Original Article

Echocardiographic Evaluation of Right Atrial Function in Patients with Precapillary Pulmonary Hypertension

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Abstract

Background: Considering that the effect of right ventricular (RV) failure on the right atrium (RA) is an essential part of the pathophysiology of pulmonary hypertension (PH), the assessment of RA function seems to have prognostic value in the course of the disease, but there are still few studies on this subject.

Objective: To evaluate myocardial strain of the RA in patients with precapillary PH.

Methods: This is an observational, longitudinal, prospective study involving 36 patients with precapillary PH, in whom two-dimensional Doppler echocardiography was performed. A control group consisting of 26 healthy individuals was used.

Results: There was a statistically significant difference in mean RA strain between the group with PH (26.3%) and the control group (40.7%). Regarding RA strain of the patients, there was a negative and moderate correlation with RA pressure, RV diameter, and RV hypokinesia; negative and weak correlation with pulmonary artery systolic pressure (PASP); negative and strong correlation with RA area; and positive and moderate correlation with, tricuspid annular plane systolic excursion (TAPSE), TAPSE/PASP, and RV strain. Patients with RA strain ≤ 23 had significantly reduced overall survival compared with patients with RA strain > 23, but this value was not a predictor of mortality.

Conclusion: It was possible to demonstrate that the analysis of myocardial strain of the RA provides more accurate information about RA function and can be used as an additional parameter in the follow-up of patients with PH, given the early evaluation of atrial dysfunction.

Keywords: Pulmonary Hypertension; Right Atrial Function; Doppler Echocardiography.

Introduction

Pulmonary hypertension (PH) is a hemodynamic condition characterized by mean pulmonary artery pressure greater than or equal to 20 mmHg at rest during right heart catheterization.[1] PH, after hypertension and coronary artery disease, is believed to be the third leading cardiovascular condition, presenting poor long-term therapeutic outcome.[2] Moreover, nonspecific clinical manifestations, the long oligosymptomatic period, and lack of knowledge about the disease lead to poor prognosis and delay in diagnosis and initiation of treatment.[3]

Patients with PH have increased afterload in the right ventricle (RV) due to increased pulmonary vascular resistance and reduced compliance.[4] Consequently, RV remodeling occurs, with increased RV end-diastolic pressure and right atrial pressure (RAP), which leads to right heart failure and a worse prognosis.[5]

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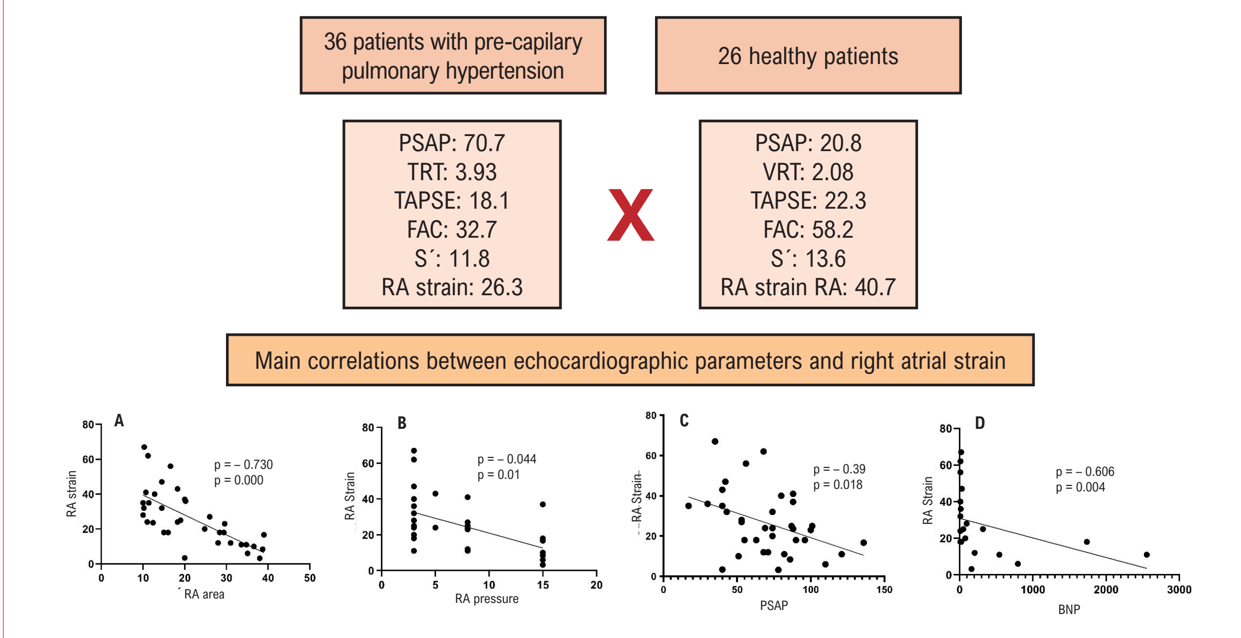
In addition to the RV, the remodeling of the right atrium (RA), with changes in size, function, and pressure, has become a focus in PH in recent years, considering that changes in RA function are relevant prognostic markers of adverse outcomes.[6] Moreover, the evaluation of RA overload and dysfunction has important implications for assessing the severity of right heart failure in the management of patients with PH.[5]

