Hemodynamic Profile of Severity at Pulmonary Vasoreactivity Test in Schistosomiasis Patients

Flávio A. A. Japyassú[3], Adriano A. Mendes[2], Ângela P. Bandeira[2], Flávio R. A. Oliveira[3], Dário Sobral Filho[2]

Setor de Hemodinâmica do Hospital Memorial São José[1], Divisão de Cardiologia Clínica PROCAPE, Universidade de Pernambuco[2], Instituto de Medicina Integral Professor Fernando Figueira – IMIP[3], Recife, PE - Brazil

Abstract

Background: The pulmonary vasoreactivity rate of Schistosomal Pulmonary Artery Hypertension (SPAH) is not known. Hemodynamic data obtained by cardiac catheterization are associated with the most commonly used clinical criteria of severity.

Objective: To estimate the percentage of positive vasoreactivity to nitric oxide in schistosomal pulmonary arterial hypertension and verify the association of hemodynamic parameters with WHO functional classification and the six-minute walk test in these patients.

Methods: A total of 84 patients with schistosomal pulmonary hypertension were selected from a database, who had been submitted to the right and left cardiac catheterization and pulmonary vasoreactivity test with nitric oxide. Data on WHO functional classification and six-minute walk test were collected for comparison with invasive data.

Results: Of the 84 patients with SPAH, 3 (3.5%) had positive criteria for pulmonary vasoreactivity. The increase in pulmonary vascular resistance was significantly associated with lower exercise capacity measured by the six-minute walk test (p = 0.045) and greater symptom severity by higher functional classifications (WHO class III/IV) (p = 0.013). The decrease in oxygen saturation in the pulmonary artery was significantly associated with higher functional classifications (p = 0.041).

Conclusion: The pulmonary response rate to the vasodilation test of schistosomiasis patients is below the values found for idiopathic pulmonary hypertension. Pulmonary vascular resistance and oxygen saturation in the pulmonary artery are hemodynamic data that can be used as markers of severity in schistosomal pulmonary hypertension. (Arq Bras Cardiol 2012;99(3):789-796)

Keywords: Pulmonary, hypertension / etiology; pulmonary artery; vascular resistance; walking; schistosomiasis.

Introduction

Pulmonary artery hypertension (PAH) is a disease of high severity, which mainly affects small pulmonary arteries and ultimately causes a triad of alterations, i.e., vasoconstriction, *in situ* thrombosis and vascular remodeling, thus leading to progressive increase in resistance to flow blood in the pulmonary circulation. This system usually has low resistance, which causes progressive right ventricular failure leading to death, which, when untreated, occurs on average 2.8 years after diagnosis of the disease with idiopathic etiology[1,2].

Prognostic predictors of pulmonary hypertension severity include: advanced functional class, poor exercise tolerance measured by the six-minute walk test, elevated mean right atrial pressure, right ventricular dysfunction, decreased cardiac index, elevated atrial natriuretic peptide levels, diagnosis of scleroderma[3].

Mailing Address: Flávio Adolfo Aranha Japyassú •
Rua Amália Bernardino de Souza, nº 710/1002. Postal Code 51021-150, Boa Viagem, Recife, PE - Brazil
E-mail: flavioaranha@hotmail.com
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Schistosomiasis is the third leading cause of endemic parasitic diseases worldwide, with more than 300 million infected individuals and approximately 600 million at risk of infection[4]. Prevalence rates between 7.5% and 21.6% of pulmonary hypertension have been reported in endemic areas, in individuals with schistosomiasis, which can reach up to 30% in the hepatosplenic forms and most described cases being classified as moderate or severe with advanced functional class[4,5]. In an autopsy-based study, cor pulmonale was detected in approximately 2.1% -33% of cases[6].

The natural history of Schistosomal Pulmonary Artery Hypertension (SPAH) has not been well established. Some less advanced cases have been prospectively studied, with a poor prognosis; however, it has been demonstrated that some patients may remain clinically stable for years, indicating a more benign clinical course when compared to other forms of PAH (3-year mortality of 14.1% *versus* one-year mortality of 15%, in idiopathic PAH)[7,8].

