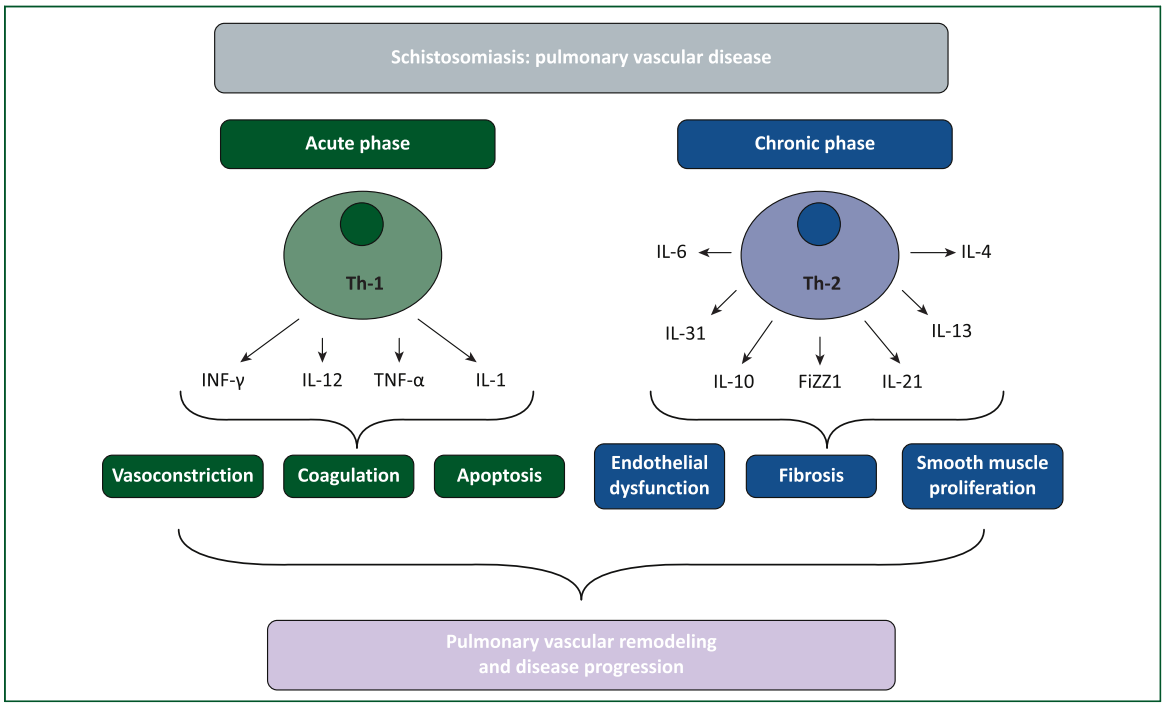

FIGURE 3. Diagrammatic representation of the possible mechanisms of pulmonary vasculopathy secondary to schistosomiasis. FiZZ, found in inflammatory zone; IL, interleukin; INF, interferon; Th, T-helper; TNF, tumor necrosis factor. Adapted with permission from Butrous et al. [3].

simian immunodeficiency virus constructs containing the HIV Nef gene have developed plexiform arteriopathy and PAH [36,42].

Patients with HIV-associated PAH typically present with symptoms that are typical to other PAH etiologies. In a retrospective review of 131 cases of HIV-related PAH, the presenting symptoms included dyspnea (85%), pedal edema (30%), cough (19%), fatigue (13%), syncope (12%), and chest pain (7%) [43]. Over a median follow-up period of 8 months, 66 patients in this series died. In another series of 82 patients with HIV-PAH, survival rates in the overall population at 1, 2, and 3 years were 73%, 60%, and 47%, respectively [44]. Although earlier studies of HIV-associated PAH suggested worse survival than that of idiopathic PAH, recent studies have demonstrated improved survival when compared with that of other PAH subgroups [10,45]. Treatment with antiretroviral therapy has not been consistently associated with improved outcomes for HIV-associated PAH [46].