For many years, transthoracic echocardiography has been used for the diagnosis and follow-up of PH, since it is the best noninvasive test for its screening. Thus, it allows estimating the pulmonary artery systolic pressure (PASP) through the direct measurement of the tricuspid regurgitation jet velocity and the estimation of RAP, allowing the evaluation of right and left ventricular functions.[7]

In addition to the usual linear parameters of RV function, the role of strain analysis of the RA has recently been studied as an earlier parameter and for prognostic evaluation of these patients. Strain is defined as the fractional change in the length of a myocardial segment, usually related to the length at end-diastole.[8]

Two-dimensional speckle tracking echocardiography (2D-STE) is a reliable technique for tracking, independent of the angle of myocardial strain, which allows noninvasive and quantitative assessment of global or regional myocardial function; it is, therefore, potentially able to explore RA strain during each phase of the cardiac cycle.[5]

Central Illustration: **Echocardiographic Evaluation of Right Atrial Function in Patients with Precapillary Pulmonary Hypertension**



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The figure summarizes the main echocardiographic parameters in patients with precapilary pulmonary hypertensio compared to healthy patients, as well as the main correlattions found in the study with right atrial deformation in the diseased group. BNP: brain natriuretic peptide; FAC: fractional area change; PASP: pulmonary artery systolic pressure; RA: right atrial; S': tricuspid annular systolic velocity; TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspid regurgitation velocity.

Considering that the impact of RV insufficiency on the RA is an essential part of the pathophysiology of PH, the assessment of RA function seems essential for a better understanding of RV function in PH, considering that the importance of the RA-RV axis in PH is growing and being increasingly studied. However, despite described evidence, there are still scarce studies on the assessment of RA dysfunction in patients with precapillary PH based on the measurement of RA longitudinal strain by 2D-STE.[5]

Therefore, this study aimed to evaluate the myocardial strain of the RA in patients with precapillary PH, correlating it with echocardiographic parameters of the right heart chambers.

Methods

Study population

This is an observational, longitudinal, prospective study, conducted from May 2019 to December 2022, involving patients with PH, followed up at the pneumology outpatient clinic of a tertiary university hospital, in whom two-dimensional Doppler echocardiography was performed, and RA strain and variables related to right and left ventricular dysfunction were evaluated. Serum brain natriuretic peptide (BNP) concentration was also measured in the patients. In addition, for comparison of the RA strain values, a control group consisting of healthy people was used.

