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Right ventricular contractility decreases during exercise in patients with non-advanced idiopathic pulmonary fibrosis

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Abstract

Early right ventricular dysfunction in patients with non-advanced idiopathic pulmonary fibrosis (IPF) has not been fully elucidated. Thus, we aimed to assess right ventricular functions in IPF patients and controls by speckle-tracking strain echocardiography at rest and peak exercise.

We screened 116 IPF patients from February to August 2019 to include 20 patients with no history of oxygen therapy, peripheral saturation levels ≥92% at rest, Gender-Age-Physiology Index score ≤5, and modified Medical Research Council score ≤3. Additionally, we enrolled 10 matched controls. Transthoracic echocardiography images were acquired at rest and during a cardiopulmonary exercise test. We analyzed 2-dimensional echocardiographic parameters and right ventricular function using the global longitudinal strain assessed by the 2-dimensional speckle-tracking technique.

In the control group, we found normal values of right ventricle longitudinal strain (RVLS) at rest and at peak exercise, the latter being much more negative (−23.6 ± 2.2% and −26.8 ± 3.1%, respectively; $P < .001$). By contrast, RVLS values in the IPF group increased from −21.1 ± 3.8% at rest to −17.0 ± 4.5% at peak exercise ($P < .001$). The exercise revealed a difference between the 2 groups as the mean RVLS values moved during peak exercise in opposite directions. Patients with IPF got worse, whereas control patients presented improved right ventricular contractility.

Right ventricular dysfunction was unveiled by speckle-tracking echocardiography during exercise in non-advanced IPF patients. We suggest that this reflects an inadequate right ventricular-arterial coupling decreasing the right ventricular longitudinal contraction during exercise in these patients. This parameter may be useful as an early index of suspected pulmonary hypertension.

Abbreviations: ATS = American Thoracic Society, CPET = cardiopulmonary exercise testing, FAC = fractional area change, GLS = global longitudinal strain, IPF = idiopathic pulmonary fibrosis, LV = left ventricular, mMRC = modified Medical Research Council, mPAP = mean pulmonary artery pressure, OTO = outflow tract obstruction, PH = pulmonary hypertension, RV = right ventricular, RVLS = right ventricle longitudinal strain, sPAP = systolic pulmonary artery pressure, SpO_2 = peripheral oxyhemoglobin saturation, STE = speckle-tracking echocardiography, TAPSE = tricuspid annular plane systolic excursion, TTE = transthoracic echocardiography, VE = volume expired per minute, VE/VCO_2 = ratio of expired volume/CO_2 output, VO_2 = values of oxygen extraction.

Keywords: exercise, idiopathic pulmonary fibrosis, pulmonary hypertension, right ventricular contractility, speckle-tracking echocardiography

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive and irreversible chronic lung disease.[1] Pulmonary hypertension (PH) is common in advanced IPF[2,3] and increases the risk of death by approximately 3-fold.[4] The prevalence varies between 3% and 86% but is most commonly 30% to 50%.[5] In Brazil,

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Algranti et al[6] recognized an increase in IPF mortality from 1979 until 2014 and concluded that is the result of 2 changes: firstly, the diagnosis methods have improved over time and allowed better detection of the disease and secondly, the increase of life expectancy of the population has determined the increase in the percentage of the aged population.

Typically, some IPF outcomes are related to PH and the adaptation of the right ventricle (RV) to the afterload changes. In these cases, RV failure components may drive mortality.[7] Despite its critical relevance, RV function remains unclear in these patients, particularly in those without severe hypoxemia at rest. Patients with non-advanced IPF and PH are probably the best study candidates to increase our understanding of "disproportional PH."

Ventriculoarterial uncoupling is the physiological consequence of failing RV adaptation. The gold standard for assessing ventriculoarterial coupling is invasive, involving cardiac catheterization; however, it is difficult to assess during exercise, as it requires manipulation of the venous return.[8] Two-dimensional transthoracic echocardiography (2D TTE) allows a complementary investigation of RV behaviors in diverse pulmonary disease stages. D'Andrea et al, used RV speckle-tracking echocardiography (STE) to evaluate the global longitudinal strain (GLS), and demonstrated that RV STE is an accurate tool for the evaluation of right ventricular function, is easy to perform, and feasible in various clinical scenarios of RV dysfunction.[9]