Human herpes virus 8. Human herpes virus 8 (HHV-8) is endemic to Mediterranean countries, South America, and Sub-Saharan Africa. HHV-8 seroprevalence varies between different geographic regions and subpopulations. In Uganda, HHV-8 seroprevalence rates of 50% have been reported for the general population, whereas in the United States, the rates are 6% or lower [47]. HHV-8 is the causative agent of Kaposi's sarcoma, and its role in the development of PAH remains controversial. In a study by Cool et al. [48], HHV-8 was expressed in the plexiform lesions of 62% of patients with PAH. However, other studies have not shown similar results [49,50]. Thus, the role of HHV-8 in PVD is unclear and requires further evaluation. Also, the effect of PH medications on HHV-8 is unclear.

Hematologic disorders

Hematologic disorders, including sickle cell disease (SCD), thalassemia, and hereditary spherocytosis, are prominent causes of PVD in resource-limited countries. Additionally, there is a higher prevalence of these diseases in malaria-endemic regions. An estimated 7% of the world population has hematologic disorders and ≤25% of this population have tricuspid regurgitation jet velocities >2.5 m/s, which reflects the upper limit of normal and corresponds to an estimated systolic PA pressure >35 mm Hg (if the right atrial pressure is assumed to be 10 mm Hg) [51]. Of the 30 million people who have SCD, 6% to 10% have PH [52].

PH secondary to hematologic disorders is multifactorial and was therefore recategorized from group 1 to group 5 PH under the 2013 Nice Classification [5]. SCD results from a single-nucleotide substitution in the beta-globin gene, rendering hemoglobin less soluble when deoxygenated and erythrocytes prone to polymerization and aggregation in the microcirculation. This leads to vascular

obstruction, ischemia, inflammation and thrombosis in addition to hemolytic anemia. Thalassemia encompasses diseases characterized by reduced or absent alpha- or beta-globin chains. These disorders can lead to a variable severity of hemolytic anemia depending on the inheritance pattern.

Among the hemoglobinopathies, PH associated with SCD has been studied the most. PH is predominantly due to diastolic dysfunction, although a minority of patients will have pre-capillary disease. Among sickle cell patients, 6% to 10% will have PH by invasive hemodynamics with less than one-half of these patients meeting criteria for PAH [53]. Patients with diastolic dysfunction are at significantly increased risk for mortality, and this risk is even greater with concomitant PH [54]. In a study of 531 SCD patients, 10.4% had PH by invasive hemodynamics and the estimated median survival time was 6.8 years after diagnosis of PH [55]. Data on the impact of PH in hemolytic disorders in resource-limited settings is sparse. In a study from Nigeria, among 208 patients screened by echocardiography, 25% had evidence of PVD and these patients had decreased functional status [56].

Hemolysis is a principle risk factor for the development of PH. Hemolysis can release cell-free hemoglobin that oxidizes nitric oxide to nitrate. Inactivation of nitric oxide, an intrinsic vasodilator, results in pulmonary vasoconstriction and propagation of PVD [13,57]. Hemolysis also leads to the release of arginase that depletes L-arginine, which is the precursor to nitric oxide. Endothelin-1 levels are also increased in hemolytic anemias [58]. In addition, chronic thromboembolism, hyperviscosity, and left heart disease are contributing factors to the development of PH [59].

High altitude and pulmonary hypertension

Approximately 140 million people live >2,500 m above sea level, with the vast majority located in resource-limited countries in the Andes, Himalayas, and the Tian Shan mountain ranges [14]. It is estimated that the population at risk is 35 million in the Andes and 80 million in Asia [60]. Hypoxia causes reactive PH with an increase in pulmonary pressures that directly correlates with the altitude (Fig. 4). In susceptible individuals, the PH can lead to progressive right ventricular dysfunction. However, there is variation in susceptibility to PH between different ethnic groups, suggesting that genetic factors may play a role in adaptation to HA. Acute PH is not usually seen in HA dwellers and the reader is referred elsewhere for an authoritative review of the definition of chronic and subacute high-altitude diseases [61].

