ABSTRACT

BACKGROUND: Right ventricular (RV) systolic dysfunction is a strong predictor of mortality in pulmonary hypertension (PH). The goal of this study was to investigate whether right atrium (RA) and RV myocardial strain related to PH using speckle tracking echocardiography provide a superior estimation of RV systolic function than 2-dimensional (2D)-echo.

METHODS: This cross-sectional study analyzed 22 patients with a diagnosis of PH stratified by right heart catheterization, and they were compared to a control group of 22 age- and sex-matched healthy subjects.

RESULTS: Global longitudinal peak systolic strain measured in the RV free wall from the apical 4 chamber view was −15% vs. −14.5% when measured from the subcostal view (p = 0.99). Mean longitudinal strain during reservoir phase, and longitudinal strain rate during atrial reservoir and passive conduit function was significantly impaired measured in the right atrial free wall in patients with PH.

CONCLUSIONS: This study showed impaired LV contractility in patients with PH assessed by speckle tracking strain. RV free wall longitudinal strain does not correlate with any of the measurements of RV systolic function obtained by 2D echocardiography. A major strength of RV longitudinal strain is its ability to assess the RV function without the limitations of 2D parameters. The subcostal RV strain is a feasible and accurate alternative to conventional RV strain from the apical view in patients with poor acoustic apical 4-chamber windows. The RA strain and strain rates values may be a valuable additive to assess right-sided heart function.

Keywords: Pulmonary hypertension; Right atrial function; Right ventricular function; Strains

INTRODUCTION

The hemodynamic and pathological impact of pulmonary hypertension (PH) on right ventricular (RV) function is a subject of great interest in experimental and clinical cardiology. RV systolic dysfunction is a strong predictor of mortality in PH.1) Conventional echocardiographic measurements to assess RV function in that scenario are of limited usefulness due to the RV chamber’s complex structure and anatomical arrangement of RV myocardial fibers.2) Several 2-dimensional (2D)-derived RV function parameters are available, but all have inherent strengths and weaknesses.3) Assessment of myocardial strain with
speckle-tracking echocardiography (STE) could be of great help to determine and quantify the impact of PH on the RV myocardium.6,7 STE is a relatively new method to quantify right and left ventricular (LV) function.8 Despite its limitations as an ultrasound technique, which depends on an adequate ultrasound window and image quality, it opens an option in cardiovascular imaging.

In this work, we compared global RV longitudinal strain between normal controls and patients with PH, correlated global RV longitudinal strain with 2D echocardiographic parameters of RV function (including tricuspid annular plane systolic excursion [TAPSE], RV fractional area change [FAC], Doppler tissue imaging [DTI]-derived RV free wall peak systolic velocity [RV peak S'] and RV dP/dt).9-11 Besides, we hypothesized that right atrium (RA) reservoir and conduit functions are impaired in patients with PH compared with controls and could reflect RV failure. Finally, we hypothesized that RV pressure overload may alter LV function.

**METHODS**

**Study population**

This cross-sectional study analyzed 22 patients with the diagnosis of PH. According to the guidelines published by the European Society of Cardiology in 2015,12 PH was defined as a mean pulmonary artery pressure ≥ 25 mmHg in the right heart catheterization. The population was followed at “Dr. Cosme Argerich” Hospital from January 2015 to January 2019, and they were compared to a control group of 22 age- and sex-matched healthy subjects.

The Research Ethics Committee of the Hospital of the Government of the City of Buenos Aires “Dr. Cosme Argerich” approved this study. All procedures followed the ethical standards of the committee on human experimentation and with the Helsinki Declaration of 1964 and later revisions. And all patients involved in this study provided written informed consent authorizing the use and disclosure of their protected health information.

All patients had been treated with PH-specific drugs (Table 1), including intravenous/inhaled prostacyclin analogs (iloprost: 1 patients intravenous and 2 patients inhaled, treprostinil: 2 patients), endothelin receptor antagonists (bosentan: 3 patients, ambrisentan: 3 patients), and phosphodiesterase 5-inhibitors (sildenafil: 11 patients), either as a single drug or combined in concordance with current guidelines recommendations.13 Although there is not enough evidence to support the use of these drugs in the clinical management of patients with PH group II, we use it empirically while they awaited heart or lung transplantation respectively.

**Inclusion criteria**

Patients older than 18 years at the time of the study, had to have a diagnosis of PH. PH is defined as an increase in mean pulmonary arterial pressure ≥ 25 mmHg at rest as assessed by right heart catheterization.13

**Exclusion criteria**

Patients were excluded from the study for any of the following: age less than 18 years, irregular heart rhythm, prolonged QRS duration, aortic or mitral regurgitation greater

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*Conflict of Interest*

The authors have no financial conflicts of interest.

