



## **EDITORIAL**

# **SCHISTOSOMIASIS PULMONARY HYPERTENSION: THE FORGOTTEN DISEASE**

By

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Pulmonary hypertension is defined as a high blood pressure in the lung circulation. The mean pulmonary pressure above 25 mm Hg is considered high and clinically labelled as pulmonary hypertension. The increase in pulmonary pressure is not related to the changes in the systemic pressure.

Pulmonary hypertension in the developed world can be familial but the majority of the cases are secondary to other diseases like congenital heart disease, connective tissue diseases, HIV infection, sickle cell anaemia, pulmonary embolism, heart failure, and chronic obstructive disease. There are more than 0.5 millions people suffering from this disease in the developed world. Pulmonary hypertension is a very severe and serious condition. It has a very high morbidity and mortality. Currently the 50% survival in untreated patients is less than 2 years; thus its prognosis is similar to cancer and other lethal clinical conditions. Pathologically the disease is manifested itself in severe narrowing of the blood

vessels and it is often associated with new growth within the blood vessels, abnormal proliferation and disarray of the three main layers of the pulmonary vessels. Tiny blood clots may form within the smaller arteries, causing blockages. The condition is usually presented with common symptoms like shortness of breath, light headedness, passing out spells (syncope); chest pains, palpitations and in terminal cases will develop symptoms due to heart failure.

There is a recent advancement in the treatment which benefits many patients symptomatically and partially halts the progress of the diseases but does not cure the condition.

### ***Pulmonary hypertension associated with Schistosomiasis***

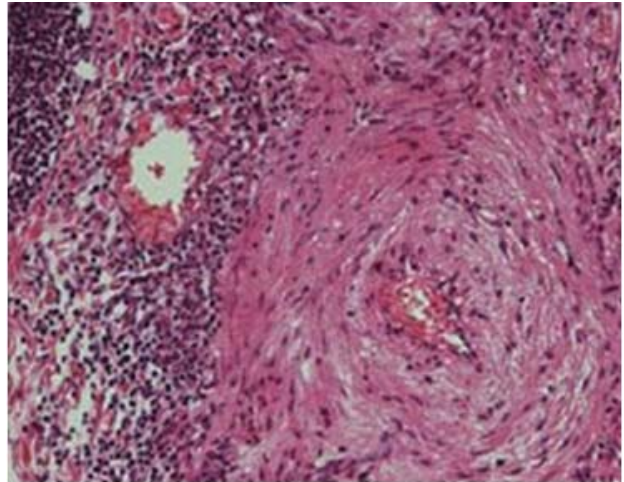
Schistosomiasis (Bilharzias)<sup>(1)</sup> is the third leading endemic parasitic disease in the world, following malaria and amoebiasis. The lung is a mandatory step in the schistosoma life cycle. This causes both

acute and chronic pulmonary lesions depending on the cycle phase. During the first pass when schistosomula enters post capillary venules and travel in the blood stream to the lungs where it undergoes major developmental changes. During this stage some pro inflammatory cytokines are released and can be detected in the plasma.<sup>(2)</sup> In some patients, in particular in non-immune hosts and visitors to the endemic areas will develop sign and symptoms of what we clinically label as *acute pulmonary schistosomiasis* (Katayama syndrome).<sup>(3)</sup> The main presentations are nocturnal fever, cough, dyspnea myalgia, headache, and abdominal tenderness. Chest radiography usually shows diffuse pulmonary infiltrates. Eosinophilia is seen in all patients.

The second form is the *chronic pulmonary diseases of schistosomiasis*; which is characterized by a patchy pulmonary granulomatous reaction and fibrosis, however in certain proportion of these patients pulmonary vascular disease can be seen. When the later happens the pulmonary pressure will increase and in severe cases a clinical presentation suggestive of pulmonary hypertension.<sup>(4-10)</sup> The majority of reported cases are due to *S. mansoni* with a few case reports due to *S. haematobium*<sup>(11)</sup> or *S. japonicum*.<sup>(12,13)</sup> There are no appropriate epidemiological studies on the prevalence of the pulmonary hypertension complication. Most of the observational studies from Brazil suggested that pulmonary hypertension occurs in as low as 5% to as high as 21 % of patients infected with schistosomiasis.<sup>(6,8,14-16)</sup> No reports of the real incidence in Africa, where the problem could be complicated with the presence of co-infection, such as HIV. Both infections can cause pulmonary hypertension alone.

The pathological features have not been studied extensively and in few cases reported in the literature and from the observation from our institute suggested that some patients presented a very severe form of blood vessels narrowing with high degree of smooth muscle proliferations. There are also extensive inflammatory cells seen in all layers of the blood vessels. Sometimes egg can