Evaluation of exercise-induced changes in pulmonary hemodynamics may improve understanding of pulmonary circulation-heart interactions. The analysis of RV function during exercise can predict RV failure in IPF.[10] Minor myocardial dysfunction emerging from abnormal systolic contractility can be accurately and non-invasively measured by STE[11] and may even be detected with minor afterload changes.[12]

Data are lacking on RV dysfunction at rest and during exercise in patients at early IPF stages with normal or near-normal oxyhemoglobin peripheral saturation (SpO_2). D'Andrea et al described RV dysfunction during exercise using STE[13]; however, they included patients with severe hypoxemia at rest (mean SpO_2, 83%) and probably patients at advanced IPF stages.

To date, there are no approved medications available for treating PH in these patients.[14] Evaluating pulmonary circulation-heart interactions and RV functions through ventricular-vascular coupling is a powerful approach that should improve understanding of the disease. Singh et al demonstrated that RV-pulmonary artery (PA) dissociation could compromise RV contractility in response to increased afterloads during exercise.[15] This increased afterload is probably insufficient to maintain a normal cardiac output and will eventually result in the deterioration of RV-PA coupling at peak exercise.

We hypothesized that increased PA pressure and consequent RV dysfunction may occur at early IPF stages as part of its development. Our objectives were detecting RV function impairments during exercise even in IPF patients without RV dysfunction at rest and utilize this measure as an early index for suspected PH.

2. Methods

This cross-sectional study was approved by the Ethics Committee of School of Medicine – University of Brasília – Brazil (protocol number CAAE: 71022817.2.0000.5558). All patients signed informed consent to participate and consent for publication. The procedures in this research were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 1983.

To achieve the estimated sample size, we evaluated 116 consecutive IPF patients between February and May 2019 who were diagnosed according to the standard criteria,[16] which included revision of chest high-resolution computed tomography and surgical lung biopsy, when required. Those patients are followed up in the center of interstitial lung diseases at the University Hospital of Brasília. Among these 116 subjects, we selected 20 for 2D TTE at rest and cardiopulmonary exercise testing (CPET). Two-dimensional TTE was performed as per the American Society of Echocardiography guidelines.[17]

Inclusion criteria for IPF patients included a Gender-Age-Physiology Index score ≤ 5, compatible with mild or moderate disease,[18] modified Medical Research Council scale[19] score ≤ 3, and $SpO_2 \geq 92\%$ at rest and in room air without oxygen therapy. Patients with locomotor diseases, severe comorbidities (eg, lung cancer, pulmonary thromboembolism, and stroke), left cardiomyopathy, combined emphysema and pulmonary fibrosis, atrial fibrillation, chronic obstructive pulmonary disease, gout, chronic kidney disease, depression, valve disorder, liver steatosis, alcohol intake, and hematologic disturbances were excluded.

Controls were recruited from elderly healthy family members and friends of the IPF patients. The subjects of the control group were strictly matched for similar age and gender to IPF patients. We selected 10 subjects for this group to achieve 1 control subject for every 2 IPF patients. The controls did not demonstrate respiratory symptoms, had no history of lung diseases, and meet the same exclusion criteria as IPF patients.

2.1. Transthoracic Doppler echocardiography at rest

The baseline resting echocardiogram before CPET was performed using a Vivid I (GE Healthcare, Milwaukee, WI, USA). Final values were obtained after averaging over 3 cardiac cycles. Conventional echocardiographic parameters were acquired to evaluate RV functions.

The modified Bernoulli equation was applied to calculate systolic PA pressure (sPAP) from tricuspid regurgitation. The formula $mPAP = 0.61 \times sPAP + 2\,mmHg$ was used,[20] assuming that sPAP equaled the right systolic ventricular pressure in the absence of RV-pulmonary stenosis or outflow tract obstruction.[21] The estimated right atrial pressure was based on the inferior vena cava collapsibility index, which was added to the sPAP.[17,22] Images were adjusted for better RV-free wall delimitation and STE analysis.

2.2. RV function assessment by 2D TTE and STE

The STE technique[23] was applied to images using the EchoPac software (v. 201; General Electric, Vingmed, Horten, Norway) offline. The beginning and end of the RV systole were defined using the event-timing feature of this software to evaluate RV longitudinal strain (RVLS). Regions of interest were marked manually, and RV-free wall edges were adjusted to enable adequate tracing of basal, medial, and apical portions of the RV myocardium. This was performed at both rest and peak exercise; images were adjusted for better delimitation of the RV free wall endocardium (Figs. 1–3). The average of 3 segments defined the measurement results.

