Schistosomiasis Heart Disease

Survival in Schistosomiasis-Associated Pulmonary Arterial Hypertension

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Objectives
The objective of this study was to evaluate the natural history of untreated schistosomiasis-associated pulmonary arterial hypertension (Sch-PAH) patients as compared to idiopathic pulmonary arterial hypertension (IPAH) with respect to hemodynamics recorded at presentation and 36 months survival.

Background
Schistosomiasis (Sch) is one of the most prevalent chronic infectious diseases in the world. Nevertheless data regarding one of its most severe clinical complications, pulmonary arterial hypertension (PAH), is scarce.

Methods
We retrospectively analyzed case notes of all consecutive patients diagnosed of Sch-PAH and IPAH referred to the Heart Institute in São Paulo, Brazil, between 2004 and 2008. None of the Sch-PAH received PAH specific treatment whereas all IPAH patients did.

Results
Sch-PH patients (n = 54) had less severe pulmonary hypertension as evidenced by lower levels of pulmonary vascular resistance (11.3 ± 11.3 W vs. 16.7 ± 10.6 W; p = 0.002) and mean pulmonary artery pressure (56.7 ± 18.7 mm Hg vs. 64.6 ± 17.4 mm Hg; p = 0.01) and higher cardiac output (4.62 ± 1.5 l/min vs. 3.87 ± 1.5 l/min; p = 0.009) at presentation than IPAH patients (n = 95). None of the Sch-PAH patients demonstrated a positive response to acute vasodilator testing, whereas 16.2% of IPAH patients did (p = 0.015). Survival rates at 1, 2, and 3 years were 95.1%, 95.1%, and 85.9% and 95%, 86%, and 82%, for Sch-PAH and IPAH, respectively (p = 0.49). Both groups had a higher survival rate when compared to IPAH survival as estimated by the NIH equation (71%, 61%, and 52%, respectively).

Conclusions
Sch-PAH has a more benign clinical course than IPAH despite a lack of demonstrable acute vasoreactivity at hemodynamic evaluation. (J Am Coll Cardiol 2010;56:715–20) © 2010 by the American College of Cardiology Foundation

Pulmonary arterial hypertension (PAH) is a life-threatening disease that may occur either in idiopathic form or in the setting of different associated medical conditions. PAH is characterized by a marked and sustained elevation of pulmonary vascular resistance (PVR), leading to an increase in pulmonary artery pressure, right ventricular failure, and ultimately death (1).

Considerable advances in our understanding of the pathogenesis and therapeutic approaches of PAH have been gained in recent years, based mainly on studies involving patients with idiopathic pulmonary arterial hypertension (IPAH) or connective tissue diseases associated with PAH (2,3). Nevertheless, there is an increasing awareness of the burden posed by PAH resulting from other causes, such as sickle cell disease, HIV, and schistosomiasis. As a result, studies addressing the clinicopathologic characteristics and outcomes of patients with these forms of the disease are beginning to emerge (4,5).

Schistosomiasis is an infectious disease caused by parasitic trematode worms that is strongly linked to poverty and lack of basic sanitation (6). The 3 main pathogenic species are Schistosoma mansoni, Schistosoma haematobium, and Schisto soma japonicum, each of which has a characteristic geographical distribution (7,8). Because of migratory practices, however, schistosomiasis prevalence is also increasing in nonendemic regions. According to the Center for Disease Control and Prevalence and the International Society of Travel Medicine database—GeoSentinel—schistosomiasis is also one of the 10 leading causes of morbidity among

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Of the following features: 1) exposure to endemic region for schistosomiasis; 2) previous treatment for schistosomiasis; and 3) presence of *Schistosoma mansoni* eggs in stool examination or rectal biopsy. All patients included in the study were referred to our center by primary or secondary care medical facilities for evaluation of dyspnea, of elevated pulmonary artery pressures as estimated by echocardiography, or both. In most cases, the diagnosis of schistosomiasis was established at our center after specific investigation and using the aforementioned criteria.

