Pulmonary Vascular Disease in the Developing World

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The prevalence, cause, and pathobiology of pulmonary vascular disease in the developing world are not known, but estimates put the prevalence at 20 to 25 million. A major contributor is infectious disease. The present review examines the association between infectious disease and other causes in the developing world and pulmonary vascular disease and the need for further research in this area.

Pulmonary Vascular Disease Associated With Schistosomiasis

Schistosomiasis (Bilharzias) is the third-leading endemic parasitic disease in the world, following malaria and amebiasis. More than 300 million individuals are infected, and another 600 million are at risk of infection. The disease ranks higher in prevalence than HIV/AIDS. It is endemic in eastern South America, the Caribbean Islands, east Asia, and some parts of China and the Middle East, with sub-Saharan Africa being the most endemic area. It is a major public health problem that is closely correlated with socioeconomic conditions. Modern endeavors to develop and construct water schemes to meet local power and agricultural needs have increased the prevalence in many parts of the world. Few countries have eradicated the disease or undertaken successful and sustainable control programs despite the collaborative efforts of local governments, the World Health Organization, the World Bank, the United Nations, and philanthropic organizations.

Schistosomiasis is caused by flatworms. There are many species of Schistosoma. S mansoni infects >120 million people in Africa and Brazil. The final target of this species is the intestinal and hepatic circulatory system. S hematobium is endemic in Africa, the Middle East, and east Asia. It targets the genitourinary circulatory system. S japonicum, which is endemic in China and southeast Asia, affects the intestinal and hepatic circulatory system.

The Life Cycle of Schistosomiasis

The worms live in the perivisceral veins of the intestine, liver, and genitourinary systems. Their eggs find their way into the urine and feces of the host, and when they are voided into the water, they hatch into a developmental stage called miracidium. This form infects certain species of freshwater snails. The miracidium inside the snails undergoes various transformational changes and produces a new parasitic form known as cercariae. The cercariae then leave the snail and remain in fresh water (for a maximum of 48 hours) but can penetrate the skin of persons working or bathing in the infected water in 3 to 5 minutes using proteolytic enzymes. After penetration, cercariae undergo transformation to schistosomula, enter postcapillary venules, and travel in the bloodstream to the lungs. There, schistosomula undergo further developmental change to enable their subsequent migration to the systemic circulation within 1 week. In the case of S mansoni and S japonicum, the worms find themselves in the mesenteric circulation and liver sinusoids. S hematobium targets the venous plexus of the bladder, ureters, and kidneys (Figure 1). The adult parasite (note that the female is held within the adult male gynecological canal) starts to lay eggs. Many of the eggs leave the body via feces or urine, and the cycle continues (for more details, see elsewhere).

The Pulmonary Involvement

The lung is a mandatory step in the parasite life cycle. The parasite causes both acute and chronic pulmonary lesions, depending on the cycle phase. Pulmonary involvement should be suspected in patients with even minor respiratory symptoms; it is more common than previously suspected.

Acute Pulmonary Schistosomiasis

Acute pulmonary schistosomiasis is also called Katayama syndrome. It appears a few weeks after infection and is due to proinflammatory cytokines and immune complexes induced by migrating schistosomula and egg deposition. It is most likely to occur in nonimmune hosts, particularly visitors to endemic regions. The main presentations are nocturnal fever, cough, dyspnea, myalgia, headache, and abdominal tenderness. This nonspecific presentation is most likely to be misdiagnosed, but the history of water contact 14 to 84 days before presentation of clinical symptoms can clinch the diagnosis. Chest radiography usually shows diffuse pulmonary infiltrates. Eosinophilia is seen in all patients, as well as increases in serum tumor necrosis factor-α, interleukin (IL)-1, IL-6, and interferon-γ levels.

