Original Article

Long-Term Evolution of Patients with Important Pulmonary Hypertension due to Schistosomiasis

José Maria Del Castillo,[1,2] Katarina Barros de Oliveira,[1] Rafael Ricardo de Oliveira Travassos,[1] Ângela Maria Pontes Bandeira,[3] Carlos Antônio da Mota Silveira,[3] Djair Brindeiro Filho[1]

Escola de Ecografia de Pernambuco (ECOPE),[1] Recife, PE – Brazil

Universidade Católica de Pernambuco (UNICAP),[2] Recife, PE – Brazil

Pronto Socorro Cardiológico de Pernambuco (PROCAPE), UPE,[3] Recife, PE – Brazil

Abstract

Introduction: **Hepatosplenic schistosomiasis mansoni, associated with pulmonary arterial hypertension (PAH), causes cardiac chamber remodeling. Little is known about its long-term evolution.**

Objective: **To evaluate the alterations caused by PAH in patients with schistosomiasis and analyze the clinical and echocardiographic evolution over a period of 10 years.**

Methods: **The study included 60 patients with PAH due to schistosomiasis and 50 healthy control patients. Clinical and echocardiographic data were evaluated, including dimensions, parietal thickness, function of the right and left chambers, and parameters of myocardial strain. Patients in the group with PAH due to schistosomiasis were followed for 10 years. Data were compared using Student's t test for unpaired samples with significance level of < 5%.**

Results: **Patients with PAH had smaller left ventricular dimension without alteration in the ejection fraction, but with decreased left ventricular global longitudinal strain and left atrial reservoir strain. The right ventricular dimensions and parietal thickness were increased, and the parameters of systolic function (tricuspid annular plane systolic excursion, fractional area change, tricuspid s' wave, and the right ventricular global longitudinal strain) were significantly reduced. During the follow-up period, 18 patients (32%) died, and death was associated with higher functional class, decreased right ventricular longitudinal strain, larger right ventricular size, decreased fractional area change, and decreased tricuspid annular s' wave velocity.**

Conclusion: **PAH related to schistosomiasis causes remodeling of the right chambers, with decreased parameters of systolic function and myocardial strain. The long-term evolution, with elevated mortality, presents with larger right ventricular dimensions, lower fractional area change, lower tricuspid annular systolic velocity, lower right ventricular global longitudinal strain, and more advanced functional class.**

Keywords: **Pulmonary Hypertension; Schistosomiasis; Echocardiography.**

Introduction

Schistosomiasis is considered a neglected tropical disease[1] originally from North Africa, caused by trematodes of the genus *schistosoma*, comprising several species. *Schistosoma mansoni* is the only one that exists in South and Central America, and it was likely introduced during the era of slavery. [2] It is widespread throughout almost all of Brazilian territory, especially in the Northeast Region, and it presents several clinical forms. The main ones are the initial phase, predominantly characterized by allergic manifestations due to the entry of cercariae transmitted into the water by snails of the *biomphalaria* species, and the late phase. During the late phase, the most frequent forms are hepatointestinal and hepatic, generally with few symptoms, and the hepatosplenic form, which may be compensated, decompensated, or complicated, and may progress to portal hypertension, splenomegaly, esophageal varices, and ascites. [2]

Approximately 10% of patients with the hepatosplenic form have the vasculopulmonary form, with pre-capillary pulmonary hypertension, caused by obstruction of pulmonary arterioles by eggs, dead worms, and/or pulmonary vasculitis due to immune complexes. In more severe cases, there may be cyanosis due to the presence of fistulas between the portal system and the pulmonary veins. It causes major dilation of the right chambers and the pulmonary artery, and little is known about its long-term evolution, even with treatment with pulmonary vasodilators. Other rarer complications are renal, neurological, pseudoneoplastic, and lymphoproliferative. The diagnosis can be direct (visualization of *S. mansoni* eggs

Mailing Address: José Maria Del Castillo •
Rua Jorge de Lima, 245, apto 303. Salute. Postal code: 51160-070. Imbiribeira, Recife, PE – Brazil
E-mail: castillojmd@gmail.com
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in feces or tissues) or indirect (based on immunological tests such as ELISA, periovular reaction, and intradermal reaction). Abdominal ultrasonography is particularly useful in the hepatosplenic form, because, in severe cases, it provides evidence of Symmers' hepatic fibrosis with greater sensitivity than percutaneous biopsy.[3]

The method of choice to assess pulmonary hypertension and its cardiac repercussions is Doppler echocardiography, allowing estimation of pulmonary pressures, dimensions, parietal thickness, and systolic function of the right ventricle (RV). Based on this fact, the objective of this study was to evaluate, through clinical and echocardiographic data, the long-term evolution of patients with hepatosplenic schistosomiasis and pulmonary hypertension.