Healthy HA natives have PH, increased pulmonary arterial smooth muscle, right ventricular hypertrophy, and erythrocytosis as adaptive mechanisms to chronic hypoxemia [62]. Physiologic decompensation occurs in 5% to 10% of residents who lose their acclimatization and develop chronic mountain sickness (CMS) [61]. The causes for CMS are multifactorial with variable contributions of hypoventilation, erythrocytosis, and remodeling of the pulmonary vascular bed. Increased blood viscosity can lead to vascular occlusion and ventilation-perfusion mismatching manifested clinically by headaches, tinnitus, dyspnea, cyanosis, and altered mental status [63]. Physiologically, hypobaric hypoxia is the consistent stimulus for HA disorders. Clinical risk factors include a previous history of CMS, lack of respiratory sensitivity to hypoxia and hypoventilation, sleep apnea and all hypopneas, obesity, and postmenopausal state.

There are clear genetic determinants for remodeling of pulmonary vasculature [64]. This in turn influences the prevalence of CMS in HA dwellers. CMS prevalence, for example, is 1.2% in native Tibetans versus 5.6% in Chinese Han population [65]. In South America, the prevalence of CMS is 6% to 8% in the male residents of La Paz, Bolivia, and 15.6% (male and female) in the Andes [14].

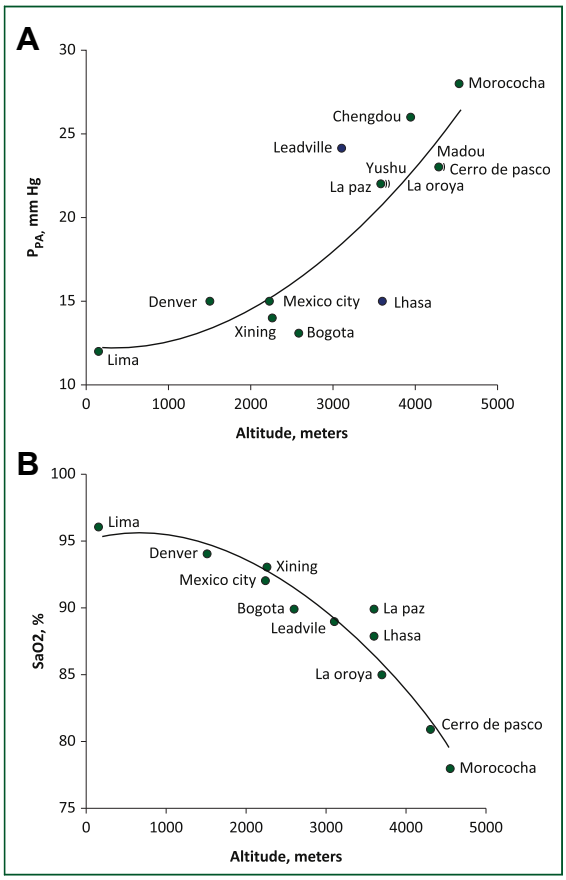

FIGURE 4. Mean pulmonary artery pressure in healthy natives in cities throughout the world, from Lima progressing to extremely high altitude in Morococha, Peru
(A) The corresponding arterial oxygen saturation, showing the relationship of hypoxemia to pulmonary arterial pressures. (B) In decompensated highlanders and sojourners, pulmonary artery pressure may rise to pathologic levels. P_{PA}, mean pulmonary artery pressure; SaO_2, arterial oxygen saturation. Reproduced with permission from the American College of Chest Physicians [14].

Phenotypic differences abound as well. Ladakhi men, who are native to northern India, lack smooth muscle in the small PA [66], and this is correlated with better function in the hypoxic environment of HA [67]. Hemoglobin concentration has been shown to be lower in the Himalayan than in the Andean natives. CMS is rare in the Himalayas, whereas it is common in the Andes. Tibetans seem to have reached optimal adaptation, whereas Andean natives seem to still be in the process of phenotypic adaptation [68–70].

