

## Pulmonary Artery Pressure, Gender, Menopause, and Pregnancy in Schistosomiasis-Associated Pulmonary Hypertension

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### Abstract

**Background:** Schistosomiasis-associated pulmonary arterial hypertension (SPAH) is a major concern worldwide. However, the role of gender-specific contributing factors in SPAH is unknown.

**Objective:** We investigated how systolic pulmonary artery pressure (SPAP) values and the presence of severe SPAP relate to gender, menopausal status, and pregnancy history in SPAH patients.

**Methods:** Seventy-nine patients diagnosed with SPAH from 2000 to 2009 were assessed and 66 were enrolled in the study. Information about age, menopausal status, pregnancy, echocardiography-derived SPAP, and invasive mean pulmonary artery pressure (mPAP) was collected from medical records. The relation between values of SPAP and mPAP and their agreement for severe disease were assessed. Regression models assessed the association of gender, menopausal status, and pregnancy history with SPAP values and the presence of severe SPAP.

**Results:** Moderate correlation and good agreement for severe disease were found between mPAP and SPAP. Mean SPAP values were similar for men and women. A trend toward higher values of SPAP was found for non-menopausal women compared to men. Higher SPAP values were found for menopausal compared to non-menopausal women; the values were non-significant after adjustment for age. Pregnancy history had no association with SPAP. Menopause and positive pregnancy had no association with severe SPAP.

**Conclusion:** In SPAH patients, neither gender, nor menopausal status, nor pregnancy history showed independent correlation with SPAP values assessed by echocardiography. (Arq Bras Cardiol. 2013;101(2):154-159)

**Keywords:** Hypertension, Pulmonary; Schistosomiasis; Pregnancy; Menopause; Echocardiography, Doppler.

### Acronym and abbreviation list

- mPAP - mean pulmonary artery pressure
- PAH - pulmonary arterial hypertension
- SPAP - pulmonary artery systolic pressure
- SPAH - schistosomiasis-associated pulmonary arterial hypertension

### Introduction

Schistosomiasis affects about 207 million people worldwide and is known as a potential trigger for the pulmonary arterial hypertension (PAH) immune-inflammatory pathway.

Schistosomiasis-associated PAH (SPAH) is recognized as one of the most important etiologies of PAH - with a prevalence of approximately 5% in patients with hepatosplenic schistosomiasis. PAH is a high-risk condition, related to elevated rates of mortality<sup>1-6</sup>. However, literature regarding the clinical presentation of SPAH is limited.

Echocardiography-derived systolic pulmonary artery pressure (SPAP) is usually used to screen patients suspected of PAH. Adding right atrial pressure to the pressure gradient between right atrium and ventricle has been validated as a method to assess SPAP over the decades<sup>7,8</sup>. In fact, SPAP assessed by Doppler-echocardiography is a well-established method in clinical practice, being widely available, inexpensive, and safe<sup>9-15</sup>.

In PAH clinical presentation, the role of gender-specific characteristics is controversial. Despite the evidence that female hormonal balance could be related to pulmonary artery pressure, studies have failed to demonstrate significant differences in the prognosis of PAH in men compared to women<sup>16-18</sup>. Moreover, the interest in menopausal aspects of PAH is growing, as postmenopausal women have shown significant susceptibility to elevated pulmonary pressure<sup>19,20</sup>.

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We investigated how SPAP values and severity relate to gender in patients with SPAH. We also explored the association of SPAP with menopausal status and pregnancy history in the female population. Finally, we compared echocardiography-derived SPAP values to values of invasive mean pulmonary artery pressure (mPAP).

## Methods

### Study design and population

We enrolled 89 patients (67% women) who had been diagnosed with SPAH by the Pulmonary Hypertension Group at University of Pernambuco (Recife, Brazil) between January 2000 and November 2009. Investigation for PAH follows the protocol suggested by Gaine and Rubin, including diagnostic right-chamber catheterization to ensure values of mPAP > 25 mmHg and pulmonary capillary wedge pressure (PCWP) < 15 mmHg<sup>21</sup>. The diagnosis of schistosomiasis is individually assessed and based on exposure history and stool samples, with confirmatory rectal biopsy and/or serology in specific cases<sup>22</sup>. In the absence of other etiology, SPAH was defined when schistosomiasis and portal fibrosis were present in a patient with PAH assessed by invasive right-chamber catheterization. Our study was approved by the local ethics committee.

