Cardiopulmonary Manifestations of Hepatosplenic Schistosomiasis

Monica Lapa, MD; Bruno Dias, MD; Carlos Jardim, MD, PhD; Caio J.C. Fernandes, MD; Paulo M.M. Dourado, MD; Magda Figueiredo, MD; Alberto Farias, MD, PhD; Jeane Tsutsui, MD, PhD; Mario Terra-Filho, MD, PhD; Marc Humbert, MD, PhD; Rogerio Souza, MD, PhD

Background — Schistosomiasis is a highly prevalent disease with >200 million infected people. Pulmonary hypertension is one of the pulmonary manifestations in this disease, particularly in its hepatosplenic presentation. The aim of this study was to determine the prevalence of pulmonary hypertension in schistosomiasis patients with the hepatosplenic form of the disease.

Methods and Results — All patients with hepatosplenic schistosomiasis followed up at the gastroenterology department of our university hospital underwent echocardiographic evaluation to search for pulmonary hypertension. Patients presenting with systolic pulmonary artery pressure >40 mm Hg were further evaluated through right heart catheterization. Our study showed an 18.5% prevalence of patients with elevated systolic pulmonary artery pressure at echocardiography. Invasive hemodynamics confirmed the presence of pulmonary hypertension in 7.7% (95% confidence interval, 3.3 to 16.7) of patients, with a prevalence of precapillary (arterial) pulmonary hypertension of 4.6% (95% confidence interval, 1.5 to 12.7).

Conclusions — Our study reinforces the role of echocardiography as a screening tool in the investigation of pulmonary hypertension, together with the need for invasive monitoring for a proper diagnosis. We conclude that hepatosplenic schistosomiasis may account for one of the most prevalent forms of pulmonary hypertension worldwide, justifying the development of further studies to evaluate the effect of specific pulmonary hypertension treatment in this particular form of the disease. (Circulation. 2009;119:1518-1523.)

Key Words: echocardiography ■ hemodynamics ■ hypertension, pulmonary ■ schistosomiasis

Schistosomiasis is a highly prevalent disease caused by parasitic trematode worms. It is estimated that >200 million people are infected by any of the species of Schistosoma, with Schistosoma mansoni, Schistosoma hematobium, and Schistosoma japonicum being the 3 most common with characteristic geographical distribution.2,3

Clinical Perspective p 1523

The first descriptions of cardiopulmonary manifestations of schistosomiasis appeared in the early 1900s.4 Most of the cardiopulmonary manifestations of schistosomiasis are thought to be related to the hepatosplenic form of the disease, which is characterized by presinusoidal block by embolized worm eggs, producing portal hypertension and portosystemic shunting. Although S mansoni and S japonicum infections are the main agents involved in schistosomal portal hypertension, the association of pulmonary hypertension (PH) with infection by those species is not unexpected. However, reports exist of pulmonary involvement in infections by S hematobium and by S mansoni without liver fibrosis.3

PH corresponds to one of the possible clinical complications of schistosomiasis.5 About 4% to 8% of patients with chronic schistosomiasis develop hepatopulmonary disease6,7; nevertheless, the incidence of PH in this subpopulation is controversial. Some studies have suggested an incidence of 20% to 30% of PH in patients with hepatosplenic disease;8–10 however, the small sample size, different definitions of PH,5,10,11 and presence of advanced hepatopulmonary disease without invasive confirmation of PH may impair the extrapolation of these results. The association of schistosomiasis and hepatotropic virus infection is well known, possibly a result of blood transfusion to treat variceal bleeding; thus, it is not possible to exclude the role of concurrent hepatitis C–related cirrhosis in studies carried out before the 1990s.12–14 The association of PH and schistosomiasis favors the concept that specific causes of PH may be of particular
importance in developing countries. The aim of the present study was to determine the prevalence of PH in hepatosplenic schistosomiasis.

Methods

Population
All patients followed up at the gastroenterology department of our university hospital for hepatosplenic manifestation of mansonic schistosomiasis were included in this study between January 2006 and August 2007. The study was carried out according to the ethical standards of the Declaration of Helsinki. The research protocol was approved by the institutional ethics board, and informed consent was obtained from all patients. The diagnosis of schistosomiasis was based on the abdominal ultrasonographic findings associated with the presence of S. mansoni ova in stool samples or rectal or liver biopsy according to the criteria of the World Health Organization. All patients were found to have esophageal varices, a surrogate marker of significant portal hypertension. Signs of active liver disease (eg, ascites, jaundice, and encephalopathy) were absent in all enrolled patients. Patients had not bled in the 6 months that preceded study enrollment. Concurrent parenchymal liver disease resulting from hepatitis B or C virus infection, metabolic liver disease, HIV infection, and alcohol-related liver disease were ruled out by appropriate tests. No patient was on therapy with β-blockers or any drug that could affect hemodynamic measurements. Antiparasitic therapy was carried out after diagnosis and for at least 6 months before hemodynamic measurements.