Clearly a better understanding of genotype-phenotype interactions is needed and is hampered by the lack of appropriate tools in resource-limited countries.

Environmentally induced pulmonary hypertension

COPD is the fourth leading cause of death in the world and among the most common causes of PVD [71]. The development of PH in COPD is associated with poor survival with an estimated 50% survival at 4 years [72]. Although tobacco smoking is an established risk factor for COPD, an estimated 25% to 45% of patients have never smoked. A World Health Organization report estimated that over 3 billion people in resource-limited settings globally use biomass fuel to cook their food every day [15]. In areas of high elevation, biomass fuels are also used for indoor heating in the winter months [73]. This household air pollution (HAP) may be the most significant risk factor for COPD globally [74].

More than 2 million annual deaths in the resource-limited world are attributed to childhood acute respiratory infections, COPD, and lung cancers due to HAP [75]. Whereas COPD, interstitial lung disease (ILD), and infectious diseases such as HIV, schistosomiasis, and tuberculosis clearly play a role in PH, less is clear about the interplay among HAP, the pulmonary vasculature, and right heart function. For one, there is significant overlap between the etiologies. HAP causes COPD and possibly PH directly as well. This can be deduced by the fact that the burden of PH is significantly greater than the burden of COPD in these countries. Similarly, the correlation between HAP and ILD has been demonstrated in numerous studies from the resource-limited world [76,77]. Thus it becomes difficult to tease out the primary cause of PH: Is it secondary to COPD or ILD? Or is it possible that HAP directly leads to PH by other less understood mechanisms? Studies are few and not methodologically rigorous. For instance, Pandey noted an association between exposure to HAP and right-sided heart failure over a series of case studies focusing on rural communities in the Hill Region of Nepal [78,79]. Another observational study showed that most cases of right heart failure were in women without other associated pulmonary or cardiac morbidity and were classified as idiopathic [80].

Environmental agents may be implicated in PH as well. Increased oxidative stress with production of reactive oxygen species, increased secretion of proinflammatory cytokines including tumor necrosis factor-alpha, and alterations in ET receptor expression are all mechanisms that conceptually play a role in the direct causation of PH [81]. Inhalation of particulate matter and ozone has been shown to increase ET1 and expression [82]. Such direct causation is difficult to prove due to the lack of basic investigative and therapeutic tools in these areas.

Cardiac etiologies of pulmonary vascular disease

Pulmonary vascular disease can result from left heart disease. Heart failure affects >23 million people worldwide and the etiologies of heart failure vary between resource-rich and resource-limited areas [83]. Whereas ischemic heart disease accounts for 30% to 40% of cases of heart failure in Europe and North America, it accounts for <10% of heart failure cases in Sub-Saharan Africa [84]. Cardiomyopathy from infectious etiologies can account for up to 25% of cases of heart failure. Chagas disease, which is caused by *Trypanosoma cruzi*, affects an estimated 7.7 million individuals in Latin America and is a major cause of left heart failure [85]. Untreated cardiac disease in children is a significant cause of PVD. It is estimated that 8% of children with CHD develop PVD and 70% of children with RHD will develop PVD later in life [86].

Congenital heart disease. The incidence of CHD is 8 to 12 per 1,000 live births, and of the 600,000 children born annually with CHD, 50% will die secondary to infection or heart failure in infancy [87]. Over 80% of CHD occurs in resource-limited settings and only 2% to 15% will receive appropriate intervention [86]. Uncorrected atrial septal defects (ASD), ventricular septal defects (VSD), and patent ductus arteriosus (PDA) are the most common congenital defects that predispose to PVD. Up to 3.2 million children with an isolated ASD, VSD, or PDA are at risk for PVD worldwide, most of which will have limited access to health care [86]. PVD can develop in 10% of ASD, 20% of VSD, and 20% of PDA, and the risk of PVD is typically greater with high-flow, high-pressure lesions. Eisenmenger syndrome is CHD-associated PVD in its most severe form and characterized by PAH with systemic pressures and a reversed (right to left) or bidirectional shunt [88]. In underserved areas, Eisenmenger syndrome occurs from common and easily corrected left to right lesions. In resource-limited areas of Africa, up to 5% to 10% of patients with CHD will have Eisenmenger syndrome at the time of referral to a cardiologist [89].