The Chronic Pulmonary Diseases of Schistosomiasis

Chronic pulmonary disease is more common in endemic areas and may present as asthma but, more important,
pulmonary vascular disease that can result in pulmonary hypertension and right heart failure (cor pulmonale). The latter is one of the debilitating and fatal sequelae of infection.6–12 The majority of reported cases are due to *S mansoni*, with a few case reports due to *S hematobium*13 or *S japonicum*.14,15

The Prevalence of Pulmonary Hypertension
The prevalence of pulmonary hypertension caused by schistosomal infection is not known. Most reports are small series, mainly from Brazil, with very few reports from Africa or Asia. Barbosa et al16 evaluated cardiopulmonary involvement in 246 patients with suspected *S mansoni* infection living in an endemic area of Brazil. High pulmonary artery pressure was found in 25% of subjects on Doppler echocardiography; of these, 80% had schistosomiasis. Other small studies in Brazil have reported pulmonary hypertension in 7.5% to 21.6% of patients with schistosomiasis,8,10,16–18 but none of these studies used appropriate epidemiological methodology. Data from specialized pulmonary hypertension centers in Brazil suggest that schistosomiasis is the cause of severe pulmonary hypertension in ~30% of referred patients19 (Figure 2). In Zimbabwe and Ethiopia, where schistosomiasis is endemic, chronic cor pulmonale is commonly seen among Africans, but accurate assessments of the contribution of schistosomal infection are not available.11

The Clinical Picture of Schistosomiasis
Pulmonary Hypertension
There are no typical clinical distinguishing features. Dyspnea on exertion, weakness, cough, giddiness and fainting, palpitation, thoracic pain, pericardial pain, and hemoptysis are all

Figure 1. Schematic representation of the Life cycle of schistosomiasis and its development inside the human body. GI indicates gastrointestinal; GU, genitourinary.

Figure 2. The distribution of pulmonary hypertension causes in a referral center in an endemic area in Brazil (Oswaldo Cruz University Hospital, Memorial São José Hospital, Real Português Hospital Recife-PE-Brazil). Courtesy of Dr Angela P. Bandeira. IPAH indicates idiopathic pulmonary arterial hypertension; CTD, connective tissue disease.
anti-infective agents (such as praziquantel) are not available. Specialized pulmonary hypertension.16,20

Granuloma formation also may lead to a delayed hypersensitivity reaction to eggs deposited or trapped in the tissues. Granulomatous lesions are seen in 21% of cases of S mansoni.23,24 Pulmonary biopsies from patients with schistosomiasis and pulmonary hypertension show evidence of granulomatous lesions and fibrosis, in addition to many pathological features of idiopathic pulmonary hypertension. Severe intimal, medial, and adventitial hypertrophy and proliferation of a plethora of inflammatory cells occur in the pulmonary vasculature (Figure 4).13

Immunological Modulation of Schistosomiasis and Its Effect on Pulmonary Circulation

The immunological response to schistosomiasis in endemic areas is still not fully understood. It varies according to the strain, species, age, gender, duration and intensity of infection, and genetic predisposition. The literature in the last 15 years illustrates the complexity of Schistosoma modulation of the host immunity and pulmonary inflammation.25

Schistosomal infections, like other parasitic helminths, are associated with a strong CD4+ T-helper 2 (Th2) response. However in the early stage (the first 3 to 5 weeks), the immunological response involves mainly Th1 cells when proinflammatory cytokines like IL-1, IL-12 interferon-γ, and tumor necrosis factor-α can be measured in the plasma and infected tissue.26 Th1 cells may be responsible for acute schistosomiasis infection (Katayama syndrome). The Th2 response follows in response to the egg and causes the production of a battery of cytokines such as IL-4, IL-6, IL-10 IL-13, IL-21, IL-31, AMCase, Ym1, and FIZZ1, as well as various chemokines.27 The Th2 cells suppress the Th1 proinflammatory response and produce protective eosinophil-rich granulomatous lesions around newly deposited eggs, but they allow the development of fibrosis.26 The inability to develop a Th2 response to regulate the initial proinflammatory response is lethal.