Material and methods

This prospective longitudinal study studied 60 patients diagnosed with hepatosplenic schistosomiasis with pulmonary hypertension (PAH group) for a period of 10 years (between January 2012 and June 2022). For comparison, 50 healthy individuals in the same age group (control group) were studied.

All patients were clinically stratified according to New York Heart Association functional class (FC).

The exclusion criteria for the PAH group were the absence of direct or laboratory diagnosis of schistosomiasis; the occurrence of previous pulmonary disease, with or without pulmonary hypertension; any type of congenital heart disease; and patients who did not complete clinical follow-up.

Echocardiographic analysis

Using conventional echocardiography, the following data were evaluated: dimensions and function of the left chambers; mean left atrial (LA) pressure using the ratio between the mitral E wave and the mean e' wave of the mitral annulus by tissue Doppler (E/e'); dimensions and function of the right chambers by tricuspid annular plane systolic excursion (TAPSE), RV fractional area change, and tricuspid annular s' wave; RV systolic pressure by tricuspid regurgitation gradient; pulmonary vascular resistance in Wood units; and the relative RV thickness, by the quotient between the basal RV diameter and the thickness of the RV lateral wall. All measurements were taken according to American Society of Echocardiography recommendations.[4]

The following formula was used to assess RV systolic pressure:

$$RVSP = TRV^2 \times 4$$

RVSP: right ventricular systolic pressure; TRV: maximal tricuspid regurgitation velocity.

The following formula was used to assess pulmonary vascular resistance:[5]

$$PVR = (TRV \times TVI_{RVOT}) \times 10 + 0.16$$

PVR: pulmonary vascular resistance; TRV: tricuspid regurgitation velocity; TVI_{RVOT}: right ventricular outflow tract time-velocity integral.

Using the speckle tracking method, the longitudinal strain of the ventricular and atrial chambers was evaluated. To obtain the global longitudinal strain of the left ventricle (LV), the apical 4-, 2- and 3-chamber views were used.[6] To obtain the global longitudinal strain of the RV, the apical 4-chamber view focused on this cavity was used.[7] The apical 4-chamber view aligned with the atrial cavities was used to obtain the longitudinal strain of the reservoir of the LA [8] and right atrium (RA). [9]

In a prospective analysis, the outcome and evolution of the patients was determined by studying the clinical records and the echocardiographic examinations performed during the study period.

Echocardiographic examinations were performed using CX50 and Affiniti 70 equipment (Philips, Andover, MA) by a single examiner. Qlab 15 (Koninklijke Philips Electronics N.V. 2020) software was used for the analysis of strain data stored in DICOM format.

Statistical analysis

Study sample size was defined by convenience. The data, between the first examination of patients in the PAH group, expressed as mean and standard deviation of the mean, were compared with those of individuals in the control group using Student's t test for unpaired samples, with a statistical significance level of < 5 %. To verify the homoscedasticity between numerical data, analysis of variances was performed (Z test). For all statistical measurements, the Bioestat 5.0 program was used.

Results

The mean age at the time of the first examination was 48 ± 12 years, with 38 female patients and 22 male patients. The control group included 50 healthy individuals in the same age group (49 ± 17 years, 30 females and 20 males).

The demographic data of the control and PAH groups are displayed in Table 1, where LV diastolic diameter and LV mass index were reduced in the PAH group.

Table 2 displays data on diastolic function, RV parameters, and RV systolic pressure in the control and PAH groups, showing a decrease in the mitral E wave and the e' wave by tissue Doppler in the PAH group, with normal E/e' ratio, decreased tricuspid annular s' wave velocity, and increased RV systolic pressure.

Table 3 displays the dimensions and function of the RV and the indexed RA volume in the control and PAH groups, with increased diameters, increased RV thickness, increased RA volume, decreased RV function parameters, and increased pulmonary resistance in the PAH group.

Table 4 shows the parameters of myocardial strain of the ventricles and atria, with a decrease in strain observed in all cavities in the PAH group.