**Functional and hemodynamic evaluations.** Baseline evaluation included demographics, medical history, physical examination, New York Heart Association functional class assessment, routine laboratory testing, a nonencouraged 6-min walk test (6MWT) as previously described (15), and right heart catheterization using standard techniques. Acute vasodilator responsiveness was evaluated using inhaled nitric oxide for 10 min, as previously described (16). A positive response to acute vasodilator testing was defined as a fall in mPAP of 10 mm Hg or more to a value of 40 mm Hg or less with a normal or increased cardiac output (17).

**Treatment of pulmonary hypertension.** All patients were treated with conventional supportive therapies, including oral anticoagulation in the absence of any contraindication (e.g., high risk of gastrointestinal bleeding), diuretics, and oxygen as needed. IPAH patients received PAH-specific therapy based on guideline recommendations (18) and drug availability in our center. Patients in New York Heart Association functional class III or IV received first-line therapy with either an endothelin-receptor antagonist or phosphodiesterase type 5 inhibitor. Some patients in New York Heart Association functional class IV who had progressive disease and worsening of symptoms received combination therapy with agents from both classes of drug.

Sch-PAH patients did not receive any PAH-specific therapy as a routine because, in our country, specific PAH treatments are authorized only for IPAH, connective tissue disease related PAH, and PAH related to congenital heart disease. Two patients received off-label specific PAH therapy after 2 and 7 months of follow-up because of progressive right heart failure. These patients were censored at the time of treatment initiation. All Sch-PAH patients received adequate antiparasitic treatment before enrollment in the study.

**Statistical analysis.** Analysis was performed using the SPSS version 10 (SPSS, Inc., Chicago, Illinois). All continuous variables are expressed as mean ± SD and categorical data are presented as proportions. For comparison of the baseline characteristics between IPAH and Sch-PAH patients, an unpaired *t* test or chi-square test was used, as appropriate. A *p* value <0.05 was considered statistically significant.

For the survival analysis, the first hemodynamic evaluation was considered to be the date of diagnosis, and the cutoff date was June 2008. All-cause mortality was used
because of the lack of information about the specific cause of death in several cases. No patients were lost to follow-up during the study period. Three-year survival was estimated using the Kaplan-Meier method. The log-rank test was used for curve comparison. Univariate analysis based on the proportional hazards model was used to examine the relationship between survival and selected baseline demographic, functional, and hemodynamic variables. Results are expressed as hazard ratios with 95% confidence intervals. Bivariate analysis was used to examine the independent effect on survival of diagnosis, controlling for hemodynamic variables.

**Results**

**Baseline data.** The study population comprised 95 IPAH and 54 Sch-PAH patients. Baseline clinical, functional, and hemodynamic data are shown in Table 1. Patients with Sch-PAH were older at diagnosis with no difference regarding body mass index, gender distribution, New York Heart Association functional class, or 6MWT results. Sch-PAH patients had a less severe hemodynamic profile at diagnosis, with lower PVR and mPAP and higher cardiac output. No differences were found in right atrial pressure or in PAOP values between the 2 groups. None of the Sch-PAH patients demonstrated an acute response to vasodilator challenge, whereas 16.2% of IPAH patients did (p = 0.015).

**First-line specific IPAH treatment.** IPAH patients predominantly were treated with endothelin receptors antagonists: 53.7% (n = 51). Phosphodiesterase-5 inhibitors were used in 25.2% (n = 24), and combination therapy was used in 14.7% of IPAH patients (n = 14). Six IPAH patients (6.3%) received only conventional supportive therapy and high-dose calcium-channel blockers.

**Survival analysis.** Overall survival rates at 1, 2, and 3 years were 95.1%, 95.1%, 85.9%, respectively, for naive Sch-PAH patients and 95%, 86%, and 82%, respectively, for treated IPAH patients (Fig. 1). No significant differences in the survival rates were observed in untreated Sch-PAH patients as compared with treated IPAH patients (p = 0.49). Nevertheless, both groups had a higher survival rate when compared with survival estimated by the NIH equation in the IPAH group (red line; survival rates estimated at 71%, 61%, and 52%).