Echocardiographic Studies
All patients underwent an echocardiographic study for the estimation of pulmonary artery pressures. Systolic pulmonary artery pressure (SPAP) was calculated as a function of the tricuspid regurgitation jet velocity as described elsewhere.

Hemodynamic Studies
Patients who presented with an SPAP >40 mm Hg at the echocardiographic study were submitted to a right heart catheterization. All patients presented with arterial oxygen saturation >90% at the beginning of the measurements. A 7F flow-directed pulmonary artery catheter (Baxter Healthcare Corporation, Irvine, Calif) was introduced in all patients. Cardiac output was measured by the standard thermodilution technique. We defined PH as the presence of mean pulmonary artery pressure ≥25 mm Hg; further classification into precapillary or postcapillary PH was based on the level of the pulmonary artery occlusion pressure; PH patients with pulmonary artery occlusion pressure <15 mm Hg were classified as having precapillary PH.

Statistical Analysis
Continuous data are presented as mean (SD). The prevalence of all forms of PH is described as a proportion and the 95% confidence interval (CI). The association between echocardiographic estimation of SPAP and the invasive measurement was assessed with the Spearman rank correlation test.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
The baseline demographic data are shown in the Table. Study design and patient distribution according to final diagnosis are shown in Figure 1. Twelve patients presented with an SPAP >40 mm Hg (18.5%; 95% CI, 10.8 to 29.5). All of these patients except 1 who refused the procedure underwent right heart catheterization. Hemodynamic parameters are summarized in the Table and are presented as raw data in Figure 2. The correlation between the SPAP estimated through echocardiography and measured at the right heart catheterization had a coefficient (r) of 0.788 (P=0.004). Invasive measurement confirmed the presence of PH in 5 patients (7.7%; 95% CI, 3.3 to 16.7). However, of these 5 patients, 2 presented with a pulmonary artery occlusion pressure ≥15 mm Hg and thus were classified as having postcapillary hypertension; the remaining 3 patients were classified as having precapillary (arterial) PH (PAH; 4.6%; 95% CI, 1.5 to 12.7). Of note is the fact that pulmonary

Table. Baseline Demographic and Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>PH Patients</th>
<th>Non-PH Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>65</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>Age, y</td>
<td>51 (12)</td>
<td>40 (11)</td>
<td>51 (12)</td>
</tr>
<tr>
<td>Gender, F/M</td>
<td>1.4/1</td>
<td>1.5/1</td>
<td>1.4/1</td>
</tr>
<tr>
<td>SPAP (echocardiography), mm Hg</td>
<td>32 (16)</td>
<td>68 (26)</td>
<td>29 (9)</td>
</tr>
<tr>
<td>Invasive hemodynamics, n</td>
<td>11</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>SPAP, mm Hg</td>
<td>45 (21)</td>
<td>64 (20)</td>
<td>30 (3)</td>
</tr>
<tr>
<td>PAPm, mm Hg</td>
<td>28 (14)</td>
<td>41 (10)</td>
<td>18 (3)</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>8 (4)</td>
<td>11 (4)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>5.3 (1.4)</td>
<td>4.8 (1.1)</td>
<td>5.7 (1.5)</td>
</tr>
<tr>
<td>PVR, IU</td>
<td>3.7 (4.5)</td>
<td>6.5 (5.7)</td>
<td>1.4 (0.6)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD). PAPm indicates mean pulmonary artery pressure; RAP, right atrial pressure; PAOP, pulmonary artery occlusion pressure; CO, cardiac output; and PVR, pulmonary vascular resistance.

Figure 1. Study design and patient distribution. PAPm indicates mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure. *One patient refused invasive hemodynamics.
vascular resistance from the 2 patients classified as having postcapillary PH was $<2.4$ IU. None of the patients diagnosed with precapillary PH presented with any other comorbidity that could be related to the development of PH, whereas 1 patient with postcapillary PH had systemic arterial hypertension, which could possibly be related to the development of PH but was clinically controlled and without any signs of left ventricular dysfunction at echocardiography.