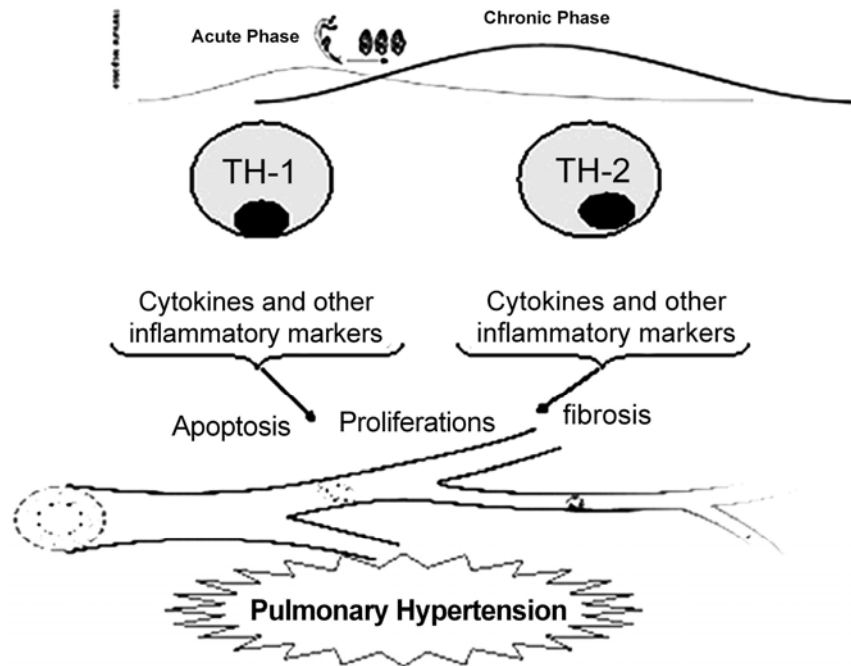
be seen within the blood vessels lesions. The histopathologic picture of the schistosomiasis pulmonary vessels diseases is not different from other causes of severe and fatal form of pulmonary hypertension (Fig. 1).



**Fig 1. Pulmonary artery from a patient with pulmonary hypertension associated with schistosomiasis showing marked intima and media thickening and adventitial inflammation.**

*(Courtesy of Dr. Rubin Tuder, a member of the Schistosomiasis Pulmonary Hypertension Taskforce, PVRI).*

The pathogenesis of pulmonary hypertension is not known and has not been studied yet. Inflammation in general plays an important role in the pathogenesis and progression of the pulmonary vessels disease that causes pulmonary hypertension. It is therefore safe to infer that the inflammatory reactions that are invoked by mainly egg antigens, which usually provoked type 2 responses, contribute to the pathological process. Many of the cytokines produced during this stage have been reported to enhance pulmonary vessels disease and perpetuate disarray of the blood vessels layers leading to increase the pressure inside these arteries (Fig. 2). This hypothesis definitely needs further studies and evaluation both in the experimental animals and in the clinical settings. The severity of pulmonary vascular disease has been correlated to the eggs' load that reaches the lungs.



*Fig 2. Schematic representation of the possible pathogenesis of pulmonary vascular diseases secondary to Schistosomiasis. Worm and egg antigens enhance Th-1 (in acute phase) and Th-2 (in the chronic phase) reactions. Various cytokines and other inflammatory markers enhance various pathological reactions in the pulmonary vasculature; including apoptotic and proliferative reactions and fibrosis. These lead to the pathological lesions as seen in Figure -1 above causing increase in pulmonary vascular resistance and the development of pulmonary hypertension.*

Portal hypertension is relatively common in schistosomiasis in particular with *S. mansoni* and *S. japonicum* due to the liver fibrosis. Portal hypertension opens more collateral circulation, thus increasing the blood flow to the lungs. The increase of blood flow to the lung will enhance the shear stress in the pulmonary vessels enhancing the pathological effect that may lead to narrowing of blood vessels and probably pulmonary hypertension. Furthermore the increase in the blood flow from the liver will increase the shunting opportunities of eggs from the adult schistosoma worm to the lungs. This effect will increase the antigenic load to the lung tissue and its blood vessels; thus enhancing the inflammatory response and the release of various cytokines that may play role in the pathogenesis of pulmonary vasculopathy.

There are no typical clinical distinguishing features. Dyspnoea on exertion, weakness, cough, giddiness and fainting, palpitation, thoracic pain,

pericardial pain and hemoptysis are all well recognised as in idiopathic pulmonary hypertension. The increase in pulmonary pressure will put more stress on the heart, in particular the right heart and can result in the right heart failure (cor pulmonale) (Fig. 2). The latter is one of the debilitating and fatal sequelae of infection. Chest radiography may show an enlarged pulmonary arterial trunk and right ventricular hypertrophy and evidence of pleural effusion.<sup>(17)</sup>

Taken in consideration the estimated 200 millions people infected with schistosomiasis worldwide even considering the lower prevalence estimate, will make schistosomiasis the most common cause of pulmonary hypertension worldwide, and yet is the least studied disease in the tropics, making this disease a really “forgotten diseases”.

**Current Activities:** Recently a concrete initiative, sponsored by the Pulmonary Vascular Research institute (PVRI) ([www.pvri.info](http://www.pvri.info)) has been established to study this problem systematically with international collaboration of specialized centres involved in the study of schistosomiasis and pulmonary vascular disease. The initiative is establishing a 5 year program to study the condition from a basic to a clinical level taking the above issues into consideration, and to create a clinical database for this condition. Also to establish a simple screening methodology to detect affected patients and to conduct pilot trials of available and affordable therapies on affected patients. Furthermore there will be educational programmes for physicians and local health professionals on the issue of the pulmonary complications of schistosomiasis. The taskforce and the PVRI will welcome the collaboration and help from any centres in the world interested in this field of research and to sponsor research fellows, graduate and postgraduate research programmes.



**Fig 3. Chest X ray from patients with severe pulmonary hypertension secondary to Schistosomiasis. Notice the enlargement of the heart, the large pulmonary vessels and the increase the blood flow to the lung (courtesy of Dr. Ângela P. Bandeira, a member of the Schistosomiasis Pulmonary Hypertension Taskforce, PVRI)**

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