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, leading to an increase in pulmonary artery pressure, right ventricular failure, and ultimately death. Nevertheless, despite its severity, in the last 20 years advances in the therapeutic management of the disease have changed the natural history of PAH. In modern days, patients with idiopathic pulmonary arterial hypertension (IPAH), connective tissue disease-associated PAH, or congenital heart disease-associated PAH benefit from prostanoids, endothelin receptor antagonists (ERAs), and phosphodiesterase-5 inhibitors, improving clinical and hemodynamic function as well as quality of life and even survival. Other etiologies in group 1 of the pulmonary hypertension classification also have demonstrated some benefit with specific PAH treatment. However, there is no evidence in medical literature about clinical efficacy of specific PAH treatment for one of the pivotal causes of PAH, the disease associated with schistosomiasis.

**Background:** Schistosomiasis-associated pulmonary arterial hypertension (Sch-PAH) may be one of the most prevalent forms of pulmonary arterial hypertension (PAH) worldwide. However, the clinical and hemodynamical response to specific PAH therapy in Sch-PAH is not known.

**Methods:** We retrospectively analyzed the charts of all patients with Sch-PAH who initiated specific PAH treatment between June 2003 and June 2010 in a single PAH reference center in São Paulo, Brazil. Clinical and hemodynamical data were retrospectively collected and evaluated in two periods: baseline and posttreatment.

**Results:** The study population consisted of 12 patients with Sch-PAH. They were treated with phosphodiesterase-5 inhibitors (seven patients), endothelin receptor antagonists (four patients), or combination therapy (one patient). Mean treatment period was 34.9±15.5 months. Patients with Sch-PAH presented significant improvements in terms of functional class, 6-min walk test distance (439±85 to 492±79 m, P=.032), cardiac index (2.66±0.59 to 3.08±0.68 L/min/m², P=.028), and indexed pulmonary vascular resistance (20.7±11.6 to 15.9±9 W/m², P=.038) with the introduction of specific PAH treatment.

**Conclusions:** We conclude that specific PAH therapy may be of benefit to patients with Sch-PAH, considering clinical, functional, and hemodynamic parameters.
In the setting of pulmonary hypertension, the relevance of schistosomiasis-associated PAH (Sch-PAH) has been better recognized in recent years. It is believed that approximately 5% of patients diagnosed with hepatosplenic Schistosomiasis mansoni may also present themselves with PAH, suggesting that Sch-PAH is potentially the most prevalent cause of PAH worldwide. Its importance might be even greater in endemic regions for schistosomiasis. Indeed, it is estimated that up to 30% of all pulmonary hypertension patients followed at reference centers in Brazil have Sch-PAH. In the updated classification of PAH, following the better understanding of the mechanisms involved in Sch-PAH as well as its hemodynamic features, Sch-PAH has been reclassified within group 1 (PAH), the group that generates the biggest interest in the area, as well as the most researched of all five groups.

Mortality rates associated with Sch-PAH were recently described in a Brazilian cohort and may reach up to 15% in 3 years. Despite being less severe than IPAH, Sch-PAH affects a young population (between the fourth and fifth decades of life), and its described prognosis justifies the need of specific therapies for this setting. Nevertheless, no information about the hemodynamic and/or clinical response to target PAH therapies in Sch-PAH is available. The objective of this study was to evaluate the clinical, functional, and hemodynamic responses of patients with Sch-PAH followed at a PAH reference center in Brazil who received specific PAH treatment.

**Materials and Methods**

**Patient Population**

All patients with Sch-PAH who initiated specific PAH treatment between June 2003 and June 2010 in a single PAH reference center in São Paulo, Brazil, were included in this study. The study was approved by the ethics board of the institution, approval 1359/06. Clinical and hemodynamic data were retrospectively collected.

PAH was defined by a mean pulmonary artery pressure (mPAP) > 25 mm Hg with a normal pulmonary artery occlusion pressure < 15 mm Hg. Patients were classified as having Sch-PAH when the presence of PAH was associated with liver ultrasonographic findings highly suggestive of mansonic schistosomiasis (left lobe enlargement and/or periportal fibrosis) and at least one of the following features: (1) exposure to endemic region for schistosomiasis, (2) previous treatment of schistosomiasis, and (3) presence of S mansoni eggs in stool examination or rectal biopsy.