PAH is defined when there is an increase in mean pulmonary artery pressure at rest ≥ 25 mmHg, measured by right cardiac catheterization[3]. This procedure is not only a reference standard for disease diagnosis, but also, through the testing of pulmonary vasoreactivity to agents, selects those patients with lower impairment of pulmonary circulation, to

establish which ones will benefit from long-term treatment with calcium channel blockers, obtaining symptomatic and survival improvement[1,9-11]. There are also prognostic information through measurements of hemodynamic variables that are associated with disease severity and risk of death, such as increased mean right atrial pressure, increased pulmonary artery pressure, decreased cardiac index, increased pulmonary vascular resistance, decreased oxygen saturation in the pulmonary artery, and others[2,11]. By means of coronary angiography, one can also diagnose extrinsic compression of the left main coronary artery by the pulmonary artery, an entity that has been increasingly described in severe PAH[12].

Once diagnosed, PAH is commonly classified according to a functional class system adapted by the World Health Organization (WHO). This functional class measures PAH severity and reflects the impact on the patient's life in terms of physical activity and symptoms. The mean survival in patients who are classified as functional class I and II is six years; in patients with functional class III is 2.5 years, and in those with functional class IV, it is only six months[3].

Patients with PAH have limitation to physical exertion, being necessary to quantify their exercise tolerance, both to evaluate their quality of life and to define the therapeutic benefits of several drugs. The six-minute walk test (6MWT), a simple but extremely important tool, has been used to solve this problem. This simple and low-cost test has demonstrated correlation with hemodynamic variables and is one of the most used prognostic criteria in this disease. Myiamoto et al.[13] reported that cardiac output, oxygen saturation in the pulmonary artery, total pulmonary resistance and mean right atrial pressure obtained from invasive examinations correlate with the distance walked at the 6MWT.

Due to the large numbers of patients with schistosomiasis who may develop PAH, a better understanding of this disease is needed. In this sense, the objective of this study is to determine the rate of pulmonary vasoreactivity in patients with SPAH and hemodynamic variables that can be associated with a clinical severity expressed by the 6MWT and WHO functional classification.

Methods

Patients were selected from the database of patients with pulmonary hypertension of the emergency room of Pronto-Socorro Cardiológico de Pernambuco (Procape), Universidade de Pernambuco (UPE), a regional reference service in PAH. From this database, we selected patients who had a diagnosis of SPAH from January 2005 to September 2009, following the appropriate protocols to define this etiology. The study was approved by the Ethics and Research Committee for study in humans of Universidade de Pernambuco (CAAE 0116.0.106.000-09) and is in accordance with the Declaration of Helsinki.

Patients were considered to have PAH when, at catheterism, they had mean pulmonary artery pressure > 25 mmHg and pulmonary capillary wedge pressure < 15 mmHg, according to the PAH consensus of 2009[3]. The need to exclude patients with high capillary pressure was due to the elimination of those with pulmonary venocapillary hypertension. To exclude the possibility of erroneous measurement of capillary pressure, left ventricular end-diastolic blood pressure was measured in every patient with capillary pressure ≥ 12 mmHg[14]. Cardiac catheterization with pulmonary vasoreactivity study with nitric oxide (40 ppm) was performed at another service, Maximagem/Hospital Memorial São José, provided by the Brazilian Public Health System (SUS), by a single examiner and using the same equipment (Philips Allura angiography equipment, Best, Holland; polygraph TEB SP12).

Cardiac catheterization was performed in the right and left cardiac chambers, with aorta, left ventricle, pulmonary artery, right ventricle and right atrium manometry using a 06-French pigtail catheter and occluded capillary wedge pressure using a 07-French wedge catheter; blood oximetry was obtained from the femoral artery and venous pulmonary artery, being analyzed in a Roche blood gas analysis system (Basilea, Switzerland). The output and resistance calculations were performed using the "FICK" formula at two moments: baseline, considered after a 10-minute rest and 10 minutes after nitric oxide inhalation. The nitric oxide was administered through a face mask at a dose of 40 ppm measured by the NOX 500 equipment.

For the diagnosis of schistosomiasis, the criterion used was the positive epidemiology, hepatic/abdominal ultrasound with characteristic findings (periportal fibrosis, splenomegaly, left hepatic lobe enlargement)[15] or coproparasitological examination positive for schistosome eggs using the the Kato-Katz method, confirmed by review of medical records[16].

For functional classification, we considered the table adapted from the World Health Organization (WHO)[17], which classifies patients with PAH in four classes, according to symptoms. Classes I/II will be considered non-severe clinical category and class III/IV as severe category for the purpose of analysis.