Graph 1 shows that, from January 2012 to June 2022, 18 patients died (32%). In this group there were no patients in FC I. There were 3 patients in FC II, 9 in FC III, and 6 in FC IV. Among the 42 surviving patients who remained under treatment with pulmonary vasodilators, there were 7 patients in FC I, 29 in FC II, 6 in FC III, and no patients in FC IV. Patients

Table 1 – Demographic data and dimensions of the left chambers, n (%) or mean ± standard deviation

Group	Sex	Age (years)	BSA (m^2)	LVDD (mm)	LVMI (g/m^2)	LVEF (%)	LAVi (mL/m^2)
Control	M 20(41%) F 30(59%)	48.95 (±17.45)	1.75 (±0.19)	49.41 (±3.84)	83.48 (±24.36)	58.68 (±5.07)	24.09 (±4.39)
PAH	M 22(37%) F 38 (63%)	48.49 (±12.01)	1.67 (±0.20)	44.57 (±6.20)	72.71 (±19.33)	59.65 (±6.59)	21.10 (±14.05)
P value		0.44	0.06	<0.0001	0.05	0.29	0.07

BSA: body surface area; F: female sex; LAVi: indexed left atrial volume; LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; M: male sex; PAH: pulmonary arterial hypertension.

Table 2 – Data obtained with flow Doppler and tissue Doppler echocardiography, mean ± standard deviation

Group	Mitral E wave (cm/s)	TD e' wave (cm/s)	E/e' ratio	PCP (mmHg)	TV s' wave (cm/s)	TRV (m/s)	RVSP (mmHg)
Control	84.78 (±13.48)	15.38 (±3.14)	5.82 (±1.81)	7.1 (±1.9)	15.00 (±1.31)	2.63 (±0.15)	32.55 (±2.94)
PAH	63.66 (±18.15)	11.40 (±3.45)	5.89 (±1.84)	8.5 (±2.1)	9.80 (±2.40)	4.23 (±0.78)	89.52 (±21.92)
P value	<0.0001	<0.0001	0.44	0.74	<0.0001	<0.0001	<0.0001

PAH: pulmonary arterial hypertension; PCP: pulmonary capillary pressure; RVSP: right ventricular systolic pressure; TD: tissue Doppler; TRV: tricuspid regurgitation velocity; TV: tricuspid valve.

Table 3 – Dimensions and functional parameters of the right chambers, mean ± standard deviation

Group	RV basal diameter (mm)	RV thickness (mm)	RV FAC (%)	TAPSE (cm)	RRVT	PVR (Wood units)	RAVi mL/m^2
Control	32.52 (±4.40)	5.06 (±0.62)	46.58 (±4.63)	2.25 (±0.38)	0.16 (±0.02)	1.25 (±0.61)	24.465 (±4.22)
PAH	43.80 (5.68)	8.93 (±2.04)	28.21 (±10.71)	1.9 (±0.46)	0.24 (±0.11)	3.51 (±1.42)	55.67 (±35.74)
P value	<0.0001	<0.0001	<0.0001	0.0011	<0.0001	<0.0001	<0.0001

FAC: fractional area change; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; RAVi: indexed right atrial volume; RV: right ventricle; RRVT: relative right ventricular thickness; TAPSE: tricuspid annular plane systolic excursion.

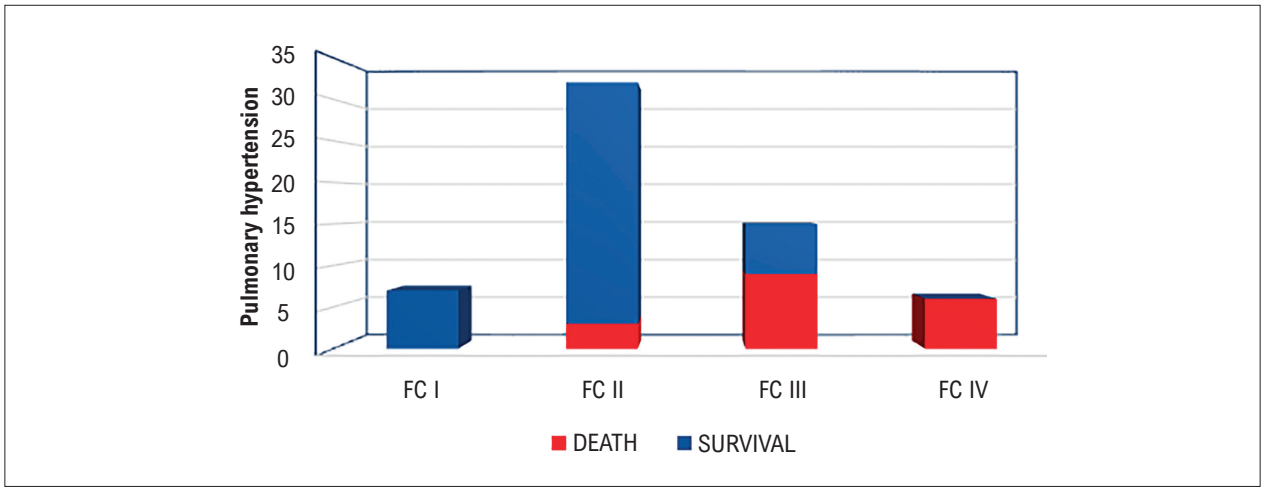
Table 4 – Strain data of right and left chambers, mean ± standard deviation