*Author Contributions*

Conceptualization: Prieto O, Cianciulli TF, Stewart-Harris A, Kazelián LR, Argento LV, Marambio GM; Data curation: Cianciulli TF, Stewart-Harris A, Kazelián LR, Marambio GM; Formal analysis: Prieto O, Cianciulli TF; Funding acquisition: Cianciulli TF; Investigation: Cianciulli TF, Rodriguez A, Lax JA, Argento LV, Marambio GM, Gagliardi JA; Methodology: Cianciulli TF, Rodriguez A, Kazelián LR, Argento LV, Marambio GM, Gagliardi JA; Project administration: Prieto O, Cianciulli TF, Rodriguez A, Gagliardi JA; Resources: Cianciulli TF, Stewart-Harris A, Saccheri MC, Argento LV; Software: Cianciulli TF, Argento LV, Gagliardi JA; Supervision: Cianciulli TF, Lax JA; Validation: Cianciulli TF, Saccheri MC, Argento LV, Gagliardi JA; Visualization: Cianciulli TF, Saccheri MC; Writing - original draft: Prieto O, Cianciulli TF, Saccheri MC; Writing - review & editing: Lax JA.
than mild, coronary heart disease, RV outflow tract obstruction, RV pacing, RV myocardial infarction, LV dysfunction and poor ultrasound window. Patients with any of these comorbidities or poor ultrasonic windows were excluded from the study to avoid any possible influence on the results of LV and RV strain measurement.

**Control group**

The control group included 22 age- and sex-matched healthy individuals. They were recruited by invitation from hospital staff without history of cardiovascular disease, and with normal clinical examination, chest X-ray, electrocardiogram, echocardiography, and 6-minute walking distance (6MWD).

**Exercise tolerance**

Exercise tolerance was measured with a 6MWD to assess the association with 2D echocardiographic parameters.

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**Table 1. Demographic data of patients with PH and control subjects**

| Demographic data                  | Patients with PH (n = 22) | Normal controls (n = 22) | p-value |
|-----------------------------------|---------------------------|--------------------------|---------|
| **Women**                         | 18 (81.8)                 | 17 (81.0)                | 0.94    |
| **Age (years)**                   | 49.9 ± 17.3               | 49.0 ± 15.0              | 0.86    |
| **Weight (kg)**                   | 65.2 ± 14.8               | 70.7 ± 14.5              | 0.23    |
| **Height (m)**                    | 1.60 ± 7.1                | 1.62 ± 6.20              | 0.24    |
| **Body mass index (kg/m²)**       | 25.8 ± 5.3                | 25.1 ± 3.1               | 0.89    |
| **Heart rate (bpm)**              | 76 ± 13                   | 70 ± 9                   | 0.23    |
| **Systolic blood pressure (mmHg)**| 119 ± 11                  | 118 ± 14                 | 0.25    |
| **Diastolic blood pressure (mmHg)**| 70 ± 8                    | 71 ± 9                   | 0.23    |

**PH etiology**

- **Group I**
  - Congenital heart disease: 8 (36.4)
  - Idiopathic: 4 (18.2)
  - Connective tissue disease: 2 (9.1)
  - HIV: 1 (4.5)
  - Hereditary: 1 (4.5)
  - Portopulmonary hypertension: 1 (4.5)

- **Group II**
  - Left side heart disease: 3 (13.6)

- **Group III**
  - COPD: 1 (4.5)

- **Group IV**
  - None: 0

- **Group V**
  - Gaucher disease: 1 (4.5)

**PH-specific therapy**

- Prostacyclins (iloprost, treprostinil): 5
- ERAs (bosentan, ambrisentan): 6
- PDE-5 (sildenafil): 11

**NYHA functional class**

- I: 2 (9)
- II: 6 (27.3)
- III: 11 (50)
- IV: 3 (13.7)

**6MWD (m)**

- 347 (420–310)
- 554 (564–550)

Data are expressed as mean ± standard deviation or median and interquartile range or as number (percentage). PH: pulmonary arterial hypertension, HIV: human immunodeficiency virus, COPD: chronic obstructive pulmonary disease, ERA: endothelin receptor antagonist, PDE-5: phosphodiesterase-5, NYHA: New York Heart Association, 6MWD: 6-minute walking distance., Group I: pulmonary arterial hypertension, Group II: pulmonary arterial hypertension due to left side heart disease, Group III: pulmonary arterial hypertension due to significant lung diseases, Group IV: chronic thromboembolic pulmonary arterial hypertension, Group V: pulmonary arterial hypertension with unclear and/or multifactorial mechanism.
2D echocardiography

All 2D echocardiogram was performed using a Vivid 7 machine (General Electric Medical Systems, Horten, Norway) with a phased array 3.5 MHz transducer. Three cardiac cycles were recorded in expiratory apnea and saved in cine loop format in the machine's hard drive, to be analyzed offline later by 2 independent observers. The following views were obtained: left parasternal (long- and short axis), subcostal 4-chamber, and apical 2-, 3- and 4-chamber views, including RV focused apical views according to the guidelines of the American Society of Echocardiography (ASE).