The inclusion criteria for the group of patients were: a) confirmed diagnosis of PH by echocardiographic and hemodynamic criteria; b) patients older than 18 years. The exclusion criteria were: a) patients with post-capillary PH (PH group II); b) presence, on echocardiographic examination, of hemodynamic congestion (E/E′ > 14), grade 2 or 3 diastolic dysfunction, or reduced left ventricular ejection fraction; c) presence of left structural heart disease or left valvular heart disease; d) pregnant women; e) inadequate echocardiographic window. To define the control group, represented by healthy people, we included patients older than 18 years, with no comorbidities, no PH, and no cardiac alterations.

This project was approved by the Ethics Committee of the Centro de Ciências Médicas of the Universidade Federal da Paraíba, under CAAE number: 21291419.6.0000.8069.

Transthoracic echocardiography

Transthoracic echocardiography examinations were performed using the GE Vivid T8 device with a 2.5 MHz M4h-5 transducer by a single echocardiographer examiner blinded to the group participants. The images were acquired in the left lateral decubitus position, according to the recommendations of the American Society of Echocardiography.[10] Video images corresponding to 3 cardiac cycles were acquired.

The ejection fraction was estimated by Simpson's biplane method. The RAP was estimated from the inspiratory collapse of the inferior vena cava. The evaluation of myocardial strain was performed on a workstation in the EchoPach V204 program, and the endocardial tracing was performed manually at the end of diastole, and the measurement was made after the examiner checked whether the quality of the endocardial border tracking was good. In the presence of 2 inadequate segments, the examination was excluded from the study. In the apical window, sections focused on the RV and RA were acquired. With this, the average quantification of the RV and RA free wall strain was performed.

Statistical analysis

Regarding data analysis, the continuous variables were presented as mean and standard deviation (SD) or as medians and interquartile ranges, if, respectively, they followed or did not follow normal distribution. Categorical variables, in turn, were presented as absolute and relative frequencies. The normality analysis was performed using the Kolmogorov-Smirnov test and applying the central limit theorem.

The groups of parametric continuous variables were compared using Student's t-test for independent samples; the comparison between groups of non-parametric variables was done using the Mann-Whitney U test. Three or more groups of variables with normal distribution in groups and subgroups were compared by the ANOVA test, with Tukey and Bonferroni post-hoc tests. Three or more groups of non-parametric variables were compared by the Kruskal-Wallis test, and Dunn's post hoc test was performed to assess the statistical significance between the subgroups. In addition, due to the lack of normality in the distribution of the sample, Spearman's correlation coefficient was used to assess the degree of correlation between two variables.

For data analysis, a normality cutoff point for RA strain of 25% [9] was considered, dividing into two groups: normal (> 25%) and reduced (≤ 25%). Fisher's exact test was used to assess the association between these groups and categorical variables such as mortality during patient follow-up. In addition, the receiver operating characteristic (ROC) curve was performed to assess the accuracy of RA strain for mortality, and a Kaplan-Meier survival curve was constructed.

Results

We evaluated 36 patients with PH, whose median age was 50.5 years, with a minimum value equal to 24 and a maximum of 81 years; 80.5% of the participants (29) were female. The control group was composed of 26 healthy patients, with a median age of 46.5 years. The minimum value was 22, and the maximum was 74 years. Fourteen patients were female (53.8%) (Table 1).

According to the World Health Organization functional classification, most patients with PH (55.5%) had class III;30.5% had class II; 11.1% had class IV, and only 2.7% had class I. Pericardial effusion was not observed in all patients (Table 2). Pericardial effusion was present in only 24.2% of the participants. Regarding BNP levels, the minimum value was 10, while the maximum value was equal to 2555, with a mean of 319.3 (SD ± 652.8).

The etiologies of PH, in decreasing order of prevalence, were: idiopathic (42.4%); connective tissue disease (15.2%); pulmonary thromboembolism (12.1%); chronic obstructive pulmonary disease (12.1%); HIV (3%); schistosomiasis (3%); kyphoscoliosis (3%); idiopathic pulmonary fibrosis (3%); interatrial communication (3%); and subsegmental stenosis of the left pulmonary artery suggestive of Alagille syndrome (3%).