The 6MWT was carried out according to the American Thoracic Society protocols[18]. After a period of 30-minute rest, each patient had their blood pressure measured and then walked along a 30-meter flat-surface corridor without obstacles, with heart rate and oxygen saturation being measured by means of portable oximeter (Digital Oximetry, model 513), during the entire test. The criteria used to establish the functional significance of six-minute walk test in patients with pulmonary hypertension were: those who walked less than 335 meters were classified as severe, and those walked more than 335 meters were classified as non-severe[13].

Patients diagnosed with PAH confirmed by right heart catheterization, from the pulmonary hypertension outpatient clinic of Procape - UPE, simultaneously submitted to the pulmonary vasoreactivity test with nitric oxide at 40 ppm, and established schistosomal etiology [positive epidemiology, abdominal ultrasonography with suggestive alterations (left hepatic lobe enlargement, periportal fibrosis), previous treatment for schistosomiasis, stool test positive for schistosome eggs] were included.

Patients aged 70 years or younger than 18 years, those with decompensated liver disease, alcohol abuse [intake greater than 210 g/week (men) or 140 g/week (women) in the last five years[19]], HIV-infected patients, those with thyroid disease, connective tissue diseases or currently using anorectic drugs, patients with pulmonary thromboembolism, familial SPAH

were excluded, as well as patients unable to undergo cardiac catheterization (ascites, cardiogenic shock, severe dyspnea at rest, not capable of staying in the supine position).

At the time of right cardiac catheterization, patients were taking diuretics and digoxin, with no prior use of endothelin antagonists or phosphodiesterase-5 inhibitors; those taking warfarin had the medication withdrawn for five days prior to the procedure.

The results of numerical variables are shown as mean ± standard deviation, the functional classification, according to the WHO, was categorized into two levels, class I/II and class III/IV; the outcome of the 6MWT was categorized into two levels, short walking distance group (≤ 335 meters) and long walking distance group (> 335 meters). Five hemodynamic variables were selected: mean right atrial pressure, mean pulmonary artery pressure, cardiac index, pulmonary vascular resistance and oxygen saturation in the pulmonary artery for association with the two aforementioned clinical variables, the six-minute walk test and functional classification by WHO.

Statistical analyzes were performed with Stata 9.2 and a p value < 0.05 was considered statistically significant. Means were compared by Student's *t* test. The association of increasing variation in functional class with decreasing mean values at the 6MWT was submitted to Cuzik's trend test and Sidak's multiple comparisons test.

Results

A total of 84 patients with PAH from the database of the pulmonary arterial hypertension outpatient clinic of Procape - UPE, with a mean age of 46.9 years, consisting of 59 women (70.6%) and 25 men (29.4%) were evaluated. The mean of the mean pulmonary artery pressure was 59.2 mmHg; the mean of other hemodynamic parameters were: pulmonary artery systolic pressure of 96.5 mmHg, mean right atrial pressure of 11.9 mmHg, cardiac index of 2.7l/min, pulmonary arteriolar resistance of 943.5 dyn/sec, oxygen saturation in the pulmonary artery of 63.3% (Table 1).

The functional class was obtained in 44 of the 84 initial patients, with 21 (47.7%) patients being functional class III/IV and 23 (52.2%) being functional class I/II. The six-minute walk test was carried out in the same 44 patients from whom functional classification was obtained, with a mean of 254.9 meters walked (Table 2).

The lower capacity to perform physical exertion at the six-minute walk test (6MWT) was associated with significantly higher values of WHO functional class, with increasing variation in functional class, accompanied by a decrease in the mean distance walked during the 6MWT ($p < 0.001$) (Table 2).

The pulmonary vasoreactivity test with nitric oxide was positive in 3 of 84 patients (3.5%) diagnosed with SPAH.

It was observed that patients younger than 40 years had higher measurements of pulmonary artery pressure and pulmonary resistance ($p < 0.001$ and $p = 0.023$, respectively), with no statistically significant differences in relation to other studied hemodynamic parameters (Table 3).

In patients with increased pulmonary resistance, there was a statistically significant association with higher functional class ($p = 0.013$) and shorter distance walked during the 6MWT ($p = 0.045$) and significant trend of association between oxygen saturation in the pulmonary artery with FC and 6MWT ($p = 0.041$ and $p = 0.085$, respectively) (Tables 4 and 5).

There was no significant association of the cardiac index, mean pulmonary artery pressure and mean right atrial pressure with functional class and 6-minute walk test.