### SPAP assessment

SPAP data were collected from the first registered echocardiogram performed and interpreted by staff cardiologists at the institution of enrolment. Suboptimal echocardiogram views or inadequate tricuspid regurgitation were present in 4 men and 9 women. The institution's protocol to assess SPAP dictates the following: (a) patient in the left lateral decubitus position; (b) color flow Doppler imaging is used to identify and guide alignment of the cursor with the tricuspid regurgitant jet; (c) using continuous-wave Doppler, tricuspid regurgitation velocity is assessed from different views to measure peak velocity (*v*); (d) transtricuspid pressure gradient is calculated using the modified Bernoulli equation ( $4v^2$ ); (e) right atrial pressure is evaluated by assessing the respiratory variation in the diameter of the inferior vena cava (values estimated as 5, 10, or 15 mmHg); and (f) SPAP is calculated by adding the transtricuspid pressure gradient to the atrial pressure estimate. The measurement is not performed if there is evidence of obstruction to pulmonary artery flow, such as pulmonary stenosis or right ventricular outflow obstruction.

### Additional data acquisition

Information on age, menopausal status, and pregnancy history at the diagnosis of SPAH was collected from medical records on all patients followed in the institution. Information on menopausal status was present in 35 women (58% menopause positive) and data on pregnancy history was collected in 20 women (13 had positive history for pregnancy; 56% vs. 73% for non-menopausal vs. menopausal women, respectively). Invasive mean pulmonary artery pressure (mPAP), assessed by diagnostic

right-chamber catheterization, was also collected if the interval to the assessment of echocardiography-derived SPAP did not exceed 6 months (*n* = 42; 81% females; age  $44.5 \pm 14.3$  years; SPAP  $96.7 \pm 28.8$  mmHg; and mPAP  $60.3 \pm 14.7$  mmHg).

### Statistical analysis

The software STATA, version 11.2, was used to perform the statistical analysis on a cross-sectional basis. Student's *t*-test was used to assess differences between mean values and the *z*-test was used to assess differences between proportions. Severe SPAP and mPAP were defined as the 4<sup>th</sup> quartile in both cases ( $\geq 120$  mmHg and  $\geq 76$  mmHg for SPAP and mPAP, respectively). The relationship between echocardiography-derived SPAP and invasive mPAP was assessed by Pearson's correlation. Percent agreement and Cohen's kappa coefficient for severe classification of SPAP and mPAP were also computed.

The relation of SPAP, gender, and menopausal status was assessed using linear regression. Logistic regression was used to compute odds ratios for severe SPAP, according to gender and menopausal status. Regression models were performed on univariate and multivariate bases, adjusted to age at diagnosis. Menopausal status as a predictor of SPAP values was compared to male gender and as a binary variable in a female-only subset. For a subgroup of women diagnosed with SPAH, an additional analysis assessed the influence of pregnancy history (used as a binary variable) in the regression models.

## Results

A total of 66 patients with data on SPAP were included. Patient characteristics are shown in Table 1, arranged according to gender and menopausal status. A moderate correlation was found between mPAP and SPAP ( $r = 0.51$ ,  $p < 0.001$ ; Figure 1). In this group, both methods classified 10 cases as severe SPAH, agreeing in 82% of the classifications (Kappa coefficient = 0.3;  $p < 0.01$ ). Mean SPAP values were similar for men and women (Table 1). In addition, no significant difference was found when menopausal women were compared to men. However, higher values of SPAP were found for non-menopausal women compared to men, with a trend in significance (Table 2).