The results of univariate analysis for the overall population are shown in Table 2. The presence of high mPAP and PVR, New York Heart Association functional class IV, or low 6MWT were associated with a worse outcome. To evaluate the direct effect of diagnosis on survival, a bivariate model that incorporated diagnosis and PVR (mean values of which were significantly different between the groups at baseline) was built; PVR emerged as an independent prognostic factor, whereas diagnosis had no effect on survival (Table 3).

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**Table 1** Baseline Clinical Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IPAH Patients (n = 95)</th>
<th>Sch-PAH Patients (n = 54)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>42 ± 12.8</td>
<td>47 ± 12.5</td>
<td>0.03*</td>
</tr>
<tr>
<td>Gender (male-to-female)</td>
<td>1.33</td>
<td>1.24</td>
<td>0.43</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>I/II</td>
<td>25 (26.6%)</td>
<td>22 (44%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>54 (57.4%)</td>
<td>22 (44%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>15 (16%)</td>
<td>6 (12%)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25 ± 5</td>
<td>27 ± 7</td>
<td>0.16</td>
</tr>
<tr>
<td>6MWT hemodynamics (m)</td>
<td>412 ± 115</td>
<td>442 ± 99</td>
<td>0.20</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>11.7 ± 7.2</td>
<td>10.1 ± 4.7</td>
<td>0.18</td>
</tr>
<tr>
<td>mPAP (mm Hg)</td>
<td>64.6 ± 17.4</td>
<td>56.7 ± 18.7</td>
<td>0.01*</td>
</tr>
<tr>
<td>CO (/min)</td>
<td>3.87 ± 1.5</td>
<td>4.62 ± 1.5</td>
<td>0.009†</td>
</tr>
<tr>
<td>PAOP (mm Hg)</td>
<td>11.3 ± 3.4</td>
<td>11.2 ± 3.2</td>
<td>0.81</td>
</tr>
<tr>
<td>PVR (IU)</td>
<td>16.7 ± 10.6</td>
<td>11.3 ± 6.4</td>
<td>0.002†</td>
</tr>
<tr>
<td>Positive response to</td>
<td>16.2%</td>
<td>0</td>
<td>0.015*</td>
</tr>
<tr>
<td>vasodilator test (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-line treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERA</td>
<td>51 (53.7%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PDE-5 inhibitor</td>
<td>24 (25.2%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Combined therapy</td>
<td>14 (14.7%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>6 (6.3%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05, †p < 0.01.

CO = cardiac output; ERA = endothelin receptor antagonists; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; NYHA = New York Heart Association; PAOP = pulmonary artery occlusion pressure; PDE-5 = phosphodiesterase 5 inhibitor; PVR = pulmonary vascular resistance; RAP = right atrial pressure; Sch-PAH = schistosomiasis-associated pulmonary arterial hypertension; 6MWT = length in nonencouraged 6-minute walk test.
The present study analyzed the outcomes of a cohort of Sch-PAH patients compared with those of a cohort of IPAH patients treated with locally available specific treatments. Our results showed that Sch-PAH has a more favorable hemodynamic profile at diagnosis and a more benign clinical course, even in the absence of specific PAH treatment. To the best of our knowledge, this is the first time that such an observation has been reported.

Sch-PAH may be one of the main causes of PAH in the world. Although the World Health Organization estimates that there are approximately 200,000 patients worldwide with IPAH (19), the United Nations Children’s Fund estimates that 8.5 million people have *Schistosoma mansoni*-associated hepatopulmonary disease (6). Extrapolating the data from a recent prevalence study (5), there may be as many as 425,000 patients with Sch-PAH worldwide, the vast majority of whom are in developing countries. However, most cases remain undiagnosed. Why patients with Sch-PAH seem to have a more benign clinical course (3-year mortality rate of 14.1%) compared with other forms of PAH is unclear. Infection with schistosomiasis is considered endemic in Brazil, and the ratio of Sch-PAH to IPAH patients attending our service (which is a national pulmonary hypertension reference center) is approximately 0.57 to 1. Thus, Sch-PAH accounts for a greater proportion of total PAH cases at our center when compared with recently reported estimates in other national or regional registries (20,21). This fact clearly underscores the need to develop treatment policies for rare diseases based on unique regional PAH profiles (10).