Environmental, nutritional, and socioeconomic factors in resource-limited settings in the world also contribute to the high mortality rate of children with CHD. Moreover, HA and genetic variations in populations can have significant effects on the incidence of CHD. There is a much greater prevalence of VSD in China and Japan than in the Western world. Those living 3,500 to 5,000 m above sea level in Peru have an 18× to 30× greater chance of having a PDA than do Peruvians living on the coast. The ductus is typically larger and with increased flow [90].

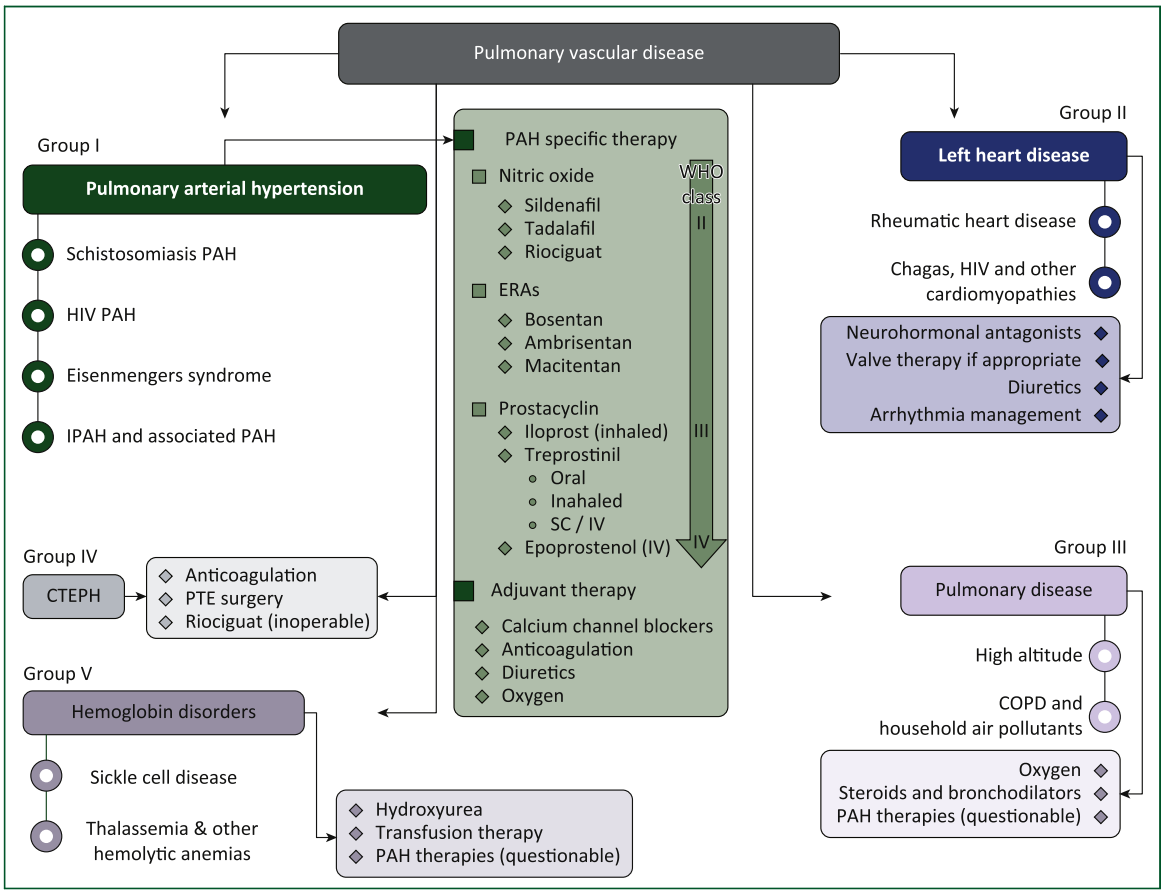

FIGURE 5. Treatment of pulmonary vascular disease. This diagram uses the Fifth World Symposium classifications for pulmonary hypertension. Pulmonary arterial hypertension (group 1) can be treated with PAH-specific therapies. The choice of medication can be determined by the World Health Organization (WHO) functional class. Class I patients are asymptomatic and may be observed, whereas class II patients have symptoms with exertion and can be managed with oral therapy, which include nitric oxide-based therapies and endothelin receptor antagonists (ERAs). Class III patients are symptomatic with minimal exertion and should be considered for oral, inhaled, subcutaneous (SC), or intravenous (IV) prostacyclin therapy in addition to other oral therapies. Class IV patients present with dyspnea at rest or with syncope and should be strongly considered for IV epoprostenol. Patients with left heart disease (group 2) should be treated for left ventricular dysfunction, valvular disease, and for arrhythmias. Pulmonary disease (group 3) in resource-limited areas is predominated by high–altitude-related disease and COPD secondary to household air pollutants. PAH-specific medications are of questionable utility. CTEPH should be considered for pulmonary thromboendarterectomy (PTE) surgery in addition to anticoagulation therapy. In operable patients or those with persistent pulmonary hypertension (PH) after PTE, riociguat may be considered. Hemoglobin disorders and hemolytic anemia are part of group 5 PH. PAH therapies are of questionable efficacy. IPAH, idiopathic pulmonary arterial hypertension; other abbreviations as in Figures 1 and 2.