Table 1 – Profile of patients with PH and the control group

Parameters	PH patients (n = 36)	Healthy group (n = 26)
Age (years) [a]	50.5 [37.2 – 65.7]	47 [38 – 59]
Female, n (%)	29 (80.5%)	15 (55.5%)
BMI (kg/m²) [b]	27.9 ± 8.7	25.3 ± 6.3
Functional class, n (%)		
I	1 (2.7)	
II	11 (30.5)	
III	20 (55.5)	
IV	4 (11.1)	
Number of medications in use, n (%)		
0	8 (22.2)	
1	12 (33.3)	
2	10 (27.7)	
3	6 (16.6)	
Etiology, n (%)		
Group I	27 (75)	
Group III	4 (11.1)	
Group IV	5 (13.8)	

[a] Values expressed as median and interquartile range; [b]Values expressed as mean and SD. BMI: body mass index; PH: pulmonary hypertension;

Regarding drug therapy, 78.2% of patients were using a phosphodiesterase-5 inhibitor (sildenafil); 45.4% were using some endothelin receptor antagonist (bosentan or ambrisentan), and 18.2% were using a prostacyclin analog (iloprost or selexipag). As for medication, 34.8% of patients were on monotherapy; 26% were on dual therapy; 17.4% were on triple therapy, and 21.7% were not on medication for PH. Patients who were not on optimal therapy had recently arrived for follow-up at the service.

As for the echocardiographic parameters of the right chambers of patients with PH (Table 2), the mean values of PASP, tricuspid regurgitation velocity (TRV), tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC) and S' wave were 70.7 mmHg, 3.93 m/s, 18.1 mm, 32.7%, and 11.8 cm/s, respectively. The mean strain of the RA and RV were 26.3% and 18.1%, respectively. As for RV hypokinesia, 33.3% had grade 0 (absent); 21.2% had grade 1 (mild); 15.2% had grade 2 (moderate), and 30.3% had grade 3 (severe).

In the control group, the mean values of PASP, TRV, TAPSE, FAC, and S' were 20.8 mmHg, 2.08 m/s, 22.3 mm, 58.2%, and 13.6 cm/s, respectively. The mean strains of the RA and RV were 40.7% and 26.7%, respectively. According to Table 2, there was a significant difference in the mean echocardiographic parameters of the right chambers between the groups with PH and the control group, including RA strain (p = 0.000), but there was no difference regarding the main parameters of the left chambers.

Table 2 – Echocardiographic parameters of right and left chambers of patients with PH and healthy patients

Variables	PH patients		Healthy group		p
	Mean	SD	Mean	SD	
PASP (mmHg)	70.7	26.5	20.8	4.5	0.000*
TAPSE (mm)	18.1	6.1	22.3	3.4	0.001*
TAPSE/PASP (mm/mmHg)	0.33	0.30	1.1	0.3	0.000*
VRT (m/s)	3.93	0.80	2.08	0.3	0.000*
FAC (%)	32.7	13.6	58.2	5.7	0.000*
S´ (cm/s)	11.8	3.9	13.6	2.3	0.072*
RA pressure (mmHg)	9.2	9.7	3.0	0	0.002*
RA area (cm²)	21.5	9.7	12	3.0	0.000*
RV diameter (mm)	41.7	11.2	29.4	4.2	0.000*
TAPSE/RV diameter	0.47	0.22	0.78	0.13	0.000*
RV strain/PASP	0.33	0.28	1.37	0.54	0.000*
RV strain (%)	18.1	7.7	26.7	4.0	0.000*
RA strain (%)	26.3	15.7	40.7	8.5	0.000*
RA area/RA strain	1.71	2.33	0.28	0.12	0.005*
EF (%)	68.4	6.2	65.2	5.6	0.319*
E/e´	6.7	1.7	7.3	2.1	0.376*
E/A ratio	1.1	0.7	1.3	0.4	0.167*
LVM (g)	124.9	49.8	127.7	35.7	0.816*