The following parameters were measured using M-mode and 2D echocardiography: LV diameter and end-diastolic volume, LV diameter and end-systolic volume, LV ejection fraction (EF), the thickness of the ventricular septum and posterior wall in diastole, RV diameter, RV dimensions (end-systolic and end-diastolic areas), RV FAC, TAPSE, right and left atrial areas and volumes, pre-bifurcation pulmonary artery diameter and inferior vena cava (IVC) diameter.\(^3\)\(^4\)

The LVEF was estimated using Simpson's method, and LV dysfunction was defined as a value below 55%.

RV inferior wall thickness was measured from the subcostal view at end-diastole by M-mode, preferable at the level of the tip of the anterior tricuspid valve, aligning the ultrasound beam perpendicular to the RV inferior wall. RV hypertrophy was defined as an inferior wall thickness > 5 mm.\(^3\)

The IVC was measured on 2D echocardiography images at approximately 2 cm from its junction with the RA. Maximal and minimal IVC diameters during the respiratory cycle were measured to calculate the IVC collapse.

The RA area and volume were calculated from 2D echocardiography at the end-systolic frame corresponding to the largest RA area and volume, just before the tricuspid valve opening, by single-plane in the 4-chamber view using the monoplane Simpson's rule. The RA border was manually traced in the same frame paying attention to excluding the tricuspid leaflets and annulus.

Color Doppler was used to excluding valve dysfunction. Pulsed-wave Doppler and DTI were performed from the apical 4-chamber view to estimate LV diastolic function.

All patients were examined in the left lateral decubitus using second-harmonic, with the adjustment of sector size for adequate frame rate and optimal LV, RV, and RA border visualization.

Conventional RV systolic function was assessed using TAPSE, RV peak S', RV FAC, and RV \(dP/dt\) according to the ASE guidelines.\(^3\)

TAPSE and RV FAC were assessed from the RV-focused apical 4-chamber view.

TAPSE was measured from the M-mode through the lateral tricuspid annulus, calculating the total excursion of the tricuspid annulus from its highest position until its lowest descent during ventricular systole. A TAPSE < 17 mm indicates RV systolic dysfunction.\(^3\)
Doppler-derived systolic velocity of the RV annulus (RV peak $S'$) were assessed in the apical 4-chamber view. RV peak $S' < 10$ cm/sec should raise the suspicion for abnormal RV function.\(^9\)

RV FAC was calculated as: $(\text{RV end-diastolic area} - \text{RV end systolic area})/\text{RV end-diastolic area} \times 100$. RV FAC $< 35\%$ indicates RV systolic dysfunction.\(^9\)

RV $dP/dt$ is the rate of pressure rise in the right ventricle and it was validated as an index of RV systolic function. It can be estimated from the ascending limb of the tricuspid regurgitation (TR) continuous-wave Doppler signal. It is commonly calculated by measuring the time required for the TR jet to increase in velocity from $-0.5$ to $-2$ m/s. Using the simplified Bernoulli equation, this represents a 15 mmHg increase in pressure. The $dP/dt$ is therefore calculated as 15 mmHg divided by this time (in seconds), yielding a value in mmHg/sec. RV $dP/dt <$ approximately 400 mmHg/s is likely abnormal and RV dysfunction can be suspected.\(^9\)

Pulmonary artery systolic pressure (PASP) was calculated from the peak velocity of the TR jet, using the modified Bernoulli equation plus right atrial pressure estimated by the IVC size and collapsibility.

Pulmonary artery acceleration time (PAAT) was calculated from the pulmonary arterial flow obtained by placing a pulsed Doppler sample volume at the pulmonary valve annulus, as the time from the onset of systolic pulmonary artery flow to peak flow velocity. PAAT correlates well with PASP. A PAAT $< 100$ msec is an indirect sign of PH.

The 2D echocardiographic parameters were performed blinded to 6MWD and other clinical data.

**STE**

LV, RV and RA strain were determined according to the guidelines of a recent consensus document of the EACVI/ASE/ Industry Task Force.\(^9\) Images were recorded with frame rates $> 40$ fps to ensure reliable analysis by the software.

Offline analysis was performed using Echo PAC PC version 108.1.5 (GE. Vingmed Ultrasound, Horten, Norway) by a single experienced reader (Omar Prieto), and the analysis was confirmed by a separate experienced reader (Tomás Francisco Cianciulli).

For the assessment of LV strain, apical 4-, 2-, and 3-chamber views were used for calculating the longitudinal strain. The LV endocardial border was traced at end systole in the 3 apical views and the automatically created region of interest (ROI) was manually adjusted to the thickness of the LV myocardium. LV longitudinal strain were measured in 17 segments which were averaged to obtained a global longitudinal strain (GLS). Normal reference ranges for GLS have been determined by meta-analysis of study control groups and healthy volunteers. In 24 studies involving 2,597 subjects, normal values ranged from $-15.9\%$ to $-22.1\%$ (mean $-19.7\%$; 95% confidence interval [CI], $-20.4$, $-18.9\%)$.\(^9\) According of these findings, we use $-15.9\%$ as a normal value of LV GLS. Strain values in the PH patients were defined higher or lower according these cutoff values.