Rheumatic heart disease. RHD can result in valvular damage due to an abnormal immune response to *Streptococcus pyogenes* infection. Between 15.6 to 19.6 million people worldwide are affected, and RHD accounts for 200,000 to 250,000 premature deaths per year [91]. Sub-Saharan Africans, East Asians, and indigenous Australians have the highest prevalence of RHD. Mitral stenosis is the most common long-term valvular lesion although aortic and tricuspid valve lesions are common in extensive disease. In resource-limited settings, treatment of RHD-associated mitral valve disease via surgery or mitral balloon valvuloplasty may not be possible due to expenses and resources. Even with intervention, PVD may persist in patients with advanced RHD [92]. Screening programs to identify children at risk for RHD and echocardiographic surveillance are thus important to prevent the development of advanced disease.

TREATMENTS FOR PULMONARY ARTERIAL HYPERTENSION

The treatment for PVD in resource-limited countries is limited by access to therapies and cost of pharmacologic

TABLE 2. Pulmonary arterial hypertension pharmacologic therapy

Drug	Study	Background	Primary Endpoint	Secondary Endpoints	Duration (weeks)	Patients
Phosphodiesterase-5 Inhibitors						
Sildenafil	SUPER-1 [95]	None	6MWD 45 m (20 mg), 46 m (40 mg), and 50 m (80 mg)	TTCW	12	227
Tadalafil	PHIRST [96]	None	6MWD 33 m (only 40 mg) 44 m (bosentan naïve)	TTCW	16	405
Soluble Guanylate Cyclase Stimulators						
Riociguat	PATENT [97] (PAH)	None, bosentan, prostanoids	6MWD 36 m difference	TTCW	12	443
	CHEST [98] (CTEPH)	None, bosentan, prostanoids	6MWD 46 m difference	TTCW	12	261
Endothelin Receptor Antagonists						
Bosentan	BREATHE-1 [99]	None	6MWD 44 m ($p < 0.001$)	TTCW*	16	213
Ambrisentan	ARIES-1 [100]	None	6MWD 31 m (5 mg) and 51 m (10 mg)	TTCW (NS) gamma	12	202
	ARIES-2 [100]	None	6MWD 32 m (2.5 mg) and 59 m (5 mg)	TTCW	12	192
Macitentan	SERAPHIN [101]	None/PDE5i/iloprost	TTCW 46.4% placebo, 38.0% 3 mg, 31.4% 10 mg	Safety	100	742
Epoprostenol	Intravenous Barst et al. [102]	None	6MWD 47 m increase with treatment versus −66 m decrease in placebo	Survival 8 deaths in placebo versus none in treatment	12	81
Treprostinil	Subcutaneous Simonneau et al. [103]	None	6MWD 16 m difference between treatment versus placebo	—	12	470
	Inhaled TRIUMPH/ McLaughlin et al. [105]	Bosentan or sildenafil	6MWD 20 m difference between treatment versus placebo	—	12	235
	Oral FREEDOM-M/ Jing et al. [106]	None	6MWD 23 m improvement	Borg dyspnea, clinical worsening, symptoms Not significant	12	349
	Oral FREEDOM-C/ Tapson et al. [107]	Bosentan and/or sildenafil	6MWD (NS)	—	16	310