Diagnosis of schistosomiasis is based on the identification of the parasites’ eggs in stool examination or rectal biopsy in individuals at risk of infection based on geographical location. Nevertheless, the absence of viable eggs does not exclude the diagnosis. Abdominal ultrasonographic findings of left lobe of liver enlargement or periportal fibrosis also may suggest the diagnosis of schistosomiasis in patients coming from endemic areas. However, the disease can develop even in the absence of manifest liver involvement. As a result, distinguishing Sch-PAH from IPAH in individuals from regions in which schistosomiasis is endemic can be challenging if there is no evidence of hepatoplastic involvement. Furthermore, lung biopsy is neither sensitive nor specific enough to establish the diagnosis (22). Thus, the presence of hepatoplastic alterations is a marker of chronic disease that raises the association between schistosomiasis and the presence of pulmonary hypertension. Serology testing (by means of the enzyme-linked immunosorbent assay technique) also is useful to identify individuals with prior exposure to different forms of schistosomiasis. However, the usefulness of this approach may be limited to assessment of patients from nonendemic areas of the disease, because massive population exposure to schistosomiasis lowers its value as a marker of disease in regions of high prevalence.

Our results revealed a nonsignificant trend for better functional and exercise capacity and less severe hemodynamic compromise at diagnosis for Sch-PAH patients as compared with IPAH patients. However, the low number of events in the Sch-PAH group did not allow the analysis of functional class and 6MWT as prognostic markers in this population. Thus, these surrogate markers remain to be validated before they can be used as end points in Sch-PAH, as is the case in IPAH (23).

Since the first case series description of invasively diagnosed pulmonary hypertension (PH) associated with schistosomiasis nearly 50 years ago (24), considerable advances have been made in the understanding of the hemodynamic characteristics of this unique patient population, as reflected in the recently updated PH clinical classification (25). It is interesting to note that a preserved cardiac output at presentation is typical, even in the presence of high pulmonary pressure levels (24). Lack of data regarding PAOP prevented the differentiation between precapillary and postcapillary PH in both early (24,26) and more recent (27) studies. Nonetheless, postcapillary PH is clearly an important cause of PH in schistosomiasis, as demonstrated by a study by Vargas et al. (28). These observations highlight the importance of invasive hemodynamic measurements for accurate diagnosis (29) of Sch-PAH. Indeed, in the current study, only patients with normal PAOP were included to ensure a homogeneous group of Sch-PAH patients.

Our study is the first to confirm the lack of acute response to vasodilator testing among Sch-PAH patients. In contrast, 16.2% of IPAH patients demonstrated an acute response to inhaled nitric oxide, which is comparable with

### Table 2: Univariate Cox Proportional-Hazards Analysis of Selected Baseline Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>0.962 (0.922–1.004)</td>
<td>0.075</td>
</tr>
<tr>
<td>Diagnosis (Sch-PAH vs. IPAH)</td>
<td>0.676 (0.218–2.099)</td>
<td>0.498</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>0.117</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>3.363 (0.737–15.355)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>6.312 (1.153–34.554)</td>
<td></td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>0.991 (0.986–0.997)</td>
<td>0.001*</td>
</tr>
<tr>
<td>mPAP (mm Hg)</td>
<td>1.048 (1.018–1.079)</td>
<td>0.002*</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>0.835 (0.546–1.275)</td>
<td>0.403</td>
</tr>
<tr>
<td>PVR (IU)</td>
<td>1.081 (1.035–1.129)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*CI = confidence interval; PVR = pulmonary vascular resistance; other abbreviations as in Table 1.

### Table 3: Bivariate Proportional-Hazards Analysis of Selected Baseline Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis (Sch-PAH vs. IPAH)</td>
<td>1.160 (0.287–4.683)</td>
<td>0.835</td>
</tr>
<tr>
<td>PVR</td>
<td>1.083 (1.033–1.134)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*p < 0.01.