For the assessment of RV free wall longitudinal peak systolic strain (RVFWSL), the images were obtained from the apical 4-chamber RV dedicated view focusing on the lateral wall.\(^9\) For assessing the inferior RV wall, the images were obtained from the subcostal view (Figures 1 and 2).
We analyze the RVFWSL separately, excluding the interventricular septum (Figure 3). For RV speckle-tracking analysis, opening and closure times of the pulmonary valve were considered. All segments were obtained with a frame rate equivalent to 80% of the patient’s heart rate.

RVFWSL is depicted with a negative curve and a peak close to the pulmonary closure. These RVFWSL curves represent the maximum longitudinal myocardial shortening during contraction in the 3 segments of the lateral and inferior RV walls.

Segments for which the automated acquisition of strain failed were corrected manually. Segments for which the acquisition of strained failed again were excluded. The ROI was
adjusted to the average myocardial thickness. Global RVFWSL was defined as the average of peak systolic strain values of basal, middle, and apical segments of the RV free wall. In accordance with the current ASE guidelines, the predefined cutoff for RV systolic dysfunction was set at global RVFWSL of $>-20\%$.\(^3\)

The strain of the right atrial reservoir (RASr) was measured in the lateral wall of the RA (Figure 4), from the RV-focused apical 4-chamber view. The right atrial function contributes to RV filling by means of its 3 components (Figure 5): a reservoir component (a positive wave that peaks at end-systolic), which receives blood from the superior and IVC during ventricular systole (RASr), and 2 distinct descending phases, a passive conduit component during early diastole and diastasis (RAScd); and a pump component (RASct), with active contraction during late diastole.\(^6\) Each strain parameter was then calculated by averaging each of the RA lateral walls.

The right atrial endocardial border was manually traced at ventricular end-systole from the apical 4-chamber view. The software then tracks speckles along the endocardial border throughout the cardiac cycle and derives the longitudinal strain and longitudinal strain rate. Septal segments were ruled out because they represent mostly fibrous components rather than muscle and for sharing the wall with the left atrium. The ROI was started 3 mm below the tricuspid ring to avoid the influence of its movement, which depends on the contraction of the right ventricle. The width of the ROI was adapted to the atrial wall thickness. RA longitudinal strain was measured in the basal, middle, and apical walls. The global RASr was calculated by averaging the values for the 3 segments of the lateral RA wall.

Three different longitudinal right strain rate were measured (Figure 5): peak strain rate during reservoir phase (pRASRr), which is a positive wave and it is coincident with RV systole.
and reflects the maximal RA distension in the reservoir phase; peak strain rate during passive conduit phase (pRASRcd) which is a negative wave and it is coincident with RV E wave and
reflects the passive RA emptying, and peak strain rate during contraction phase (pRASRct) which is a negative wave and it is coincident with RV A wave and reflects active RA emptying.

**Statistical analysis**

Continuous variables were expressed as means and standard deviations or medians and interquartile range (IQR) according to their distribution. Qualitative data were expressed as percentages.

The hypothesis of a normal distribution of continuous variables was tested by QQ-plot analysis and the Kolmogorov-Smirnov test.

To compare quantitative variables with a normal distribution, Student t-test for independent data and variables with non-normal distribution, the Wilcoxon test was used.

Logistic regression was performed to obtained independent predictors for functional class.

The intraclass coefficient was used to determine inter- and intra-observer reproducibility for strain from data for ten randomly selected patients using an identical cine loop for each view.

Pearson's correlation was used to establish the relation between RV free wall strain and right atrial strain in patients with PH. Logistic regression was performed in order to compare the correlation between RV free wall longitudinal strain with the measurement of RV systolic function obtained by 2D echocardiography. All p-values < 0.05 were considered to be statistically significant. All analyses were performed with Epi-info 2000 v. 3.5.1 (Centers for Disease Control and Prevention, Atlanta, GA, USA) and Stata 3 (StataCorp, College Station, TX, USA).

**RESULTS**

The demographic data of the 22 patients with a diagnosis of PH and 22 control subjects are described in **Table 1**. As shown, the demographic of this population is similar in age and sex. The mean age was 49.9 ± 16.15 years, and 81.4% were female. Patients with PH had a significantly worse New York Heart Association (NYHA) functional class and a shorter 6MWD. The majority of the patients with PH were in NYHA class II (27%), III (50%), or IV (13.7%).

In the normal group, the 6MWD was 554 (564–550), while in patients with PH, it was significantly less: 347 meters (420–310), p < 0.001.

According to the current clinical classification of PH into 5 groups, based upon etiology and mechanism, the most frequent causes of PH (**Table 1**) was included in group I (pulmonary arterial hypertension): Eisenmengers's disease due to congenital heart disease (36.4%).

We analyze the RV free wall separately, excluding the ventricular septum, and to synchronize the analysis with the time of opening and closure of the pulmonary valve (**Figure 3**).