*E/A ratio: amplitude of the E wave of the mitral flow/amplitude of the e wave of the tissue Doppler curve in the mitral annulus; E/e': ratio between diastolic velocity E of mitral flow and diastolic velocity e' of mitral annulus; EF: ejection fraction; FAC: fractional area change; LVM: left ventricular mass; PASP: pulmonary artery systolic pressure; PH: pulmonary hypertension; RA: right atrial; RV: right ventricle; S': tricuspid annular peak systolic velocity; SD: standard deviation; TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspid regurgitation velocity. * Student's t test.*

In the group with PH, there was no significant difference in mean RA strain between the female and male sexes (p = 0.8). There was no correlation of RA strain with age (p = −0.215; p = 0.208) and dyspnea grade (p = −0.314; p = 0.104), nor was there a difference in mean RA strain between dyspnea grades (p = 0.237). However, there was a statistically significant difference in mean RA strain between patients with and without pericardial effusion (p = 0.011).

A negative and moderate correlation was found between RA strain and BNP levels (p = −0.606; p = 0.004). The Kruskal-Wallis test showed that the degree of hypokinesia has an effect on RA strain (p = 0.005). In addition, Dunn's post-hoc test showed that there are differences between the groups with absent and severe grade hypokinesia (p = 0.002).

As per Table 3, regarding RA strain, there was a negative and moderate correlation with RA estimated pressure, RV diameter, and RV hypokinesia; a negative and weak correlation with PASP; and a negative and strong correlation with RA area. In addition, a positive and moderate correlation was observed between RA strain and TAPSE, TAPSE/PASP, TAPSE/RV diameter, and RV strain, as well as a positive and weak correlation with FAC and RV strain/TAPSE. Some correlations are expressed in Figure 1.

Figure 2 shows the echocardiographic representation of patients with PH who had, respectively, the highest (62%) and lowest (3.2%) RA strain in the sample evaluated. Both had the same PH etiology, but patient 2 died at the age of 24 years.

Table 3 – Spearman's correlation between RA strain and echocardiographic parameters of patients with precapillary PH

Echocardiographic variables	Correlation	
	ρ (correlation coefficient)	p value
PASP (mmHg)	−0.39	0.018
TAPSE (mm)	0.46	0.005
TAPSE/RV diameter	0.65	0.000
RV strain/PASP	0.36	0.031
RV strain (%)	0.69	0.000
RV hypokinesia	−0.61	0.000
Pericardial effusion	0.52	0.001
TAPSE/PASP	−0.27	0.108
VRT (m/s)	0.28	0.09
FAC (%)	0.12	0.45
S´ (cm/s)	−0.44	0.01
RA pressure (mmHg)	−0.73	0.000
RA area (cm²)	−0.64	0.000
RV diameter (mm)	−0.39	0.018

FAC: fractional area change; PASP: pulmonary artery systolic pressure; RA: right atrial; RV: right ventricle ; S': tricuspid annular peak systolic velocity; TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspid regurgitation velocity.

During a mean follow-up period of 22.3 ± 14.9 (1 to 43) months, 6 patients died (18.2%), of whom 5 (83.3%) had RA strain < 25%. No patients were lost during follow-up. The mean RA strain of the patients who died was 15.6 (SD = 10.22), whereas, in the surviving patients, the mean was 28.4 (SD ± 15.9). There was no statistically significant difference in the means of RA strain between these two groups ($p = 0.067$). Furthermore, there was no association between mortality and the presence of normal or altered RA strain ($p = 0.209$).

The ROC curve model demonstrated that the RA strain cutoff point for which there is the highest sensitivity (83.3%) and specificity (63.3%) for association with mortality was a value ≤ 23, with the area under the ROC curve equal to 0.744 ($p = 0.019$) (Figure 2).