Abbreviations as in Tables 1 and 2.
previously published data (17). Previous investigators have speculated that Sch-PAH simply may represent another form of portopulmonary hypertension without coexistent liver failure (30). Le Pavec et al. (31) recently reported results from a case-control study of portopulmonary hypertension and, similarly, did not identify any acute responders to acute vasodilator challenge. In that study, the survival rates observed among patients with portopulmonary hypertension without cirrhosis were similar to those found in our study, strengthening the hypothesis that Sch-PAH and noncirrhotic portopulmonary hypertension may share some pathophysiologic mechanisms. Several processes may contribute to the development of Sch-PAH, including the mechanical impact Schistosoma eggs within the pulmonary vessels (32), inflammation within the lung vasculature (33), and an increase in pulmonary blood flow that develops as a consequence of arteriovenous shunts characteristic of portal hypertension (34).

Survival analysis did not show any difference between untreated Sch-PAH and treated IPAH populations. Nevertheless, there was a significant difference in baseline hemodynamics between the 2 groups that could have influenced the survival analysis significantly. To account for the possible effect of baseline hemodynamics on Sch-PAH survival, a bivariate model was built that incorporated diagnosis and PVR, because the later represents a compromise between the vascular pressure levels and cardiac function and was found to be significant by univariate analysis. A multivariate model could not be constructed because of the limited number of events in the cohort as a whole, which may have driven to an overfitted model. The results from the bivariate model suggested that the diagnosis of Sch-PAH had no significant effect on survival, even accounting for hemodynamics at baseline. Indeed, the survival of untreated Sch-PAH patients was no different from that of IPAH patients receiving specific PAH therapy, suggesting the former population had a more benign clinical course. The suggestion of an improved survival among our Sch-PAH cohort is supported further when predicted IPAH survival (as estimated by the NIH equation) is calculated (12). The favorable results revealed in our study, however, do not preclude the need for studies that specifically address the impact of specific PAH therapy in Sch-PAH patients, given the substantial 3-year 14.1% mortality rate we observed in this group.

Our results have to be interpreted in the light of some limitations imposed by the study design. Recently reported data regarding survival in IPAH in a large, multicenter, prospective cohort revealed a significantly lower survival rate at 3 years than was the case in our cohort (35). Our study was performed in a single tertiary center, with a retrospective analysis of prevalent and incident cases. As a consequence, survival rates might have been overestimated.

Evidence to support the use of specific PAH treatment for Sch-PAH patients remains scarce in the literature. Cases of favorable responses with the use of sildenafil have been reported (36). However, there is a lack of compelling data from randomized controlled trials in support of this strategy. There is also lack of data regarding the effect of antiparasitic treatment on pulmonary arteriopathy. In schistosomiasis-associated hepatosplenic disease, the effect of antiparasitic treatment is greatly variable, ranging from complete resolution of portal fibrosis to no response (37). Although antiparasitic treatment is not believed to have a significant effect over the pulmonary circulation, at least one case report has been published showing significant improvement in pulmonary hemodynamics after treatment for Schistosoma haematobium (38). Nevertheless, all of our Sch-PAH patients received adequate treatment for Schistosoma mansoni before study enrollment.

Study limitations. Our study has some limitations that need to be acknowledged. The monocentric nature of the study and the fact that our center is located in a nonendemic region of schistosomiasis infection may account for some degree of selection bias. However, we believe that our status as one of the largest reference centers in Brazil for both PAH and schistosomiasis-related hepatosplenic disease lessens the potential impact of this limitation. The comparison of Sch-PAH with IPAH is useful to understand better the respective clinical courses, because both groups simultaneously were followed concomitantly. However, a historical group of naïve IPAH patients would help to understand better any differences in disease progression that may exist between IPAH and Sch-PAH.

Conclusions

We conclude that Sch-PAH, which may represent one of the most prevalent forms of PAH, has a better hemodynamic profile at diagnosis and a more benign clinical course as compared with IPAH, even in the absence of acute response at the vasodilator challenge during hemodynamic evaluation. Nevertheless, the 3-year mortality found in our study population underscores the need for additional studies to establish formally the impact of specific PAH therapies in Sch-PAH patients.

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REFERENCES


Key Words: schistosomiasis • pulmonary hypertension • survival.