**Functional and Hemodynamic Evaluations**

Baseline evaluation included demographics, medical history, physical examination, New York Heart Association (NYHA) functional class assessment, routine laboratory testing, a nonencouraged 6-min walk test (6MWT), as previously described, and right-sided heart catheterization using standard techniques. Both clinical and hemodynamic reevaluation were performed in all patients at different follow-up intervals as dictated by the patient clinical status.

**Treatment**

In the absence of any contraindication (eg, high risk of gastrointestinal bleeding or presence of esophageal varices), patients received oral anticoagulation; diuretics and oxygen were prescribed as needed during the whole observational period. Patients with Sch-PAH do not receive PAH-specific therapy as a routine in our center due to the absence of controlled clinical data supporting this indication. Also, in Brazil specific PAH treatments are systematically available only for IPAH, connective tissue disease-related PAH, and PAH related to congenital heart disease. Nevertheless, all patients enrolled in this study received specific PAH treatment as rescue therapy due to progressive right ventricular dysfunction, following current recommendations for IPAH as a guideline. Patients in functional class III or IV received first-line therapy with either an ERA or a phosphodiesterase-5 inhibitor. The choice between the agents was based merely on drug availability. One patient presenting in NYHA functional class IV with rapidly progressive disease and worsening symptoms received combination therapy with agents from both classes as first-line therapy.

**Statistical Analysis**

Analysis was performed using the SPSS 15 statistical package (SPSS, Inc). All continuous variables are expressed as mean ± SD; categorical data are presented as proportions. For comparison between baseline and posttreatment clinical and hemodynamic characteristics, a paired t test was used. A P value < .05 was considered statistically significant.

**Results**

The study population consisted of 12 patients with Sch-PAH. All patients had endemic exposure to schistosomiasis and highly suggestive liver ultrasonographic findings; additionally, four patients examined also had positive stool at the time of diagnostic investigation. Specific treatment was predominantly based on use of phosphodiesterase-5 inhibitors (n = 7, 58.3%). ERAs were used in four patients (33.3%) and first-line combination therapy in one patient (8.4%).

Baseline and posttreatment clinical, functional, and hemodynamic data are shown in Table 1 and Figure 1. The mean period of treatment between baseline and posttreatment evaluations was 34.9 ± 15.5 months. The majority of patients with Sch-PAH improved functional class with the introduction of specific PAH treatment (nine of 12 patients) (Fig 1A). 6MWT distance (Fig 1B), cardiac index, and indexed pulmonary vascular resistance (Table 1) also improved with the therapy. No difference was found in mean pulmonary arterial pressure (mPAP) as a consequence of treatment.

**Discussion**

The present study demonstrated that patients with Sch-PAH may have significant clinical, functional, and
empirically use already available classes of medications for PAH to these patients, provided that they also present themselves with dyspnea on exertion and/or symptoms of right ventricular insufficiency. However, there are significant differences between IPAH and Sch-PAH: The hemodynamic profile at diagnosis is markedly better in Sch-PAH, as compared with IPAH and survival in Sch-PAH seems to be better that in other PAH forms. These findings need to be accounted for when designing appropriate controlled studies in this specific subset of patients.

Considering the high prevalence of schistosomiasis worldwide (200 million patients, 8.5 million with hepatosplenic disease,\textsuperscript{22} potentially more than 400,000 patients with Sch-PAH\textsuperscript{16}) when compared with the other relatively rare etiologies of PAH, including IPAH (about 170,000 patients worldwide\textsuperscript{25}), the 15% 3-year mortality described in Sch-PAH\textsuperscript{13} is of absolute relevance. Moreover, although Sch-PAH seems to have a slower progression, eventually patients deteriorate in a similar fashion to IPAH. Thus, one might speculate that specific PAH therapy to Sch-PAH may obey the same general principles of IPAH treatment.\textsuperscript{17}

Additionally, the magnitude of response to specific PAH therapy found in patients with Sch-PAH in this study is encouraging. Despite the long time interval between evaluations, an increase of 16% in CI was observed. In the same direction, the 6MWT increased by 12%, and most patients improved the functional class. Even after 35 months, patients with Sch-PAH still demonstrated clear signs of clinical and hemodynamic improvement.