The systolic peak longitudinal strain reflecting muscle fiber contraction was expressed as a percentage and has a negative

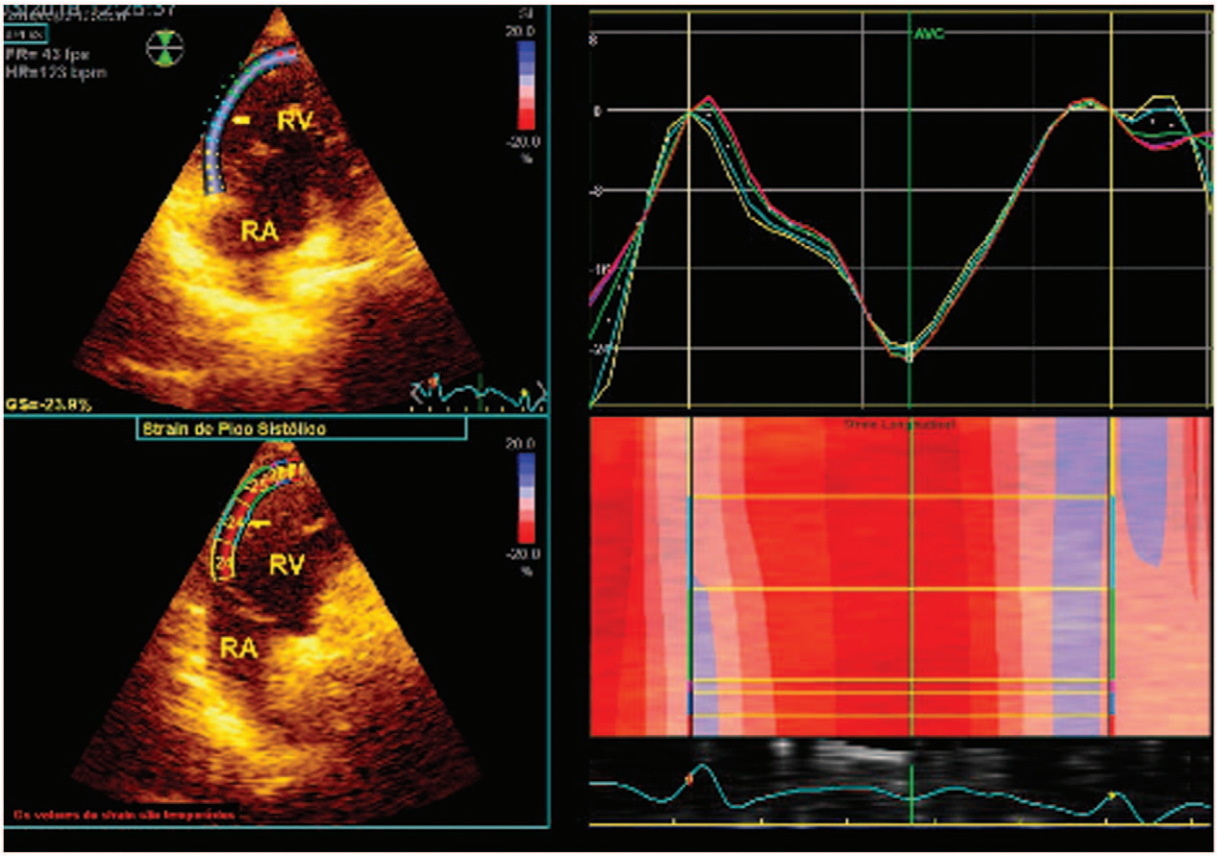

Figure 1. Normal RVLS% obtained at rest in a patient with IPF. IPF = idiopathic pulmonary fibrosis, RVLS = right ventricle longitudinal strain.

value.[23] Current reference values for global RV free wall STE suggest that values $\leq -20\%$ are normal.[17]

2.3. CPET with simultaneous echocardiography

All participants were tested using an incremental ramp protocol. A cycle ergometer (CG-04; Inbramed, Porto Alegre, RS, Brazil) was used with a progressively increasing load. The protocol consisted of pedaling for 1 min at 60 rotations/min without load (0 W). The load was then increased in 5-W steps from 5 to 30 W/min. As per the American Thoracic Society recommendations,[24] we recorded the dyspnea level, exercise capacity, maximum predicted value of oxygen extraction ($V'O_2$), and patient age. These parameters were analyzed during an incremental load period of 8 to 12 min. The effort was considered to be maximal if the subject achieved predicted $V'O_2$ with a plateau, predicted maximal heart rate, respiratory exchange ratio greater than 1.15, ventilatory limitation or BORG scale rating of 9to 10.