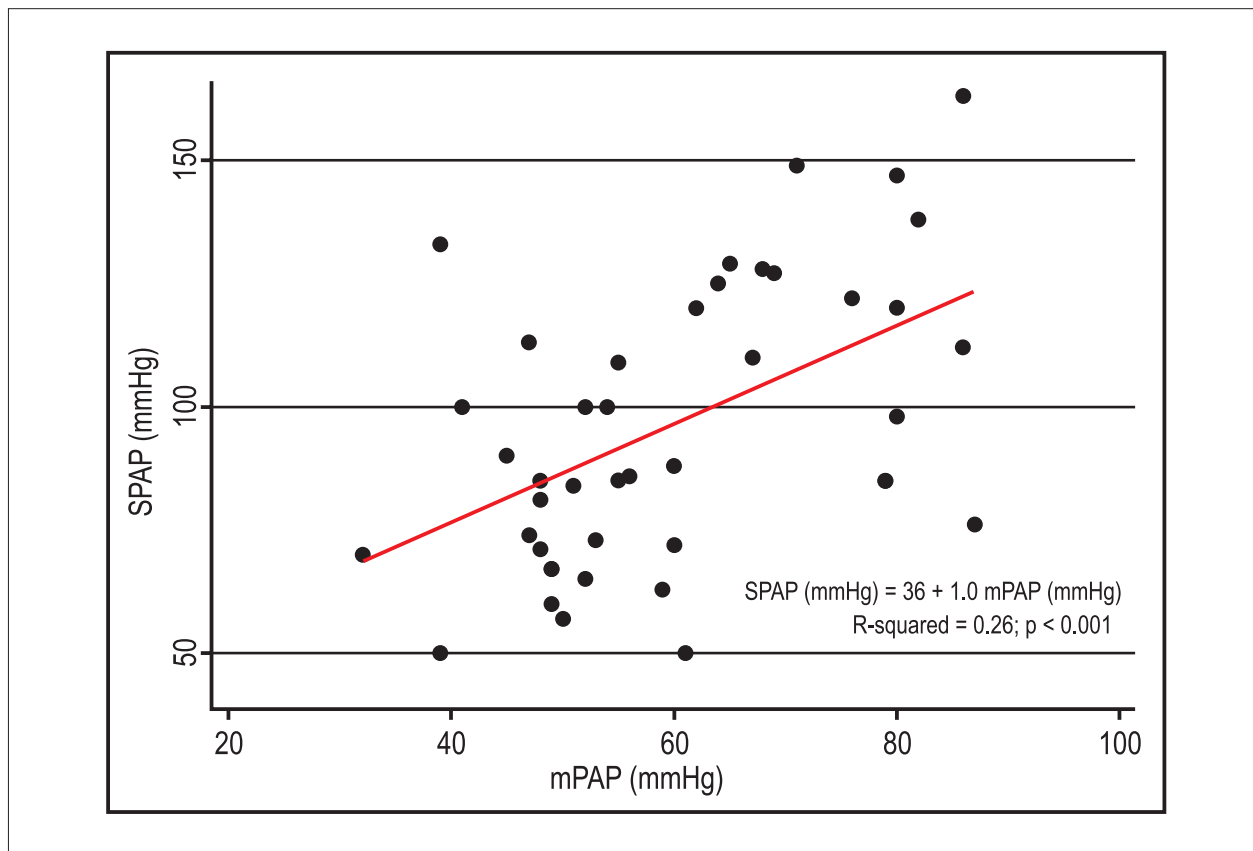
Among females, statistically significant higher mean SPAP values and ages were found for menopausal women (Table 1). However, the differences become non-significant after adjustment for age. The mean SPAP was  $118.3 \pm 32.3$  mmHg and  $95.1 \pm 26.2$  mmHg ( $p = 0.1$ ) for women without and with previous pregnancy, respectively. No statistical significance was found when history of pregnancies was added as a covariate (Table 2).

Considering the prediction of severe SPAH (SPAP > 120 mmHg), the presence of menopause and a positive history for pregnancy were consistently associated with low odds ratios; however, although trends were present, no statistically significant odds ratio was reported (Table 3).

**Table 1** – Characteristics of patients with schistosomiasis-associated pulmonary hypertension, arranged according to gender and menopausal status

Variable	Gender (mean ± SD)			Menopausal status (mean ± SD)		
	Men (n = 15)	Women (n = 51)	p	Absent (n = 15)	Present (n = 20)	p
Age at diagnosis (years)	46.8 ± 12.8	45.9 ± 15.1	0.8	29.4 ± 6.8	58.4 ± 9.8	< 0.0001
SPAP (mmHg)	87.8 ± 31.6	93.8 ± 28.3	0.5	110.7 ± 26.0	86.5 ± 20.0	0.003
Number of pregnancies	NA	3.2 ± 2.8	NA	1.6 ± 0.5	4.2 ± 3.2	0.098

SD: standard deviation; SPAP: systolic pulmonary artery pressure; NA: non-applicable. Mean number of pregnancies excludes patients without history of pregnancy (7 cases overall; 2 with positive menopausal status). T-test was used to acquire p-values.