There are several proposed mechanisms of disease for Sch-PAH: (1) embolic disease by egg impact in the pulmonary circulation and mechanical obstruction\textsuperscript{26}; (2) passage of the worm or the egg by the lungs, inducing endothelial dysfunction by inflammatory mediator release and abnormal scarring\textsuperscript{27,28}; and (3) like portopulmonary hypertension (PoPH), the pulmonary overflow caused by the opening of portocaval shunts in the presence of portal hypertension induces endothelial dysfunction and PAH.\textsuperscript{29} Based on the last mechanism, it is tempting to correlate the known benefits of the specific PAH therapy in the setting of PoPH\textsuperscript{6} to Sch-PAH. Nevertheless, it is clear today that PoPH and Sch-PAH are not the same disease; while 1% to 2% of portal hypertension patients develop PAH,\textsuperscript{30} approximately 5% of schistosomotic hepatosplenic patients present PAH,\textsuperscript{10} suggesting that different mechanisms might be involved in PAH genesis. A published cohort of PoPH patients showed that the outcome of these patients is influenced by the degree of liver insufficiency and by cardiac function,\textsuperscript{31} but it is important to emphasize that patients with Sch-PAH do not routinely present

Table 1—Clinical and Hemodynamical Data at Baseline and Post-Specific PAH Treatment for Patients With Sch-PAH (N = 12)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Posttreatment</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>46.2 ± 9.8</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>5 (41.6)</td>
<td>.002</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>5 (41.6)</td>
<td>...</td>
</tr>
<tr>
<td>III</td>
<td>9 (75)</td>
<td>2 (16.8)</td>
<td>...</td>
</tr>
<tr>
<td>IV</td>
<td>3 (25)</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>6MWT, m</td>
<td>439 ± 85</td>
<td>492 ± 79</td>
<td>.032</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAP, mmHg</td>
<td>11.0 ± 5.9</td>
<td>10.8 ± 3.8</td>
<td>.65</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>64.0 ± 19.1</td>
<td>58.7 ± 17.1</td>
<td>.13</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>2.7 ± 0.6</td>
<td>3.1 ± 0.7</td>
<td>.028</td>
</tr>
<tr>
<td>PAOP, mmHg</td>
<td>12.1 ± 3</td>
<td>13.7 ± 4.4</td>
<td>.24</td>
</tr>
<tr>
<td>PVR, International Units</td>
<td>12 ± 6.5</td>
<td>9.1 ± 4.8</td>
<td>.038</td>
</tr>
<tr>
<td>First-line treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDE-5 inhibitor</td>
<td>0</td>
<td>7 (58.3)</td>
<td>...</td>
</tr>
<tr>
<td>ERA</td>
<td>0</td>
<td>4 (33.3)</td>
<td>...</td>
</tr>
<tr>
<td>Combined therapy</td>
<td>0</td>
<td>1 (8.4)</td>
<td>...</td>
</tr>
</tbody>
</table>

Data are given as mean ± SD or No. (%). Mean period between evaluations: 34.9 ± 15.5 mo. 6MWT = distance on nonencouraged 6-min walk test; CI = cardiac index; ERA = endothelin receptor antagonist; mPAP = mean pulmonary artery pressure; 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.
liver dysfunction in association with portal hypertension. Nonetheless, data regarding use of specific PAH therapy in patients with PoPH, as in patients with IPAH, should not be directly extrapolated to other groups such as Sch-PAH.

When the data of patients with Sch-PAH is analyzed considering previous information obtained in patients with IPAH, some issues may be noted. Three patients with Sch-PAH had functional class IV at diagnosis while the others had functional class III. However, this does not match with a quite high baseline walking distance (440 m). This kind of discrepancy between functional class and 6MWT has been described in other forms of PAH, such as in PoPH. Considering the comorbidities present in chronic schistosomiasis, it might be expected that other factors may influence dyspnea besides the hemodynamic limitation. However, it is important to emphasize that the high variability of 6MWT may also prevent further speculation in this case series, reinforcing the point with regard to the absence of a consensus on the value of 6MWD in non-IPAH PAH.