Cardiovascular and ventilatory variables were assessed once all expiratory gas measurements at each breath had been documented (Quark PFT; Cosmed, Rome, Italy). Pulse oximetry findings (Ipod; Nonin Medical, Inc., Plymouth, MN, USA), heart rates, and electrocardiographic parameters were continuously recorded. $V'O_2$ released CO_2 ($V'CO_2$), CO_2 pressures, volume expired per minute (V'E), and final expiratory O_2 were registered every 15 seconds. The auscultatory method was employed to record systolic and diastolic blood pressures at all load increases. The gas exchange method allowed the non-invasive estimation of the anaerobic threshold.[24] Equal scales, which include the V-slope technique (slope of the $V'O_2$ versus $V'CO_2$ graph), were used to analyze this parameter. To determine the performance of ventilatory equivalents ($V'E/V'CO_2$ and $V'E/V'O_2$) and their final expiratory pressures,[24] the ventilatory method was used, validating the V-slope technique.

The BORG effort perception scale[25] was applied to evaluate muscle fatigue sensations and dyspnea during CPET, and echocardiographic images were obtained from modified apical 4 chambers view, focusing right chambers to better identify tricuspid regurgitation and RV free wall.[17] Simultaneous images were stored every minute for the offline sPAP analysis.

During the recovery period, tricuspid regurgitation spectral traces were recorded for 3 to 4 minutes.

2.4. Statistical analysis

The data are presented as the mean ± standard deviation, and 95% confidence intervals (95% CIs) are shown. Normal distribution was confirmed by the Kolmogorov–Smirnov test for all continuous variables. Student *t* test for independent samples was used to compare means of continuous variables. Categorical variables are presented as percentages. We used the chi-squared test to compare proportions. Analyses between RVLS measures and CPET variables were calculated using Pearson correlations.

We performed a multiple linear regression to explore any probable association between conventional echocardiographic