The echocardiographic variables are shown in **Table 2**. In patients with PH, the mean systolic pressure in the pulmonary artery was 73.8 ± 24.2 mmHg. Linear regression analysis between the non-invasive and invasive estimation of systolic arterial pressure showed a significant
correlation ($r = 0.85; p < 0.001$). Patients with PH exhibited anatomic and functional impairment of the RV echocardiographic parameters.

Patients with PH showed significant difference in LVEF compared with normal subjects: $58\% \pm 11\%$ vs. $67.3\% \pm 1.9\%$, $p < 0.0002$ (Table 2).

Patients with PH did showed significant difference compared with normal subjects in: right atrium area ($26.6 \pm 8.7$ cm$^2$ vs. $14.1 \pm 2.5$ cm$^2$, $p < 0.0001$), right atrium volume ($106.9 \pm 58.4$ mL vs. $38.7 \pm 14.8$ mL, $p < 0.0002$) and RV inferior wall thickness ($10.4 \pm 2.1$ mm vs. $4.1 \pm 1.0$ mm, $p < 0.0001$), PA diameter ($36.0 \pm 6.2$ mm vs. $21.8 \pm 2.7$ mm, $p < 0.0001$) and PAAT ($58.3 \pm 15.8$ msec vs. $134.3 \pm 16.4$ msec, $p < 0.0001$).

All echocardiographic-derived parameters of RV systolic function (TAPSE, RV peak $S'$, RV FAC, RV dP/dt) were significantly different between patients with PH and controls, consistent with RV dysfunction, and higher PA pressure in patients with PH (Table 2).

The correlations between 2D echocardiographic measurement for RV systolic function (TAPSE, RV peak $S'$, RV FAC, and RV dP/dt) with the functional class assessed by 6MWD were not statistically significant ($p > 0.05$). The correlation between RV longitudinal peak systolic strain (LPSS) with the functional class assessed by 6MWD was not statistically significant ($p > 0.05$).

Logistic regression analysis showed that RV free wall longitudinal strain were not associated with the measurement of RV systolic function obtained by 2D echocardiography ($p = 0.60$).

### Table 2. Echocardiographic variables

| Variables                              | Patients with PH (n = 22) | Normal controls (n = 22) | p-value |
|----------------------------------------|---------------------------|--------------------------|---------|
| LVDD (mm)                              | 45.8 ± 8.4                | 48.8 ± 4.1               | 0.19    |
| LVSD (mm)                              | 22.7 ± 9.4                | 28.5 ± 4.7               | 0.75    |
| LVEF (%)                               | 58.0 ± 11.0               | 67.3 ± 1.9               | < 0.0002|
| Left atrium diameter (mm)              | 45.6 ± 7.5                | 35.8 ± 3.6               | < 0.0001|
| Aorta (mm)                             | 31.1 ± 3.9                | 29.6 ± 3.8               | 0.92    |
| RV- 4 CV end-diastolic diameter (mm)   | 46.7 ± 7.1                | 28.6 ± 3.9               | < 0.0001|
| TAPSE (mm)                             | 18.8 ± 6.7                | 26.4 ± 2.5               | < 0.0001|
| RV peak S’ (cm/sec)                    | 8.9 ± 2.4                 | 13.5 ± 1.3               | < 0.0001|
| RV FAC (%)                             | 19.0 ± 8.0                | 44.3 ± 7.4               | < 0.0001|
| RV dP/dt (mmHg/sec)                    | 436 ± 147                 | 779 ± 20                 | < 0.004  |
| RV inferior wall thickness (mm)         | 10.4 ± 2.1                | 4.1 ± 1.0                | < 0.0001|
| RA area (cm$^2$)                       | 26.6 ± 8.7                | 14.1 ± 2.5               | < 0.0001|
| RA volume (mL)                         | 106.9 ± 58.4              | 38.7 ± 14.8              | < 0.0002|
| PASP (mmHg)                            | 73.8 ± 24.2               | 20.3 ± 2.1               | < 0.006  |
| Tricuspid regurgitation                 |                           |                          |         |
| Absent                                 | 1 (4.5)                   | 19 (86.4)                | < 0.0001|
| Mild                                   | 16 (72.7)                 | 3 (13.6)                 | < 0.0001|
| Moderate                               | 5 (22.7)                  | 0                        | < 0.0001|
| Mean RA pressure (mmHg)                | 14.3 ± 4.4                | 5.0 ± 0                  | < 0.0001|
| Mean PASP (mmHg)                       | 73.8 ± 24.2               | 20.3 ± 2.1               | < 0.0001|
| Pulmonary artery diameter (mm)         | 36.0 ± 6.2                | 21.8 ± 2.7               | < 0.0001|
| Pulmonary artery AT (msec)             | 58.3 ± 15.8               | 134.3 ± 16.4             | < 0.0001|

Data are expressed as mean and ± standard deviation or as number (percentage).