Inflammatory cells (macrophages, T and B lymphocytes) have been detected in various parts of the remodeled small pulmonary arteries and in plexiform lesions in many forms of pulmonary hypertension. Furthermore, elevated serum levels

Figure 3. Chest radiograph (A), magnetic resonance imaging (B), and pulmonary angiography (D) in patient with World Health Organization class IV pulmonary hypertension secondary to schistosomiasis from Brazil. C, Magnetic resonance imaging of the liver with typical Symmers’ fibrosis. Courtesy of Dr Angela P. Bandeira.

Figure 4. Histopathological sections from patients with severe pulmonary hypertension secondary to schistosomiasis (A through C) and from an experimental mouse model (D and E). A, Complex vascular lesions in a branching segment of a pulmonary artery of a patient with pulmonary hypertension associated with schistosomiasis. B, Pulmonary artery from a patient with pulmonary hypertension associated with schistosomiasis showing marked intimal thickening and adventitial inflammation. C, Plexiform lesion in a pulmonary artery with pulmonary hypertension associated with schistosomiasis. D, Muscularized pulmonary artery of a mouse infected with S mansoni. E, Presence of Schistosoma egg and associated inflammation impinging on the adventitia of a muscularized pulmonary artery of a mouse lung. Courtesy Drs Rubin Tuder and Alan Cheever.
of proinflammatory cytokines IL-1 and IL-6, chemokines (CX3C, fractalkine, RANTES), and various types of autoantibodies (anti-nuclear, anti-endothelial, anti-fibroblast, and anti-fibrillin-1) have been detected in severe pulmonary hypertension patients with connective tissue disease and HIV. Therefore, inflammatory and immunological reactions to schistosomiasis may contribute to the development of pulmonary hypertension (Figure 5).

The increase in proinflammatory cytokines like IL-1 and tumor necrosis factor-α may contribute to the vasoconstriction tone and remodeling of the pulmonary vessels in certain animal models, which may be due to various mechanisms, among which is the upregulation of rho kinase. Some cytokines also alter the amounts of various surface components of the blood vessel wall and significantly decrease the functional cell surface thrombin receptor (thrombomodulin), thus promoting coagulation in the pulmonary vessels.

Other changes in the inflammatory process may cause endothelial dysregulation of cell-cell adhesion and transendothelial migration, which contribute to the pulmonary vasculopathy. A significant increase in serum soluble intercellular adhesion molecule-1 was observed in patients with schistosomiasis compared with control subjects. Furthermore, schistosomal infection can disturb the nitric oxide pathway. Schistosoma eggs and Th2 cytokines induce arginase activity, which is suppressed by interferon-γ; this disequilibrium favors the development of granulomatous formation and may lead to further damage to the pulmonary vessels.

IL-13 is a pleiotropic cytokine produced in large quantities by activated CD4+ Th2 lymphocytes. It is known to induce airway hyperresponsiveness but also endothelial vascular cell adhesion molecule-1 expression, thus playing a role in asthma, acute lung injury, fibrosis. IL-13-dependent fibrosis develops either directly or through transforming growth factor-β and probably matrix metalloproteinase-9-dependent mechanisms, both playing important roles in the pulmonary vascular remodeling process. The direct effect of IL-13 on vascular smooth muscles has not been studied systematically, but it was noticed recently that IL-13 is a potent antiproliferative factor in pulmonary artery smooth muscle cells, probably via upregulation of the decoy receptor IL-13RA2 on the pulmonary artery smooth muscle.

Other Th2 cytokines like FIZZ1, recently renamed hypoxia-induced mitogenic factor, contribute to the pulmonary remodeling secondary to hypoxia. It promotes cell proliferation and migration and the production of vascular endothelial growth factor in pulmonary endothelial cells, which are important components in the remodeling process and the production of reactive oxygen species. Apoptosis plays a vital role in the pathogenesis of pulmonary hypertension with spatio-temporal diversity. Early stages of pulmonary vessel remodeling are characterized by increased apoptosis in the endothelial layer, but the apoptosis decreases in later stages, particularly in the intimal and medial layers, which results in enhanced proliferation. Fas, a membrane-anchored protein related to the tumor necrosis factor receptor family that induces apoptosis, can be antagonized by soluble Fas and thus inhibit apoptosis. In patients with schistosomal pulmonary hypertension, serum levels of soluble Fas are significantly higher compared with patients with cor pulmonale resulting from chronic obstructive pulmonary disease. This factor may contribute to the remodeling process of schistosomal pulmonary vascular disease.