Group	LV GLS (%)	LA LS (%)	RV GLS (%)	RA LS (%)
Control	-19.96 (±1.0)	37.74 (±10.84)	-28.80 (±8.56)	40.18 (±13.01)
PAH	-17.27 (±4.65)	30.84 (±15.8)	-12.9 (±7.9)	20.9 (±8.5)
P value	<0.0001	<0.0001	<0.0001	<0.0001

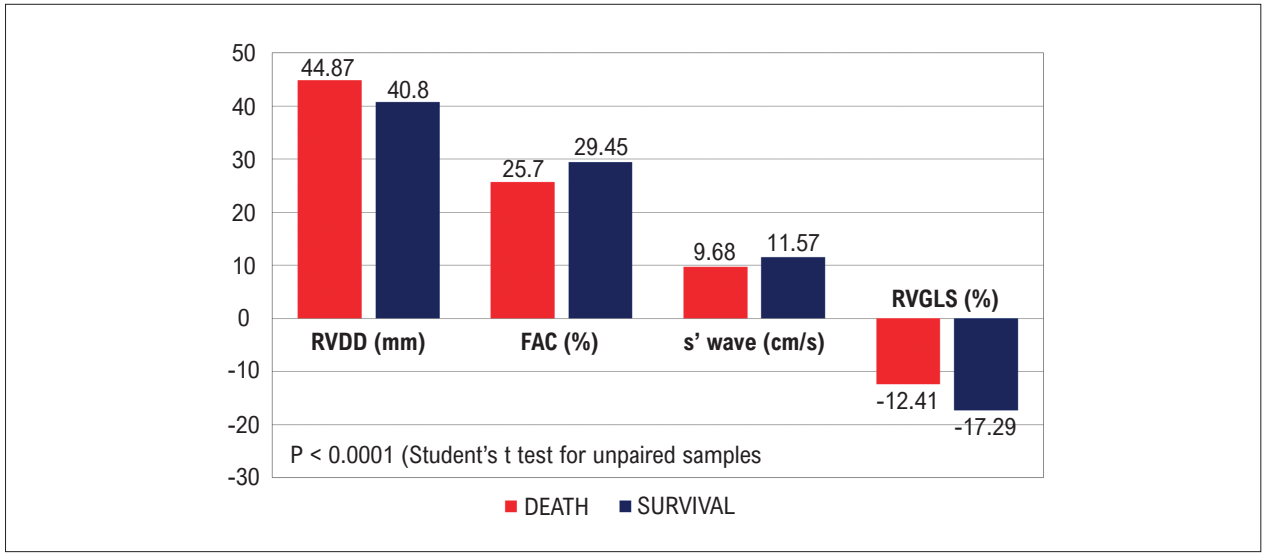
LA LS: left atrial reservoir longitudinal strain; LV GLS: left ventricular global longitudinal strain; PAH: pulmonary arterial hypertension; RA LS: right atrial reservoir longitudinal strain; RV GLS: right ventricular global longitudinal strain.

who died had a significantly lower mean age (45.7 ± 13.1 years versus 51.1 ± 10.8 years, $p < 0.0001$).

Regarding the echocardiographic parameters, as shown in Graph 2, the patients who died had larger RV diameter (44.9 ± 9 mm versus 40.8 ± 5 mm, $p < 0.0001$), lower RV fractional area change (25.7% ± 9.2% versus 29.5% ± 10.2%, $p < 0.0001$), lower tricuspid annular s' wave (9.7 ± 2.1 cm/s versus 11.6 ± 2.6 cm/s, $p < 0.0001$), lower absolute RV global longitudinal strain (−12.4 ± 5.3% versus −17.3 ± 4.5%, $p < 0.0001$), and lower absolute LV global longitudinal strain (−14.2% ± 3.9% versus −16.7% ± 3.4%, $p < 0.0001$). TAPSE, relative thickness of the RV



Graph 1 – *Pulmonary hypertension outcome. FC: functional class.*



Graph 2 – *Pulmonary hypertension Echocardiographic parameters of the right ventricle. DdVD: diâmetro diastólico do ventrículo direito; FAC: mudança da área fracional;FAC: fractional area change; RVDD: right ventricular diastolic diameter; RVGLS: right ventricular global longitudinal strain.*

walls, and tricuspid regurgitation velocity did not show significant differences.