PH: pulmonary hypertension, LVDD: left ventricular diastolic diameter, LVSD: left ventricular systolic diameter, LVEF: left ventricular ejection fraction, TAPSE: tricuspid annular plane systolic excursion, RV- 4 CV: right ventricular 4 chamber view, RV peak S': Doppler tissue imaging-derived right ventricular free wall peak systolic velocity, FAC: fractional area change, PASP: pulmonary artery systolic pressure, AT: acceleration time.
Images of sufficient quality for the calculation of regional RV longitudinal strain were obtained in all patients. Strain could not be traced because poor tracking in 3 of 132 segments (4%).

Global RVFWSL was decreased in patients with PH: −15% (IQR −19, −10) vs. −26% (IQR −28.5, −25.3) in control subjects (p < 0.0001).

Global RVFWSL from the apical 4-chamber view (Table 3) was −15% (−19%, −10%) vs. −14.5% (−18%, −11%) when measured from the subcostal view (p = 0.99). Segment by segment analysis did not show significant differences either: basal 4-chamber was −6.5% (−21%, −11%) vs. −15.5% (−20%, −11%) from the subcostal view (p = 0.99), middle 4-chamber was −16.5% (−21%, −12%) vs. −16.5% (−20%, −12%) from the subcostal view (p = 0.99), apical 4-chamber view was −12% (−18%, −8%) vs. −13.5% (−19%, −10%) from the subcostal view (p = 0.93).

Linear regression analysis in patients with PH showed an excellent correlation between global RVFWSL measured from 4-chamber view: −15% (−19%, −10%) and subcostal view: −14.5% (−18%, −11%), p = 0.99 (Table 3).

The global RASr measured in the right atrial free wall (Table 4) was decreased in patients with PH: 35.4% ± 19.2% vs. 49.3% ± 2.9% in control subjects (p < 0.01). Measures of pRASRr and pRASRcd, were significantly impaired in PH patients compared with controls: 1.4 sec\(^{-1}\) (IQR 1.3, 2.3) vs. 2.75 sec\(^{-1}\) (IQR 1.9, 3.4), p < 0.006 and 1.55 sec\(^{-1}\) (IQR 0.8, 2.1) vs. 2.2 sec\(^{-1}\) (IQR 1.7, 3.5), p < 0.06, respectively.

In contrast, measures of pRASRct did not significantly differ in PH patients compared with controls. RA active function is not only preserved but also has a greater relative contribution to RV diastolic filling.

Although no significant difference in global LV LPSS was found between patients with PH and control subjects (p = 0.57), the segmental analysis did show a significant difference in 5 segments corresponding with the basal anterior, basal inferoseptal, basal anteroseptal, middle inferoseptal, and middle anteroseptal segments (Table 5) in which the strain was lower than −15%.

| Table 3. Measurements of global and segmentary strain in the RV free wall from subcostal view and 4-chamber view in patients with pulmonary hypertension |
|-----------------|------------------|------------------|-------------|
| Variables       | Apical 4-chamber view (n = 22) | Subcostal view (n = 22) | p-value     |
| Global RV free wall longitudinal strain (%) | −15 (−19, −10) | −14.5 (−18, −11) | 0.99        |
| Basal segment of RV longitudinal strain (%) | −16.5 (−21, −11) | −15.5 (−20, −11) | 0.99        |
| Mid segment of RV longitudinal strain (%) | −16.5 (−21, −12) | −16.5 (−20, −12) | 0.99        |
| Apical segment of RV longitudinal strain (%) | −12 (−18, −8) | −13.5 (−19, −10) | 0.93        |

Data are expressed as median and interquartile range.

RV: right ventricle.

| Table 4. Measurements of strain and strain rate in the right atrium in patients with PH |
|-----------------|-----------------|-----------------|-------------|
| Variables       | Patients with PH (n = 22) | Normal controls (n= 22) | p-value     |
| RASr (%)        | 35.4 ± 19.2     | 49.3 ± 12.9     | < 0.01      |
| pRASRr (sec\(^{-1}\)) | 1.4 (1.3, 2.3) | 2.75 (1.9, 3.4) | < 0.006     |
| pRASRcd (sec\(^{-1}\)) | 1.55 (0.8, 2.1) | 2.2 (1.7, 3.5) | < 0.06      |
| pRASRct (sec\(^{-1}\)) | 2.02 (1.4, 4.7) | 2.23 (1.3, 3.4) | 0.68        |

Data are expressed as mean ± standard deviation or median and interquartile range.

PH: pulmonary hypertension, RASr: right atrial strain during reservoir phase, pRASRr: peak right atrial strain rate during reservoir phase, pRASRcd: peak right atrial strain rate during passive conduit phase, pRASRct: peak right atrial strain rate during contraction phase.
**Reproducibility**

The intraclass correlation coefficient for intra-observer reproducibility was 0.95 (95% CI, 0.90, 0.98). The corresponding correlation coefficient for inter-observer reproducibility was 0.91 (95% CI, 0.85, 0.95).