Using this cutoff point for Kaplan-Meier survival analysis, patients with RA strain ≤ 23 were found to have significantly reduced overall survival compared to patients with RA strain > 23 (log-rank $p = 0.031$) (Figure 2). However, Cox regression analysis did not identify RA strain ≤ 23% as a predictive factor for mortality (HR = 7.53, 95% CI = 0.87 to 65.04, $p = 0.066$).

Discussion

In our sample, the main echocardiographic parameters of the right chambers of patients with PH, such as PASP, TAPSE, TAPSE/PASP, TRV, and FAC (with the sole exception of S’), were significantly different compared to the parameters of the control group. RA strain, the focus of this study, also showed a significant difference between the groups.

Similarly, a group of authors[11] showed that RA longitudinal strain was reduced in patients with PH compared with controls (27.1 ± 11.6 versus 56.9 ± 12.7, adjusted $p < 0.001$), even after adjusting for RA area and invasive RAP. Another study[12] showed that the total longitudinal strain and total RA emptying fraction were significantly lower in patients with PH than in controls.

According to our analyses, in patients with PH, there was a strong negative correlation between RA strain and RA area. Compared with other studies, worse RA reservoir strain was also correlated with larger RA size among patients with PH ($r = -0.50$, $p < 0.0001$).[11] Furthermore, larger RA area and impaired RA function, explored by strain, were associated with worse outcomes in patients with idiopathic PH.[13]

We found a negative and weak correlation between RA strain and RAP. Previous studies[11,14,15] showed a significant negative correlation between RA strain and mean RAP, with correlation coefficients respectively equal to −0.35; r = −0.31 and −0.37 ($p < 0.005$).

Furthermore, we identified a negative and weak correlation between RA strain and PASP, which may be related to the fact that estimated PASP is no longer recommended as a key variable to assign