(continued)

TABLE 2. Continued

Drug	Study	Background	Primary Endpoint	Secondary Endpoints	Duration (weeks)	Patients
Iloprost	Inhaled AIR/ Olschewski et al. [108]	None	6MWD and FC 36 m in treatment arm 59 m in IPAH group	—	12	203 PAH and CTEPH
Prostacyclin IP-Receptor Agonists						
Selexipag	Oral GRIPHON*	Bosentan and/ or sildenafil	Morbidity/mortality	6MWD (NS)	4 yrs	1,156

Dashes indicate that data are not available. 6MWD, 6-minute walk distance; CTEPH, chronic thromboembolic pulmonary hypertension; FC, functional class; IP, prostaglandin I2 receptor; IPAH, idiopathic pulmonary arterial hypertension; NS, not significant; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase-5 inhibitors; TTCW, time to clinical worsening; other abbreviations as in Table 1.
*Ongoing trial; results not published.

therapies. The goals of therapy are to achieve clinical improvement, hemodynamic improvement, and mortality benefits. PAH requires treatment specific for the disease (Fig. 5).

Anticoagulation with warfarin may be considered in patients with idiopathic PAH [93], although most of the data supporting the use of anticoagulation was prior to the use of PAH-specific therapy. The use of anticoagulation therapy should be limited to those patients with chronic thromboembolic PH (group 4) and may be considered for advanced idiopathic PAH with New York Heart Association class III and IV symptoms provided international normalized ratio monitoring is available. Calcium channel blockers may be used in idiopathic PAH patients who demonstrate positive vasoreactivity testing [12].

Specific therapy for PAH focuses on pulmonary vasodilation, limiting thrombosis, and promoting pulmonary vascular remodeling. A full discussion of the therapies for PAH is beyond the scope of this article and readers are referred to more comprehensive reviews [94]. Current therapies focus on 3 primary pathways involving nitric oxide, ET, and prostacyclin (Table 2).

Nitric oxide binds to soluble guanylate cyclase and through the production of cyclic guanosine monophosphate acts as a potent vasodilator and inhibits cell proliferation. Inhibition of phosphodiesterase-5 (PDE5), which degrades cyclic guanosine monophosphate, can promote pulmonary vasodilation and remodeling. Sildenafil and tadalafil are 2 PDE5 inhibitors that have been demonstrated to improve short-term and long-term morbidity and mortality in PAH [95,96]. Riociguat acts as a stimulator of soluble guanylate cyclase and is independent of nitric oxide expression to promote pulmonary vasodilation. It has been demonstrated to improve exercise tolerance and decrease clinical worsening in both PAH and chronic thromboembolic PH [97,98].

ET1 levels are elevated in PAH and interacts with ET receptors A and B. Activation of ET_A leads to pulmonary vasoconstriction and smooth muscle cell proliferation, whereas ET_B acts to clear ET1 and may induce vasodilation through nitric oxide and prostacyclin release from endothelial cells. Endothelin receptor antagonists (ERA) have proven efficacy in the treatment of PAH. Bosentan is a nonselective ERA, which requires liver function test monitoring due to elevated transaminases observed in roughly 13% of patients [99]. Ambrisentan has a higher ET_A selectivity and does not require liver function test monitoring [100]. In clinical practice there has been no significant difference between these 2 drugs based on ET receptor selectivity and both therapies were shown to significantly improve 6-min walk time. Macitentan was studied in the largest prospective PAH trial that included 742 patients and demonstrated a significant reduction in morbidity and mortality [101].