Schistosomal pulmonary vasculopathy is frequently seen with Symmer’s fibrosis; in those without Symmer’s fibrosis, portal hypertension is common. It was estimated that 11% to 33% of patients with portal hypertension caused by schistosomiasis will develop pulmonary hypertension. Aggravation of pulmonary hypertension also has been described after the surgical treatment of schistosomiasis-associated portal hypertension with a shunt procedure. It is thought that the development of portal-systemic collateral circulation leads to a hyperdynamic circulatory state, contributing to an
increased flow and shear stress to the pulmonary circulation, and facilitates shunting of eggs from the liver to the lungs, thus increasing the immunological burden on the lungs and pulmonary circulation. Therefore, portal hypertension may play a role in the development of pulmonary vasculopathy.

The Issues and Problems
We can only speculate on the number of patients affected by schistosomiasis-associated pulmonary vascular disease because the real prevalence is not yet known. Because >200 million people are infected worldwide, we can consider schistosomiasis to be the major cause of pulmonary hypertension worldwide; it may even be the leading cause of pulmonary hypertension in endemic areas. However, the prevalence, clinical profile, and pathology are still unknown. More studies are needed to assess the effect of coinfection with other conditions such as HIV that are known to cause pulmonary hypertension and are prevalent in developing countries.

Recent advances in the treatment of pulmonary hypertension have not been implemented in the management of patients with pulmonary hypertension secondary to schistosomiasis. Therefore, the need to develop an inexpensive and affordable treatment warrants further attention.

Pulmonary Vascular Disease Associated With Other Helminthic Diseases

*Wuchereria bancrofti* is a thread-like worm that causes filariasis (elephantiasis). It is widespread in India, Sri Lanka, and many other countries in Asia, Africa, and Central and South America. More than 20 million people are infected with this parasite worldwide. Filariasis was attributed to the higher incidence of pulmonary hypertension between 1967 and 1970 in Sri Lanka compared with the United Kingdom, but the real prevalence of these complications has not been studied. The parasite causes interstitial fibrosis, and if the infection is sufficiently severe, pulmonary hypertension may result.

*Clonorchis sinensis* (Chinese liver fluke) is a widespread parasite found in southeast Asia. Infection of the biliary passage (cholangiohepatitis, oriental pyogenic cholangitis) occurs after the consumption of raw fish. Few cases of pulmonary hypertension have been associated with this parasite.

Pulmonary Vascular Disease Associated With HIV
The global AIDS epidemic report of 2006 estimated that 38.6 million people worldwide were living with HIV in 2005; 63.5% are in sub-Saharan Africa alone. HIV has been associated with multiple infectious and noninfectious pulmonary diseases. Since the first description of the HIV association with pulmonary hypertension by Kim and Factor in 1987, other cases and series have been reported (for current review articles, see Petrosillo et al).

The incidence of pulmonary hypertension seems to be ~1000 times higher in HIV-infected patients than in the general population. It has been estimated that 0.5% of HIV-infected patients will have symptomatic pulmonary hypertension. Data from a pulmonary hypertension regist
causes of pulmonary hypertension had evidence of infection with human herpesvirus 8 (HHV-8) (the etiological factor of Kaposi’s sarcoma). This observation has not been supported by many serological tests for HHV-8 in patients with pulmonary hypertension. However, most of these studies were performed in countries where HHV-8 infection rates are very low. HHV-8 infection is endemic in many Mediterranean countries, South America, and sub-Saharan Africa. High seroprevalence rates of up to 58% in young children were found in Ghana, Tanzania, Cameroon, and Uganda, but it is rare in many Asian populations. However, the pattern and prevalence vary between these countries. It is therefore imperative to assess the role of HHV-8 in pulmonary vascular disease in endemic areas to provide further information on the role, if any, of this virus in the pathobiology of pulmonary hypertension, therefore providing a reasonable model to study the controversial role of HHV-8 infection in the pathogenesis of pulmonary hypertension.