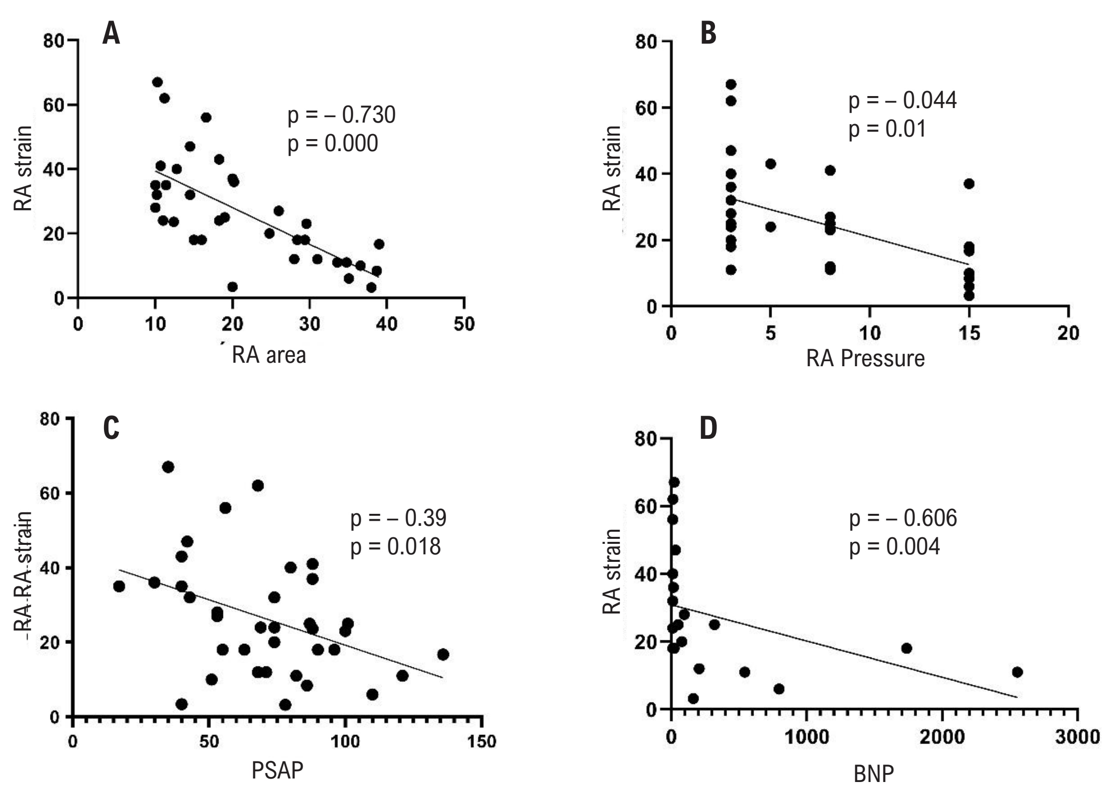

Figure 1 – *Correlation plots of RA strain with RA area, RA pressure, PASP, and BNP. BNP: brain natriuretic peptide; PASP: pulmonary artery systolic pressure; RA: right atrial.*