**Figure 1** – Scatter plot for the correlation between echocardiography-derived SPAP and invasive mPAP in patients with schistosomiasis-associated pulmonary hypertension (n = 42). SPAP: Systolic pulmonary artery pressure by echocardiography; mPAP: mean pulmonary artery pressure by invasive measurement.

## Discussion

More than 770 million people worldwide are at risk of contracting schistosomiasis<sup>2,23</sup>. The prevalence of elevated pulmonary pressures in patients with schistosomiasis is still controversial, but it has been reported as one of the most important etiologies of PAH<sup>1-5,24,25</sup>. This is the first study to assess the influence of gender on echocardiography-derived SPAP and to investigate the role of menopausal status and pregnancy history among patients diagnosed with SAPAH.

The estimation of SPAP by Doppler echocardiography is validated, safe, usually feasible, and universally adopted in screening protocols for PAH<sup>8,26-28</sup>. We showed a moderate correlation between echocardiography-derived SPAP and invasive measurement of mPAP in patients with SAPAH (Figure 1), with 82% of agreement and a fair Kappa coefficient when classifying the most severe cases. mPAP values assessed by right-chamber catheterization are considered the gold standard for the diagnosis of PAH. Similar to our study, diverse reports have shown that the correlation between SPAP values estimated by echocardiography and determined invasively is moderate to strong<sup>7,11,12,29,30</sup>.

**Table 2 – Linear regression models for SPAP (mmHg) according to gender, menopausal status, and pregnancy history**

Predictor	n	Regression coefficients (p value)		
		Univariate	MODEL 1	MODEL 2
Female (vs. male)	66	6.0 (0.48)	13.7 (0.09)	
non-menopausal women (vs. male)	51	22.9 (0.02)	23.4 (0.05)	NA
Menopausal women (vs. male)	51	-1.3 (0.88)	5.4 (0.59)	
Menopausal present (vs. absent) <sup>§</sup>	36	-24.2 (0.003)	-8.4 (0.58)	-38.7 (0.11)
Pregnancy present (vs. absent)	20	-23.1 (0.10)	-13.9 (0.31)	-20.1 (0.15)

SPAP: systolic pulmonary arterial pressure; NA: non-applicable. MODEL 1 – adjusted for age; MODEL 2 – age, menopausal status, and pregnancy history in the same model. § In MODEL 2, analysis used n = 20.

**Table 3 – Logistic regression models for severe SPAP (≥ 120 mmHg) according to gender, menopausal status, and pregnancy history**

Predictor	n	Odds Ratio (p value)		
		Univariate	MODEL 1	MODEL 2
Female (vs. male)	66	1.2 (0.77)	1.7 (0.51)	
non-menopausal women (vs. male)	51	2.0 (0.41)	5.5 (0.19)	NA
Menopausal women (vs. male)	51	0.4 (0.38)	0.4 (0.39)	
Menopausal present (vs. absent) <sup>§</sup>	36	0.2 (0.09)	0.4 (0.62)	0.03 (0.14)
Pregnancy present (vs. absent)	20	0.2 (0.14)	0.3 (0.27)	0.1 (0.13)

SPAP: systolic pulmonary arterial pressure; NA: non-applicable. MODEL 1 – adjusted for age; MODEL 2 – age, menopausal status, and pregnancy history in the same model. § In MODEL 2, analysis used n = 20.

We found a predominance of females in our SPAH patients (67%). A similar predominance of females has been reported for other PAH etiologies, but the real influence of gender in PAH is still controversial. The higher prevalence of PAH in women compared to men, the thrombogenic effects of estrogen, and the fluctuation of estrogen metabolites may indicate potential negative effects of female physiology on the pulmonary vasculature<sup>31,32</sup>. Estrogen, however, also showed benefits for pulmonary vasculature in both acute and chronic experimental models of pulmonary hypertension<sup>31,32</sup>. We found similar values of SPAP in men and women with SPAH. Moreover, gender had no statistically significant predictive ability for SPAP when adjusted for age at diagnosis (Table 2).