Prostacyclins are the third major group of PAH-specific therapy and are available in oral, inhaled, subcutaneous, and intravenous forms. Prostacyclins are released by endothelial cells and promote pulmonary vasodilation and have significant antithrombotic, antiplatelet, and antiproliferative properties. Epoprostenol is available as continuous intravenous therapy and has proven mortality benefits [102]. It is also available in an inhaled form for acute treatment of PAH. Treprostinil has a longer half-life and has demonstrated clinical improvement as intravenous, subcutaneous [103,104], inhaled [105], and oral therapies [106,107]. Treprostinil can be delivered via continuous infusion, inhalation, or orally. Iloprost is a prostacyclin that is administered via inhalation and has demonstrable benefits on clinical function [108] (Table 2).

These therapies have been studied primarily in idiopathic PAH and associated PAH. Clinical studies on PAH etiologies encountered in resource-limited settings have been limited. In Sch-PAH, PDE5 inhibitors, ERA, and prostacyclin analogues have been successfully used [109]. PAH therapies have also been effective in HIV-associated PAH [110–113]. Moreover, in patients without significant comorbidities, monotherapy with PDE5 inhibitors has been shown to improve clinical symptoms and in some cases dramatically reverse PH [114]. Treatment for SCD-associated PH has not been well established. Bosentan

has been associated with hemodynamic improvement in SCD-associated PH in a small study [115]. However, dose-related decreases in hemoglobin by 1 g/dl may limit the use of ERA. Sildenafil therapy, however, was not associated with a significant treatment effect and led to increased hospitalizations secondary to pain crises [116]. L-arginine, which acts as a nitrogen donor for the synthesis of nitric oxide, has been demonstrated to decrease PA systolic pressures by 15.2% [117].

THERAPY GOALS IN RESOURCE-LIMITED AREAS

It is estimated that only 10% of all healthcare expenditures are allocated to resource-limited countries, which bear a disproportionate 88% of the global disease burden [118]. Furthermore, PVD in industrialized nations only represents 3% of the global burden of disease. Rectifying the imbalance requires access to medical care and resources and proper training of healthcare staff to recognize and prevent PVD in patients at risk. The vast majority of patients with PVD globally will have limited to no access to therapies and for those that have PAH, pharmaceutical therapeutics may be prohibitively expensive. Bosentan and sildenafil are available in Latin America, India, and east Asia, whereas prostacyclins may be limited to tertiary referral centers [119,120]. International clinical trials in PAH have increased the availability of PAH-specific therapies to resource-limited settings.

Ideally, PVD centers should also be established throughout resource-limited countries with a focus strictly on the prevention, management and treatment of PVD and to provide training to healthcare workers and physicians. Physicians should also be able to identify patients with risk factors that put them at a higher risk of developing PVD, such as those with HIV or those who live in areas where schistosomiasis is endemic [121]. In patients with PAH, PVD centers should be able to perform diagnostic catheterization and dispense PAH-specific therapies. Yearly echocardiograms should be performed in most patients with PAH and catheterization should be repeated yearly in higher risk patients to monitor for therapeutic response.

SUMMARY

The international community must recognize the urgency and threat of preventable pulmonary and cardiac diseases [122]. PVD affects a significant number of people globally and most existing therapies are expensive. However, preventative measures focused on those at highest risk may help curtail the incidence of PVD. Treatments can also be developed and tested through clinical trials in resource-limited countries, and the expense of conducting such trials is often lower than that in more resource-rich settings. Spreading awareness of the importance of PVD and cardiovascular disease, encouraging collaborative efforts between physicians in resource-limited countries, developing new diagnostic and treatment methods, and conducting inexpensive clinical trials in the field will help decrease the prevalence of PH in resource-limited countries.

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