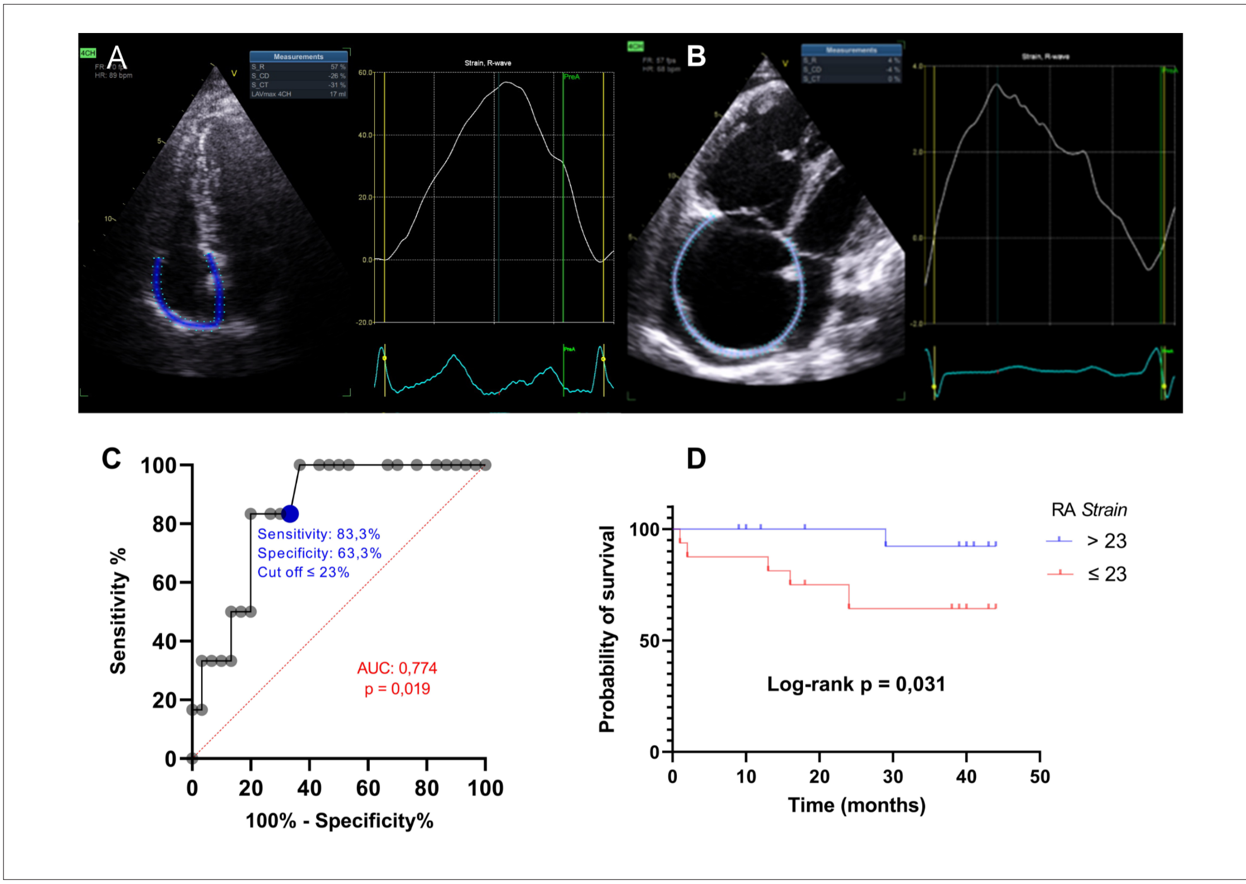

Figure 2 – *A) Echocardiographic image of the patient with the highest RA strain value (62%). PSAP: 35 mmHg; TRV: 2.86 m/s; TAPSE: 27 mm; TAPSE/PASP: 0.77 mm/mmHg; RA AREA: 10.3 cm^2; Etiology: idiopathic pulmonary arterial hypertension. B) Echocardiographic image of the patient with the lowest RA strain value (3.2%). PASP: 78 mmHg; TRV: 3,98 m/s; TAPSE: 17 mm; TAPSE/PASP: 0.22 mm/mmHg; RA area: 38 cm^2; Etiology: idiopathic pulmonary arterial hypertension. C) ROC curve for the relationship between right atrial strain and mortality. D) Probability of survival according to right atrial strain. PASP: pulmonary artery systolic pressure; TRV: tricuspid regurgitation velocity; TAPSE: tricuspid annular plane systolic excursion; RA: right atrial.*

the echocardiographic probability of HP,[1] given the inaccuracies in the estimation of RAP and the amplification of measurement error using derived variables.

In our study, the mean TRV value of patients with PH was outside normality, but there was no significant correlation with RA strain since the presence or absence of PH cannot be reliably determined by TRV alone, requiring other complementary parameters.[1]

In our sample, there was a positive and moderate correlation between RA strain and TAPSE/PASP. It is known that the TAPSE/PASP ratio is a noninvasive method that makes it possible to measure the RV-pulmonary artery coupling, which may help in risk stratification and prognosis of PH.[1]

We also found a significant correlation of RA strain with RV strain, RV diameter, and RV hypokinesia, confirming that assessment of RA function by strain is intrinsically related to RV dysfunction in PH.

In our study, BNP showed a significant correlation with RA strain. There was also a significant difference in the means of RA strain between BNP values stratified according to the risk of PH.[1] In some studies,[11,12] worse RA longitudinal strain also had a significant correlation with higher NT-proBNP levels, regardless of RA size, RAP, and RV dysfunction.

Finally, patients in our sample with RA strain ≤ 23 had significantly reduced overall survival compared with patients with RA strain > 23, but this value was not predictive of mortality, which may be related to the sample size, the limited number of events (only 6), and the heterogeneity of PH etiology. However, in a cohort[17] of patients with PH, it was observed that the functions of reservoir, conduit, and contraction of the RA, assessed by strain, were independent predictors of mortality and hospitalizations. A recent study[9] showed that RA strain was independently and strongly associated with 5-year mortality in patients with PH.

Conclusions

Our study demonstrated important associations between RA strain and echocardiographic parameters of RV dysfunction in PH, demonstrating that the analysis of RA myocardial strain provides more accurate information about RA function and shows potential prognostic value compared to traditional risk markers used in clinical practice. It is relevant to conduct further studies with the aim of consolidating RA strain as an earlier parameter for evaluation of overload and dysfunction of the RA to assess the severity of right heart failure in the management of patients with PH.

Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, statistical analysis, writing of the manuscript and critical revision of the manuscript for intellectual content: Carvalho WA, Carvalho AA, Martins ER, Medeiros Neto AH, Bacal F, Tavares M.

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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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Centro de Ciências Médicas da Universidade Federal da Paraíba under the protocol number 21291419.6.0000.8069. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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*Supplemental Materials

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