Pulmonary artery vasoreactivity is affected by changes in estrogen levels, even in a physiological range<sup>33</sup>. Menopausal status represents an important decrease in the circulating estrogen in women. Among patients with systemic sclerosis, postmenopausal women have shown an increased risk for the development of PAH<sup>19</sup>. In fact, the majority of pulmonary hypertensive women in the University of Colorado Pulmonary Hypertension Center were postmenopausal<sup>20</sup>. Our study has intrinsic limitations related to the information on menopausal status collected from medical records. In addition, the real influence of hormonal imbalance could not be assessed, due to the absence of serum hormonal values in our data.

In the subset of SPAH patients who were women, the association between menopausal status and SPAP had no statistical significance when adjusted for age (Table 2). In univariate analysis with SPAH patients, non-menopausal females showed significantly higher SPAP values compared to men; however, this association had borderline statistical significance (p = 0.05) after adjustment for age (Table 2). Our results suggest that the differences found comparing post-menopausal and non-menopausal subjects are due to the influence of age on SPAP. In fact, the positive correlation between SPAP values and age has been seen in a large population of participants free of PAH. In this population, the relationship seems to be mediated by left ventricular diastolic dysfunction and systemic vascular stiffening<sup>34</sup>.

Hormonal and hemodynamic changes that occur during pregnancy contribute to the high maternal mortality in women with pulmonary vascular disease<sup>35</sup>. The influence of previous pregnancies on the clinical presentation of SPAH, however, is unknown. In 20 women at the time of diagnosis for SPAH, we assessed the influence of a positive pregnancy history on the values of SPAP. Thus, the reduced number of patients probably limited the analysis. In our population, positive pregnancy history did not show statistically significant association with SPAP in women with SPAH.

There is evidence that female hormonal imbalance may relate to the severity of pulmonary pressure values. Experimental models showed more severe pulmonary hypertension in chronically hypoxemic rodents that have had their ovaries removed than those with intact ovaries. In this study, the return of estrogens after an ovariectomy led to a regression to baseline levels of pulmonary pressure<sup>36</sup>. Moreover, a history of previous pregnancies showed prognostic value in pregnant patients with pulmonary hypertension<sup>37</sup>. We investigated how gender, menopausal status, and pregnancy history predicted severe SPAP values (> 120 mmHg) in SPAH patients, but found no statistically significant association (Table 3).

Our study contributes to the knowledge of SPAH clinical presentation and its relation to gender, menopausal status, and pregnancy history; however, the role of gender-specific characteristics in the pathological processes of SPAH is yet to be defined. Further studies are needed to establish the relations between gender particularities and SPAH clinical presentation.

## Conclusion

In a population of SPAH patients, neither gender, nor menopausal status, nor pregnancy history showed a statistically significant, independent relationship to SPAP values assessed by echocardiography. Differences in SPAP that appear to be related to menopausal status seem to be mediated by age differences.

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## Author contributions

Conception and design of the research: Armstrong AC, Bandeira AMP, Correia LCL, Lima JAC, Sobral Filho DC; Acquisition of data: Armstrong AC, Bandeira AMP, Melo HCO, Silveira CAM, Albuquerque E, Moraes Jr. JC, Silva AML, Sobral Filho DC; Analysis and interpretation of the data: Armstrong AC, Bandeira AMP, Correia LCL, Melo HCO, Silveira CAM, Albuquerque E, Moraes Jr. JC, Silva AML, Lima JAC, Sobral Filho DC; Statistical analysis: Armstrong AC, Bandeira AMP, Correia LCL, Sobral Filho DC; Writing of the manuscript: Armstrong AC, Lima JAC, Sobral Filho DC; Critical revision of the manuscript for intellectual content: Armstrong AC, Bandeira AMP, Correia LC, Melo HCO, Silveira CAM, Albuquerque E, Moraes Jr. JC, Silva AML, Lima JAC, Sobral Filho DC.

## Potential Conflict of Interest

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

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