Discussion

When comparing patients with pulmonary hypertension due to schistosomiasis with healthy individuals, we observed a decrease in LV size and mass index, probably due to RV dilation that pushes the interventricular septum. The ejection fraction did not change, but LV longitudinal strain was significantly reduced, suggesting that there is also subclinical systolic dysfunction in this cavity.[10] This condition has been observed in other studies, indicating that myocardial involvement is not restricted to the right cavities.[11, 12] With regard to diastolic function, there was a significant decrease in the velocity of the mitral E wave and mean e' wave by tissue Doppler in patients with PAH; however, the E/e' ratio was normal, allowing estimation of mean LA pressure within the normal values, which characterizes pre-capillary pulmonary hypertension. Tricuspid regurgitation velocity and, consequently, RV systolic pressure were significantly increased, characterizing pulmonary hypertension. We did not use correction with diameter and expansion of the inferior vena cava due to the great variability of this measurement, which makes it unreliable.[13]

When we evaluated the right cavities, the differences were more evident, with important dilation of the cavity, increased lateral wall thickness, and decreased functional parameters (RV fractional area change, tricuspid annular s' wave velocity, and TAPSE), RA dilation, and significantly increased pulmonary resistance.

Relative RV thickness, determined by the quotient between the basal RV diameter and the diastolic thickness of the lateral wall, obtained from the subcostal position, was significantly increased, as a response to the remodeling of the cavity caused by the pressure overload, translating the relationship between the diameter of the cavity and wall thickness. The RV has the particularity of remodeling by simultaneously increasing cavity size and wall thickness, in both pressure and volume overload.[10] Under physiological conditions, relative RV thickness is low, adapted to the low pressure of the right cavities. Under pressure overload, the relationship between cavity dilation and wall thickness reflects the degree of concentric or eccentric remodeling that occurs in response to increased pressure.[14] One study used relative thickness of the RV, analogously to that of the LV, to determine the type of remodeling in this cavity.[15] The greater the predominance of hypertrophy at the expense of cavity dilation (concentric remodeling), the more favorable the evolution of patients. The cutoff value used to detect better survival was ≥ 0.21. In the present study, we were unable to verify this condition, because there was no significant difference between survivors (whose relative RV thickness was 0.22 ± 0.05) and patients who died (whose relative RV thickness was 0.21 ± 0.05).

All myocardial strain parameters were reduced. In addition to LV longitudinal strain, LA reservoir longitudinal strain was decreased, although still within normal limits. The global longitudinal strain of the RV and RA were markedly reduced, indicating systolic dysfunction of the right cavities observed on the echocardiogram. The longitudinal strain values of the RV lateral wall were not used because, in this study, there were no relevant differences in relation to the global longitudinal strain of this chamber.

When we compare the results of the patients who died with those who survived, in addition to FC, where all patients in FC IV died, while no patient in FC I had this outcome (Graph 1), RV dimensions, RV fractional area change, tricuspid annular s' wave velocity, RV global longitudinal strain, and LV global longitudinal strain showed a significant relation with death (Graph 2). The decrease in LV longitudinal strain may be related to the greater severity of pulmonary hypertension which, by affecting the RV musculature, also decreases LV systolic function.[11, 12]

Conclusion

Pulmonary hypertension related to the hepatosplenic form of schistosomiasis causes remodeling of the right chambers, with decreased parameters of RV systolic function and myocardial strain. Patients who died during the 10-year follow-up showed larger RV dimensions, lower fractional area change, lower tricuspid annular systolic velocity, lower RV global longitudinal strain, and more advanced functional class.

Author Contributions

Conception and design of the research: Del Castillo JM, De Oliveira KB, Bandeira AMP, Brindeiro Filho D; Acquisition of data: Del Castillo JM, De Oliveira KB, Bandeira AMP, Brindeiro Filho D; Analysis and interpretation of the data: Del Castillo JM, De Oliveira KB; Statistical analysis and Writing of the manuscript: Del Castillo JM; Critical revision of the manuscript for intellectual content: De Oliveira KB, Travassos RRO, Bandeira AMP, Silveira CAM, Brindeiro Filho D.

Potential Conflict of Interest

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

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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