In the studied series, the increasing variation in functional class was accompanied by a decrease in the mean distance walked during the 6MWT. Cuzick's trend test indicates that this result could not be explained by chance ($p < 0.001$). Sidak's multiple comparisons test shows a significant difference between the means of any pair of functional classes ($p < 0.007$). In the studied series, the mean distance walked was significantly higher in patients with functional class I or II, when compared with those with functional class III or IV ($p < 0.001$).

Discussion

The present study analyzed a series of 84 cases of SPAH from a reference center in northeastern Brazil (Procape), submitted to pulmonary vasoreactivity test with nitric oxide, being, to the best of our knowledge, the study with the largest number of patients with this etiology.

The invasive data show that the selected patients were severe cases, with mean pulmonary artery pressure of 59.3 mmHg and cardiac index of 2.7 L/min/m^2 (Table 1) and followed the overall gender distribution found in literature, of around two women for every man[5,20].

The pulmonary vasoreactivity test with nitric oxide does not only provide the information that the patient can be successfully treated with calcium-channel blockers [9], but is also a test with prognostic value[3,21]. Three of the 84 patients (3.5%) had positive criteria for vasoreactivity to nitric oxide in the sample, which analyzed from the viewpoint of hemodynamic parameters, showed a tendency to present lower values of mean right atrial pressure ($p = 0.0534$) and pulmonary artery ($p = 0.0870$), consistent with a less severe hemodynamic profile.

It has been shown that those individuals with the positive criteria at pulmonary vasoreactivity test show lower basal hemodynamic impairment, with vasoconstriction predominating in these patients when compared to the remodeling phenomenon[21,22]. These patients may have sustained hemodynamic and clinical response to the introduction of non-selective vasodilators to pulmonary circulation, with improved prognosis, specifically with calcium channel blockers, which are accessible and affordable drugs[9,23,24]. The hemodynamic testing turns out to be a practical tool that provides data reflecting the process of vascular remodeling[25,26].

In the study by Fernandes et al. designed to analyze survival in patients with SPAH, the study of 54 schistosomiasis patients *versus* 95 idiopathic ones showed that no patient with schistosomiasis was vasoreactive, against 16.2% of positive vasoreactivity in idiopathic ones[8]. This study suggests that the etiology of pulmonary hypertension may be closely associated to portal hypertension, a physiopathogeny that shows no significant pulmonary vasoreactivity[8,3], which

Table 1 – Demographic and hemodynamic variables

Characteristics	n	Mean	SD
CLINICAL			
Age, years	84	46,9	12,6
Height, m	84	1,57	0,08
Weight, kg	84	59,2	11,2
Body surface, m^2	84	1,59	0,16
BMI, kg/m^2	84	23,9	3,9
HEMODYNAMIC			
PASP (mmHg)	84	96,6	25,6
mPAP (mmHg)	84	59,2	14,7
mRAP (mmHg)	84	11,9	6,8
CI (L/min)	84	2,7	0,9
PAR (dyn/cm)	84	943,5	446,5

PASP: pulmonary artery systolic pressure; mPAP: mean pulmonary artery pressure.
mRAP: mean right atrium pressure; CI: cardiac index; PAR: pulmonary arteriolar resistance.

Table 2 - Clinical characteristics of patients

Characteristics	N	6MWT	p value
Functional Class (WHO)		Mean walked distance (SD)	
I/II	21	360,1 (75,3) m	p<0,001*
III/IV	23	158,8 (95,5) m	

*WHO: World Health Organization; SD: standard-deviation; m: meters; 6MWT: six-minute walk test; * Student's t test.*

Table 3 – Comparison of means of hemodynamic characteristics according to age

Characteristic	Age	N	Mean	SD	p value*
Cardiac index ($L/min/m^2$)					0,357
	≤ 40	25	2,6	0,5	
	> 40	59	2,8	1,0	
Mean pulmonary artery pressure (mmHg)					< 0,001†
	≤ 40	25	67,6	2,6	
	> 40	59	55,7	1,8	
Pulmonary resistance (Dyn/sec/cm5)					0,023†
	≤ 40	25	1112.0	465.0	
	> 40	59	872.0	55.0	
Mean right atrium pressure (mmHg)					
	≤ 40	25	12,6	8,6	0,602
	> 40	58	11,7	5,8	
Oxygen saturation (%)					0,689
	≤ 40	25	64,0	7,7	
	> 40	59	63,2	8,7	