**Pulmonary Vascular Disease Associated With Hemolytic Anemia**

Pulmonary hypertension has been reported in various forms of chronic inherited hemolytic anemias like sickle cell anemia, various forms of thalassemia, hereditary spherocytosis, and some forms of microangiopathic hemolytic diseases such as thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. The precise cause and pathobiology of pulmonary hypertension in patients with hemolytic anemias have not been well defined. Chronic intravascular hemolysis may disturb nitric oxide bioavailability, promoting endothelial dysfunction, smooth muscle dystonia, enhancement of coagulopathy, and increased oxidant and inflammatory stress, all of which will lead to the development of proliferative changes seen in patients with pulmonary hypertension.

Chronic inherited hemolytic anemias are among the most common genetic defect globally. The World Health Organization has estimated that at least 7% of the world’s population are carriers of ≥1 forms, and 300 000 to 400 000 babies with severe forms of these diseases are born each year. There is a high prevalence in malaria-endemic areas because inherited hemoglobin disorders have major advantages for protecting against malaria, but these disorders are now encountered in most countries because of population migration and political and socioeconomic changes. For example, 8% of African American have the sickle cell trait. An observational study with Doppler echocardiography suggested a prevalence of pulmonary hypertension in the range of 10% to 30% among patients with sickle cell anemia. The prognosis of patients diagnosed with pulmonary hypertension was poorer than that for patients with no signs of pulmonary hypertension. As a result of the wider geographical distribution, it is important to assess its impact on health in many developing countries. There were no significant reports on the incidence, prevalence, or impact on the general health in these countries, especially because it can be complicated by coinfections like HIV and schistosomiasis. Recent therapeutic trials of this condition demonstrated the benefit of oral anti–pulmonary hypertension medications like endothelin receptor blockers, phosphodiesterases 5 inhibitors, or arginine therapy.

**Pulmonary Vascular Disease Associated With High Altitude**

It is estimated that >140 million people live and work at an altitude of >2500 m above sea level. Of these, 80 million live in Asia, and 35 million live in the Andean mountains (see review by Penaloza and Arias-Stella). Hypoxia causes an increase in pulmonary pressure, which affects right ventricular performance and exercise ability. Exposure to high altitude from birth to adolescence results in changes in the oxygen transport system, so that a greater aerobic exercise performance is needed to reflect a successful adaptation to life at high altitude. Remodeling of the pulmonary vessels suggests incomplete adaptation that is compatible with normal life at high altitude and can be a significant health problem in these parts of the world. There is, however, considerable variation in susceptibility to hypoxia-induced pulmonary hypertension among different ethnic groups adapted to life at high altitude, which suggests genetic factors. There is evidence that natural selection is ongoing in some parts of the world at high altitude (eg, the Tibetan population) where women estimated to have the genotypes for high oxygen saturation of hemoglobin (and less physiological stress) have higher offspring survival. Therefore, identifying the genetic basis of resistance to hypoxia would provide insight into the physiology of the normal response and is crucial for discovering the steps along the routes to functional adaptation. Many investigators pursued candidate molecules, eg, assessment of genetic polymorphisms in the renin-angiotensin and nitric oxide synthesis systems, CYP11B2, and endothelin-1, as well as assessment of polygenic traits.

There is a clear need for global studies searching for genes that increase or decrease susceptibility to high-altitude pulmonary hypertension and other high-altitude–related diseases. This could be partly a focused genome screen, which makes no previous assumption of the underlying pathogenesis; linkage analysis; a single-nucleotide polymorphism search; or a population difference study comparing genes of interest between inhabitants of high altitude and those of people from different regions such as South America, Asia, India, and Europe.