Recent data demonstrated no acute response to vasodilator test in Sch-PAH, therefore there would be no indication of a high dose of calcium-channel blockers as primary therapy in this group. The choice between ERA and the phosphodiesterase-5 inhibitor in this study was made mainly by the availability of the drug in our center at the moment of therapy initiation. There was no significant side effect in the seven patients using the phosphodiesterase-5 inhibitor, the four patients using ERAs, or the one using combined therapy. Particular attention was paid to the patients with Sch-PAH using ERAs and the one with combined therapy because patients with hepatosplenic schistosomiasis have hepatic blood flow impaired due to portal hypertension, generating some degree of relative ischemia and possibly amplifying vulnerability to the potential hepatotoxicity of this class of drugs. Nevertheless, no significant abnormal levels of liver enzymes were identified during the course of study (data not shown). In fact, some drugs of this class, such as bosentan, have been safely used in PoPH in several reports. Cases of favorable response with the use of sildenafil in Sch-PAH have been previously reported, but without hemodynamic confirmation of PAH diagnosis and post-treatment control.

Other forms of specific treatment in Sch-PAH also should be considered. Being an infectious disease for which a single dose treatment is widely available, the need for implementing the antiparasitic treatment to this population—even with the purposes of discontinuing the chronic infection, and avoiding both re-infection and infestation of other patients—is quite obvious. Nevertheless, there is a possible role of antiparasitic treatment on pulmonary arteriopathy as well. It is known that, in hepatosplenic disease, this modality of treatment may improve the tissue architectural destruction induced by the disease, sometimes even promoting complete resolution of the granulomatous process. Despite the fact that this effect has never been specifically studied in the pulmonary circulation, at least one case report has been published showing significant improvement in pulmonary hemodynamics after treatment of Schistosoma hematobium. Nevertheless, all of our patients with Sch-PAH received adequate treatment of S mansoni at the time of diagnosis, therefore, before any specific PAH treatment was initiated.

Our study has several limitations that have to be taken into consideration before any extrapolation of our data. It is a retrospective case series with a limited number of patients followed at a single tertiary center. It should be solely considered as an exploratory hypothesis generating study. Not all patients with

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**Figure 1.** Clinical data at baseline and post-specific pulmonary arterial hypertension (PAH) treatment for patients with schistosomiasis-associated pulmonary arterial hypertension. A, Proportion of patients in respective New York Heart Association (NYHA) FC. B, Length in 6MWT. *P < .05. **P < .01. 6MWT = non-encouraged 6-min walk test; FC = functional class.
Sch-PAH were treated, and this surely led to selection bias, minimized by the fact that the comparison was done to the patient him or herself and not to a control subject. It would have been extremely valuable if a larger number of patients could have been treated with targeted therapies; however, the limited drug availability imposes a major limitation in this matter. Therefore, it is particularly important to gather data that support the use of specific therapies in Sch-PAH. Nevertheless, this is a first step in establishing the clinical response to specific PAH therapy to patients with Sch-PAH, and also the first report to provide evidence of potential efficacy of target therapies in the setting of Sch-PAH, enabling and reinforcing the need for controlled trials. We conclude that specific PAH therapy may be of benefit to patients with Sch-PAH, considering clinical, functional, and hemodynamical parameters.

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Author contributions: Dr Souza had final approval of the manuscript and guarantees the manuscript. Dr Fernandes: contributed to study conception and design and the drafting and writing of the manuscript. Dr Dias: contributed to data interpretation and writing of the manuscript. Dr Jardim: contributed to the revision of the manuscript. Dr Hovnanian: contributed to data interpretation and writing of the manuscript. Dr Hoette: contributed to data interpretation and writing of the manuscript. Dr Morinaga: contributed to the drafting and writing of the manuscript. Dr S. Souza: contributed to data analysis and writing of the manuscript. Dr Suesada: contributed to the revision of the manuscript. Dr Breda: contributed to the revision of the manuscript. Dr R. Souza: contributed to study conception and design and writing of the manuscript.

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