**DISCUSSION**

In our study, we found that the STE parameter of RV (RVFWSL) and RA (RASr, RAScd, pRASr, pRAScd and pRASRct) does not correlate with any of the measurements obtained by 2D echocardiography (TAPSE, RV peak S\(^{'\prime}\), RV FAC and RV dP/dt).

The 2D assessment of RV systolic function has several disadvantages. A major strength of global RVFWSL is its ability to assess the RV function without the limitations of the 2D parameter.

While TAPSE is a robust and highly reproducible measure of RV systolic function and an independent predictor of prognosis in patients with PH, this measurement is obtained only in specific views of the RV. It may be overestimated in patients with PH and apical clockwise rotation. TAPSE assumes that the longitudinal movement of the basal segment of the RV free wall represents the function of a complex 3D structure. Furthermore, it is angle-dependent, may be load-dependent, and there are no large-scale validation studies.

RV peak S\(^{'\prime}\) has several disadvantages. This technique is less reproducible for non-basal segments is angle-dependent, and there are limited normative data. Moreover, it assumes that the function of a single segment represents the function of the entire right ventricle, which is not likely in conditions that include wall motion abnormalities, such as RV infarction or pulmonary embolism.\(^3\)

RV FAC calculated from a single apical 4-chamber view is obtained by tracing the RV endocardium both in systole and diastole from the annulus. Care must be taken to trace the free wall, excluding the trabeculations.\(^3\) RV FAC is dependent on imaging plane, causing

**Table 5. Left ventricular strain measurements**

| Variables                  | Patients with PH (n = 22) | Normal controls (n = 22) | p-value |
|----------------------------|--------------------------|--------------------------|---------|
| GLS, mean (%)              | −17.9 ± 4.9              | −19.9 ± 2.1              | 0.57    |
| Basal anterior (%)         | −14.5 (−21, −7)          | −18.5 (−22, −15)         | 0.06    |
| Basal anterolateral (%)    | −17 (−21, −14)           | −17 (−19, −14)           | 0.87    |
| Basal inferolateral (%)    | −17.5 (−23, −11)         | −18.5 (−22, −15)         | 0.74    |
| Basal Inferior (%)         | −18 (−22, −14)           | −19.5 (−21, −17)         | 0.45    |
| Basal inferoseptal (%)     | −13 (−19, −8)            | −17 (−19, −15)           | 0.01    |
| Basal anteroseptal (%)     | −14.5 (−18, −11)         | −19 (−20, −16)           | 0.004   |
| Middle anterior (%)        | −20 (−22, −18)           | −22 (−23, −19)           | 0.42    |
| Middle anterolateral (%)   | −17.5 (−21, −13)         | −19 (−20, −16)           | 0.29    |
| Middle inferolateral (%)   | −20.5 (−23, −14)         | −16.5 (−20, −15)         | 0.42    |
| Middle inferior (%)        | −18.5 (−23, −16)         | −19.5 (−22, −18)         | 0.49    |
| Middle inferoseptal (%)    | −14 (−22, −13)           | −18.5 (−20, −18)         | 0.034   |
| Middle anteroseptal (%)    | −15 (−20, −13)           | −20 (−21, −18)           | 0.002   |
| Apical anterior (%)        | −20 (−23, −20)           | −22 (−26, −20)           | 0.42    |
| Apical lateral (%)         | −17.5 (−21, −14)         | −20 (−23, −18)           | 0.11    |
| Apical inferior (%)        | −20.5 (−23, −16)         | −22 (−23, −20)           | 0.13    |
| Apical septal (%)          | −17.5 (−23, −14)         | −20.5 (−23, −20)         | 0.13    |

PH: pulmonary hypertension, GLS: global longitudinal strain.
considerable inter- and intra-observer variability in patients with suboptimal endocardial definition and also limited by its assumptions regarding complex RV geometry.

There are less studied and more sparsely dP/dt used in right ventricle than for the left ventricle. Because of the lack of data in normal subjects, RV dP/dt cannot be recommended for routine uses. There are limited data in both normal subjects and pathologic conditions. RV dP/dt is load dependent and it will be less accurate in severe TR because of neglect of the inertial component of the Bernoulli equation and the rise in RA pressure.

PAAT correlates well with PSAP but is not an assessment of RV function.

Recently, STE has been recommended as a superior method for assessing RV function, which has the advantage of being angle-independent. Moreover, it can detect RV dysfunction more accurately and sensitively than TAPSE, RV FAC, RV S’ velocity or dP/dt.\(^\text{17}\)

Our study showed that STE measurements in the RA and RV lateral walls are decreased in patients with PH. The increased afterload for RV due to high pulmonary arterial pressure produces fibers’ impairment located in the right ventricle and right atrial free walls. Other authors have reported that this technique offers a simpler, more accurate, and faster analysis than nuclear magnetic resonance.\(^\text{18}\)

In our study, we decided to analyze the RV free wall separately, excluding the interventricular septum, and synchronize the analysis with the time of opening and closure of the pulmonary valve. The sequence of this study appears to be representative; however, it requires the operator to maintain an optimal image since the acquisition of defective images results in subsequent measurement errors.