**Pulmonary Vascular Disease Associated With Cardiac Diseases**

Rheumatic valvular heart disease, mainly mitral valve disease, is one of the major causes of pulmonary vascular disease. Although this condition is almost disappearing in the developed world, it is still very prevalent in the developing world. Most of the complications are due to late surgery and lack of preventive measures (see the review by Essop and Nkomo).

Pulmonary vascular disease is a major complicating factor for patients with congenital heart defects, mainly those with left-to-right shunts. The major problem in the developing world is late diagnosis and surgical repair. Furthermore, nutritional issues and the socioeconomic conditions in several
countries contribute to the high mortality of children with congenital heart disease.93

The prevalence and differential distribution of congenital heart disease are unknown in many developing countries. There is differential distribution of the cardiac malformations in different countries; for example, in Peru, those living >3500 to 5000 m above sea level have an 18- to 30-times greater incidence of patent ductus arteriosus than their fellow countrymen living on the coast.94 There is a high proportion of subarterial ventricular septal defect in China and Japan (≈35% versus 5% in whites). The main cause is unknown, although probably genetic; other likely explanations are nutritional status and the development of clinical diagnostic skill. A concerted effort with wide collaboration of international bodies and specialized centers is needed to provide educational and consensus documents to highlight the issues in the diagnosis and management worldwide and collaborative comparative research in this field.

Endomyocardial fibrosis is an idiopathic disorder of a progressive nature that is seen mainly in the tropical and subtropical regions within 15° of the equator. Its geographic distribution includes areas in Africa, India, and South America. It is more common in poor socioeconomic groups, but short-term visitors to an endemic area may acquire the disease. The disease is part of a spectrum of a disease process with the underlying process of patchy fibrosis of the endomyocardial surface of the heart. It involves the inflow tracts of the right and left ventricles and may affect the atrioventricular valves, leading to tricuspid and mitral regurgitation and resulting in the development of restrictive cardiomyopathy. Pulmonary hypertension may develop in severe cases as a result of heart failure and restrictive filling properties that lead to congestion,94,95 but the real prevalence has not been studied.

Other Causes Contributing to Pulmonary Vascular Disease in the Developing World

Diet, drug, and pollution substances such as anorectic agents, cocaine, methamphetamine, contaminated rapeseed cooking oil, and L-tryptophan can cause pulmonary hypertension.96 For example, in 1981, >20 000 people in Spain were poisoned with adulterated rapeseed cooking oil sold in bulk that caused pulmonary hypertension, polynuropathy, and myositis, with the primary pathological features of endothelial proliferation and tissue fibrosis affecting women almost exclusively. The toxins responsible for these changes have not been conclusively identified.97 It is not known whether consumption of these substances by the people in the developing world can lead to pulmonary vascular disease. In Central America (Guyana, Panama, Honduras, Surinam, and some Caribbean Islands), the practice of smoking tobacco leaves cured by mineral oil formerly caused severe pulmonary hypertension. In Africa and Central America, plant alkaloids are used to make tea, eg, bush tea from the seeds of plants like rattlebox (Crotalaria spectabilis), which contains monocrotaline (pyrrolizidine alkaloid), a substance well known to cause severe pulmonary hypertension in rats.98 Furthermore, domestic pollution caused by burning wood, charcoal, liquefied petroleum gas, or cow dung in poorly ventilated housing causes chronic obstructive lung disease and may predispose to pulmonary hypertension and cor pulmonale in northern India, Africa, and the highlands.99

Conclusions

It is obvious that the number of patients with pulmonary vascular disease in developing countries is much larger than in the developed world. This difference is due mainly to the underlying causes that are not present in many Western and developed countries. In addition, the different socioeconomic situations and genetic variations play an important role. The current increase in the prevalence of pulmonary vascular diseases in the developed world after the introduction of effective anti–pulmonary hypertension drugs leads us to consider the notion that it is time to learn more about the prevalence in the developing world. Doing so will help us understand the intricacies of the pathobiology of the different forms of pulmonary vascular disease.

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