** Student's t Test. † "statistically significant" p value.*

Table 4 – Comparison of means of hemodynamic characteristics according to the distance (short or long) at the six-minute walk test

Characteristic	6MWT	N	Mean	SD	P value*
Cardiac index (L/min/m^2)					0.349
	≤ 332	29	2.7	1.2	
	> 332	15	2.9	0.9	
Mean pulmonary artery pressure (mmHg)					0.392
	≤ 332	29	60.6	13.6	
	> 332	15	56.6	16.5	
Pulmonary resistance (Dyn/sec/cm5)					0.045†
	≤ 332	29	1079.3	492.4	
	> 332	15	796.2	390.6	
Mean right atrium pressure (mmHg)					0.837
	≤ 332	28	12.0	6.5	
	> 332	15	11.5	6.5	
Oxygen saturation (%)					0.085
	≤ 332	29	61.8	9.7	
	> 332	15	66.8	7.2	

** Student's t Test ; † "statistically significant"; p value; 6MWT: six-minute walk test*

Table 5 – Comparison of means of hemodynamic characteristics according to functional class

Characteristic	FC	N	Mean	SD	p value*
Cardiac index (L/min/m2)					0.552
	I/II	21	2.8	0.7	
	III/IV	23	2.7	1.3	
Mean pulmonary artery pressure (mmHg)					0.081
	I/II	29	55.2	15.7	
	III/IV	15	62.9	12.7	
Pulmonary resistance (Dyn/sec/cm5)					0.013†
	I/II	21	800.2	417.2	
	III/IV	23	1149.4	471.9	
Mean pressure of right atrium (mmHg)					0.741
	I/II	21	11.5	5.7	
	III/IV	22	12.1	7.2	
Oxygen saturation (%)					0.041†
	I/II	21	66.4	8.4	
	III/IV	23	60.8	9.2	

** Student t Test; † "statistically significant"; p value; FC: functional class.*

is in disagreement with other studies that indicate many similarities between these etiologies, with SPAH being recently reclassified from group IV to group I[17,27-29]. The findings in the analysis are consistent with the fact that patients with SPAH are vasoreactive, but at a value below those recorded for idiopathic PAH, which is around 20%[30].

Although the physiopathogenesis of schistosomiasis can have the hypothesis of hepatic fibrosis/portal hypertension, there has been a change in paradigms and there is evidence that the degree of pulmonary hypertension is not associated with the severity of portal hypertension, disclosing an association of the latter with hepatopulmonary syndrome (liver disease, arterial hypoxemia, intrapulmonary vascular dilatation)[6,31], as well as considering the influence of inflammation and immunity, by means of chemical mediators such as interleukins 1 and 6, among others, in the genesis of pulmonary hypertension[31-33].

Three hemodynamic variables are directly related to risk of death: mean pulmonary artery pressure, mean right atrial pressure and cardiac index[11]. Other variables also seem to play a role in prognosis such as oxygen saturation in the pulmonary artery, pulmonary vascular resistance and the systemic and pulmonary resistance relation[3]. D'Alonzo et al.[2] showed that an increase of 55 to 85 mmHg in the mean pulmonary artery pressure was associated with a decrease in survival from 48 to 12 months, and the risk of death was associated with a decrease in cardiac index and increase in the mean right atrial pressure (OR = 1.99), especially when the value exceeded 20 mmHg, thereby leading to a mean survival time of about one month[2].

In the study of survival in primary PAH, where Sandoval et al.[11] proposed an equation for the evaluation of survival estimate at one, three and five years, the univariate analysis of hemodynamic variables associated with a lower survival showed a hazard ratio of 3.40 and 4.28 ($p < 0.01$ and $p < 0.005$), respectively, for pulmonary vascular resistance and oxygen saturation in the pulmonary artery, thus demonstrating the importance of individualized hemodynamic measures when calculating the probability of survival of idiopathic patients[11]. In our sample, the data suggest that, in the schistosomal etiology, pulmonary vascular resistance has a more significant role regarding the estimate of clinical severity and may be a reference for monitoring and evaluation of therapy in these patients.

Patients with SPAH under 40 years of age had a statistically significant association with higher levels of mean pulmonary artery pressure ($p < 0.001$) and pulmonary resistance ($p = 0.023$) (Table 3); this higher severity profile can be translated in the fact that diseases with less evolution time would not show adaptation mechanisms upon changes in lung compliance, as may occur in large aneurysmatic dilatations of the pulmonary vessels, observed during the course of the disease.