RV pressure overload may alter LV systolic function in patients with PH, but its mechanism has not been fully elucidated. Although no significant difference in Global LV longitudinal strain was found between patients with PH and control subjects (p = 0.57), the segmental analysis did show a significant difference in 5 segments corresponding with basal anterior, basal inferoseptal, basal anteroseptal, middle inferoseptal and middle anteroseptal segments, in which the strain was lower than −15%. The results of this study suggest that incipient LV systolic dysfunction may be present in patients with PH, possibly as an effect of ventricular interdependence, in agreement with previous studies.\(^\text{19}\) The strain analysis cannot separate the left and right components of the ventricular septum, which could explain lower values in the 4 septal segments. These findings are in concordance with the results of lower LFEF in patients with PH compared with normal subjects (58% ± 11% vs. 67.3% ± 1.90%, p < 0.0002). It suggests that LV systolic function involvement may also be an independent factor, regardless of the ventricular septal contractility changes.

Anatomically, the right ventricle and the left ventricle share an interventricular septum. The RV free wall has transverse fibers, while oblique fibers encircle the left ventricle. The interventricular septum has primarily oblique fibers that extend into de RV outflow tract. This anatomical distribution of transverse and oblique fibers could explain why we exclude the interventricular septum in assessing RV longitudinal strain.

When analyzing RV, GLS, inclusion, or exclusion of the interventricular septum provides significantly different results because the interventricular septum has lower absolute
strain values compared to RV free wall. Although the interventricular septum contributes importantly to RV systolic function, it is mainly a component part of the left ventricle and the majority of studies measures RV free wall myocardial deformation only.\textsuperscript{15}

In concordance with Haeck et al.,\textsuperscript{20} we demonstrated that RV strain obtained from subcostal and apical 4-chamber views were similar. Although prior studies have analyzed different views, they did not report the analysis from the subcostal approach,\textsuperscript{21} which calculates RV strain when the apical window is suboptimal or in the perioperative situation.

Elevated RA pressure is of prognostic value in patients with PH, but little is known about the anatomical and functional abnormalities of the RA. We have observed that RASr measured in the RA free wall was decreased compared to that seen in control subjects. This functional abnormality of the RA was independent of its size.

Our study assessed the impact of PH on the deformation of fibers located in the RA free wall. RASr, pRASRr and pRASRcd were significantly impaired in PH patients compared with controls, independent of RA size, and likely reflect RV failure and overload. In contrast, pRASRct is preserved and has a greater relative contribution to RV diastolic filling. Similar results were previously published by Willens et al.\textsuperscript{22} in patients with PH.

However, the evaluation of the structure and function of the RV is unreliable to perform with echocardiography due to the complex distortion of the RV geometry. On the contrary, the RA has a simpler geometric structure. Therefore, its evaluation with strain and strain rate allows an easier, simpler, and faster way to evaluate RV decompensation.\textsuperscript{23}

TR could have some effects on RASr, pRASRr, and pRASRcd, but most of the patients with PH had mild TR (72.7%), and 22.7% had moderate TR. The absence of severe TR makes it unlikely that mild or moderate TR has any influence on the right atrium strain and strain rate.

Other authors have assessed this with similar results.\textsuperscript{21} We have confirmed that RA strain and RA strain rate values are decreased in patients with PH compared to control groups, regardless of the impairment of RV myocardial strain.

RA longitudinal strain and strain rate may provide a simpler, easier, more reliable, and faster measure of RA function, especially among patients with a massively dilated RV that was unable to be fully included in the echocardiographic windows.

There are several limitations to this study. First, it was performed at a single center, which might constitute a referral bias. However, this is a common limitation of similar studies. Therefore, we cannot obtain definitive conclusions but can only formulate a hypothesis that requires confirmation by future multicenter trials.

Similar to other studies in PH patients, sample size in this study included a small number of patients with PH of various etiologies, who were assessed in a non-randomized manner. The largest number of patients had Eisenmenger’s disease secondary to non-operated congenital heart disease. Hence, a larger study, including more patients with a single etiology of PH, would be required to validate our findings.
The echocardiographic speckle-tracking technique is dependent on good image quality. However, the technique has excellent inter-observer and intra-observer correlations, as we presented in this study.

Finally, we don’t know if our study results could be affected because all patients were receiving treatment.

This study showed incipient impaired LV contractility in patients with PH assessed by speckle tracking strain, irrespective of ventricular septal involvement. We found that the STE parameter of RV (RVFWSL) and RA (RASr, RAScd, pRASRr, pRASRcd and pRASRct) does not correlate with any of the measurements obtained by 2D echocardiography (TAPSE, RV peak S', RV FAC and RV dP/dt). A major strength of RV longitudinal strain is its ability to assess the RV function without the limitations of 2D parameters. Also, we concluded the subcostal RV strain is a feasible and accurate alternative to conventional RV strain from the apical view in patients with poor acoustic apical 4-chamber windows. The RA strain and strain rates values may be a valuable additive to assess right-sided heart function.

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