Discussion

Our study showed a 7.7% prevalence of PH in patients who fulfilled stringent diagnostic criteria for hepatosplenic schistosomiasis, with a prevalence of precapillary PAH of 4.6%. Although this prevalence appears lower than those previously reported, a closer look at the 3 studies that performed invasive measurements reinforces our findings. If we consider those studies$^{5,10,11}$ and the current definition of PH (mean pulmonary artery pressure $\geq 25$ mm Hg)$^{18}$, the incidence of PH varies from 6.3% to 13.5% in patients with hepatosplenic schistosomiasis, which is in complete accordance with our results.

Our study further allowed the determination of PAH in the setting of schistosomiasis hepatosplenic disease. These numbers reflect the impact of this diagnosis in the setting of PH, particularly in endemic areas; a recent study demonstrated that PH associated with schistosomiasis may represent up to 30% of PH patients followed up at reference centers in Brazil.$^6$ Moreover, our data support the assumption that PAH associated with schistosomiasis may represent the most prevalent cause of PAH.

The prevalence of hepatosplenic disease in schistosomiasis is variable; it varies between 4% and 8% but can be much higher in highly endemic areas.$^{19}$ Of the 200 million people infected, $\approx 120$ million may develop symptomatic schistosomiasis$^2$; if 5% of these individuals develop hepatosplenic disease, the extrapolation of our data would result in
>270 000 patients with PAH globally distributed. These numbers reveal the potential magnitude of the disease, particularly if faced with the 15 to 52 cases per 1 million prevalence of PAH recently described in the Western world (French national registry\textsuperscript{20} and Scottish data\textsuperscript{21}). Our results also reinforce the concept that specific PAH causes may have a significant role in developing countries.\textsuperscript{15} Together with schistosomiasis, other diseases presenting at the same significant prevalence of PH such as sickle cell disease\textsuperscript{22} or HIV infection\textsuperscript{23} that are highly prevalent in developing countries raise the need for different approaches for PH according to specific regional characteristics.

Although schistosomiasis is still among the most prevalent infectious diseases worldwide, according to the World Health Organization, severe cases of the disease have become gradually less common since the population-control initiative programs and mass drug administration in many countries such as in Brazil in the 1980s. An analysis of the impact of the Schistosomiasis Control Programme in Brazil is given by Amaral et al.\textsuperscript{24} Such approaches may have decreased the burden of hepatoplenic disease and PH, even considering the variable responses to antiparasitic treatment\textsuperscript{25} and the latency that would be expected, specifically in the setting of PH.

An interesting approach has been taken by the World Health Organization Global Alliance Against Chronic Respiratory Diseases, a voluntary alliance of internationally recognized organizations from developing and developed countries aiming to reduce the burden of chronic respiratory diseases.\textsuperscript{26} The alliance works by improving the awareness, diagnosis, prevention, and treatment of several respiratory conditions, specifically in developing countries. With regard to PH, this approach should help to decrease the burden of the condition that is currently either ignored or recognized too late in these countries.

The pathophysiology of PH associated with schistosomiasis is matter of debate. As a consequence of the portal flow, the eggs of Schistosoma may implant in the venules of the liver, leading to granuloma formation and periportal fibrosis with subsequent portal hypertension. In the presence of portal hypertension, portacaval shunts become patent, and the eggs flow to the lung capillaries, where they lodge. The pivotal work of Shaw and Ghareeb\textsuperscript{6} emphasized the mechanical role of the ova in causing vascular obstruction. However, later studies provided evidence that mechanical obstruction was not the only factor related to the development of PH, suggesting that inflammation and an imbalance of substances involved in the control of vascular tonus (called “vasospastic factors” at that time) had a significant role in the genesis of the vasculopathy.\textsuperscript{27–31} Preliminary results of an ongoing study comparing the lung specimens from necropsies of patients with idiopathic PAH and schistosomiasis PH support that the spectrum of vascular lesions found in schistosomiasis is not related to the presence of eggs or granuloma and may be indistinguishable from those found in idiopathic PAH.\textsuperscript{32}

The clinical presentation of these patients is indistinguishable from that of idiopathic PAH patients.\textsuperscript{6} The radiological features suggest an insidious process with remarkable dilatations of the pulmonary arteries.\textsuperscript{6} In terms of hemodynamic pattern at diagnosis, a recent study comparing consecutive newly diagnosed patients with schistosomiasis-related PAH (n = 38) and idiopathic PAH (n = 63) from the same period of time showed that schistosomiasis patients presented with a more preserved hemodynamic profile at diagnosis.\textsuperscript{33} These data, together with the prevalence described in our study, point to the need for specific diagnostic approaches for hepatoplenic schistosomiasis in areas where the disease is highly prevalent.