Regarding the clinical parameters studied, we observed that despite the mean walked distance was around 254.9 meters below the cutoff considered as the worse prognosis in the literature, the distribution of patients in functional class I/II and III/IV was almost the same (47.8% and 52.2%, respectively) (Table 2)[13]. However, when analyzing the association between longer and shorter distance walked and higher functional classification, it was observed that the mean distance walked was significantly longer in patients with functional class I or II when compared with those with functional class III or IV ($p < 0.001$.)

Myiamoto et al.[13] showed that the distance walked decreases in proportion to the increase in functional class and those who walked fewer than 332 meters had a higher mortality rate when compared to individuals who walked more than that distance[13,34]. These authors also showed that, for each 50-meter increase in the 6MWT, there was an 18% decrease in the risk of death.

The functional class as a marker of severity showed that functional class I or II patients have a median survival of 58.6 months compared with 31.5 months for patients in class III and six months for those in functional class IV[2]. In a prognostic study with more symptomatic patients (class III/IV), these had significantly lower heart rates and higher risk of death when compared to classes I / II (2.1 ± 0.7 *vs*. HR. 2.8 ± 0.8, $p < 0.007$), but there was no significant difference regarding the mean pulmonary artery pressure and pulmonary resistance[20].

In this sample we observed that patients who had the most advanced functional class, i.e., were more symptomatic, had a statistically significant association with lower levels of oxygen saturation in the pulmonary artery and higher values of pulmonary resistance ($p = 0.041$ and $p = 0.013$, Table 5). The 6MWT showed associations similar to those described for functional class, but with lower significance, $p = 0.085$ for oxygen saturation and $p = 0.045$ for pulmonary resistance (Table 4), which can indicate that, in our series, the cutoff for severity in relation to the walked distances is smaller.

There was no significant association between mean right atrial pressure, a parameter closely associated in the literature as an indicator of severity and worse prognosis[2] with functional class or 6MWT. One explanation could be the fact that in this series, the mean right atrial pressures obtained were not very high, which can be translated into a mean pressure of 11.9 mmHg, lower than the value of 12 mmHg used in the literature as a cutoff for severity[2]. Moreover, there was no association with mean pulmonary artery pressure. Of the 84 patients with SPAH, it was observed that 3.5% of them showed criterion for a positive vasoreactivity test with nitric oxide, below the value found for the idiopathic form (10% -20%)[30,35,36] and different from that found by Fernandes et al.[8], in which of 54 schistosomiasis patients, there were no vasoreactive cases. This finding consists in new data that would show that the pulmonary vasoreactivity test is useful in the assessment of severity in patients with schistosomiasis.

When comparing the selected hemodynamic variables (cardiac index, mean pulmonary artery pressure, oxygen saturation in the pulmonary artery, mean right atrial pressure and pulmonary artery resistance) with the functional classification and distance walked, it was observed that the pulmonary artery resistance was negatively associated with the distance walked and positively correlated with the functional classification, showing, in this study, that pulmonary resistance is not only a diagnostic tool, but also help in clinical decision-making due to its characterization of severity in patients with SPAH.

Study limitations include the monocentric nature of the study and the fact that it was carried out in a reference center in an endemic area for schistosomiasis, which may have

caused a selection bias, with more severe patients and disease with a more advanced clinical course. This was a study of hemodynamic data obtained during cardiac catheterization procedures, in which there was an estimate of clinical severity in comparison with the 6MWT and WHO functional classification, requiring, however, a long-term clinical follow-up of patients for prognostic evaluation.

Conclusion

A positive response percentage of 3.5% (3 of 84 patients) was obtained at the pulmonary vasoreactivity test with nitric oxide in patients with SPAH, below the value found for other etiologies; this unprecedented information should be taken into account, considering the significant number of patients involved in the study.

This response frequency indicates that, in this etiology, one cannot use calcium channel blockers for the treatment without testing the pulmonary vasoreactivity. Pulmonary vascular resistance and oxygen saturation in the pulmonary artery are hemodynamic variables to be used as markers of SPAH severity. Patients younger than 40 years constitute a subgroup at higher risk due to worse hemodynamic patterns, probably due to the shorter time of adaptation of the pulmonary circulation to high pressure regimens found in this etiology.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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