Our study also strengthens the role of Doppler echocardiography as a screening tool. In a manner similar to what has been demonstrated in other diseases such as scleroderma\textsuperscript{14} or HIV infection,\textsuperscript{23} the prevalence of echocardiographic PH, defined by the presence of a SPAP >40 mm Hg, is much higher than the real prevalence of PH as measured by invasive hemodynamic measurements. This finding is of singular importance, particularly for the development of public health policies for the control and/or treatment of PH. These policies should be established according to proper prevalence data; in this regard, echocardiographic studies have a major role for the indication of right heart catheterization, still the gold standard for the diagnosis of PH. Moreover, as previously demonstrated in systemic sclerosis\textsuperscript{34} and sickle cell disease,\textsuperscript{35} pulmonary artery pressure elevation in schistosomiasis patients may correspond to the presence of precapillary or postcapillary PH, which should benefit from distinct therapeutic approaches; thus, any novel treatment strategy tested in such populations will require mandatory right heart catheterization to properly define PAH and to exclude postcapillary disease.

The response of PAH associated with schistosomiasis to specific PAH treatment is still a matter of study. Preliminary reports have shown an improvement in right ventricular evaluation, assessed by magnetic resonance imaging with the use of sildenafil.\textsuperscript{36} In addition, the same hemodynamic and 6-minute walk test worsening with the use of β-blockers, as recently described in portopulmonary hypertension of different origins,\textsuperscript{37} has previously been demonstrated in schistosomiasis patients.\textsuperscript{38} Our finding of a high prevalence of PH in schistosomiasis patients may indicate the need for a review of current recommendations to decrease the portal pressure of patients with esophageal varices through nonselective β-blocker therapy in this subset of patients with both portal hypertension and PH.\textsuperscript{39,40}

Antiparasitic treatment is not believed to have a significant effect on the pulmonary hemodynamics, which is different from what happens to the liver, in regard to the regression of hepatosplenomegaly and fibrosis,\textsuperscript{8} although a case report in which antiparasitic treatment demonstrated a direct effect on the pulmonary hemodynamics has been published.\textsuperscript{41} All patients included in this series received specific antiparasitic treatment before the enrollment in the study, preventing any further speculation about its effectiveness in PH.

Our study has limitations that need to be acknowledged. Indeed, the study sample is small and composed of patients referred to a tertiary care hospital in a nonendemic area of schistosomiasis in Brazil. We therefore acknowledge that this sample may not be representative of the actual prevalence of PH in infected patients from an endemic area, which should be the focus of further studies using similar approaches based on noninvasive screening and invasive confirmation of PH.
Although our 95% CIs are large, they indicate that PH in the setting of hepatosplenic schistosomiasis is sufficiently high to allow the assumption that it is one of the most prevalent causes of PAH worldwide. These data highlight the need for clinical trials assessing the safety and efficacy of specific therapeutic regimens in this clinical condition.

Conclusions

We conclude that the prevalence of PH and, particularly, PAH in hepatosplenic schistosomiasis is sufficiently high to allow the assumption that it is one of the most prevalent causes of PAH worldwide. These data highlight the need for clinical trials assessing the safety and efficacy of specific therapeutic regimens in this clinical condition.

Disclosures

None.

References


**CLINICAL PERSPECTIVE**

This is the first study to prospectively evaluate patients with the stringent diagnosis of hepatosplenic schistosomiasis, a highly prevalent condition in the developing world, for the presence of pulmonary hypertension. Our findings showed that hepatosplenic schistosomiasis may account for one of the most prevalent forms of pulmonary hypertension worldwide; moreover, in this setting, pulmonary hypertension may be related to precapillary or postcapillary mechanisms, strengthening the importance of invasive hemodynamic measurements for the proper diagnosis. Awareness of this form of pulmonary hypertension should be reinforced, and suggested diagnostic algorithms should be adapted, primarily in areas where schistosomiasis is prevalent. Our data also point to the need for further studies to evaluate the safety and efficacy of specific pulmonary hypertension treatment in this particular form of the disease.