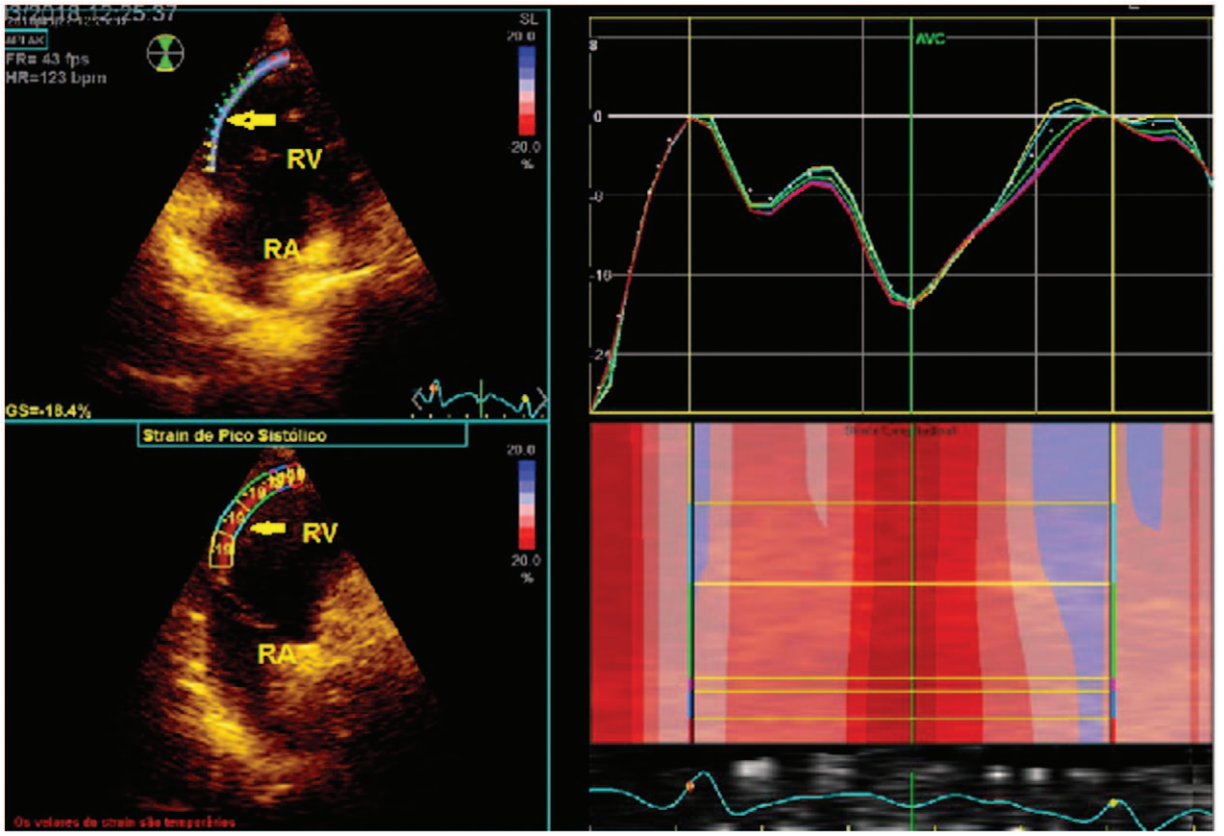

Figure 2. Abnormal RVLS% obtained at peak exercise in the same patient with IPF. IPF = idiopathic pulmonary fibrosis, RVLS = right ventricle longitudinal strain.

variables and ΔRVLS (RVLS at effort peak minus RVLS at rest). In the beginning, all variables were included simultaneously, and the final model was obtained by the forward stepwise way, taking into account $P \leq .05$ to enter a variable in the model and $P \geq .10$ to rule it out.

To estimate the sample size, we used the software G*Power (v.3.1; Heinrich-Heine-University, Dusseldorf, Germany). Firstly, we set an allocation ratio of 1 control to 2 IPF patients. As the values of those studied variables' effect size are unknown in this specific situation, we took into account an arbitrary Cohen effect size d of 1.0, which represents a large one, as we expected big differences between patients and controls. Then, we selected an acceptable value of 0.70 for statistical power. The result was 2 groups of 10 and 20 patients.

Data were analyzed using SPSS for Mac OS X© (v.25.0.0; SPSS, Inc., Chicago, IL, USA). Results were considered statistically significant at $P < .05$.

2.5. Data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

3. Results

The study population comprised 30 participants: 10 controls and 20 patients with IPF. Table 1 summarizes the demographic, echocardiographic, and pulmonary function test data at baseline. The 2 groups did not differ in terms of sex ($P = .605$) and age ($P = .219$). From the data, diabetes was found in 4 patients (20%) and fast glucose mean was 99.8 ± 17.4, 1 patient was breast cancer treated (3.3%), 1 FPI patient smoked (3.3%), 9 FPI patients were ex-smokers (45%) and 10 no-smokers (50%).

As seen in Table 1, regarding conventional TTE parameters, the following variables presented significant differences between groups: RV fractional area ($P < .001$), left atrial volume ($P = .011$), and tricuspid annular plane systolic excursion ($P = .012$). However, the mean values and all the individuals' values in those 3 variables were within the normal range. There were no significant differences between the study groups in terms of right atrial volume ($P = .199$), Mitral E/E' (mitral valve E velocity by mitral annular E' velocity ratio) values for left ventricular end-diastolic pressure ($P = .458$) and peak tissue Doppler imaging values of the lateral tricuspid systolic annulus velocity ($P = .695$).

As seen in Table 2, the resting mPAP difference, determined by echocardiography, was higher in the IPF group than in controls ($P = .008$). As expected, mPAP values increased during exercise in both groups. However, peak exercise mPAP values were even higher in IPF patients ($P = .015$).

Echocardiographic data revealed that in the control group, all participants had normal RVLS values at rest and at peak exercise, the latter demonstrating considerably greater negativity (−23.6 ± 2.16% and −26.8 ± 3.1%, respectively, 95% CI: 2.0–4.4, $P < .001$). This indicates that the RV contractility had increased overall. Differently, in the entire IPF group, RVLS values changed

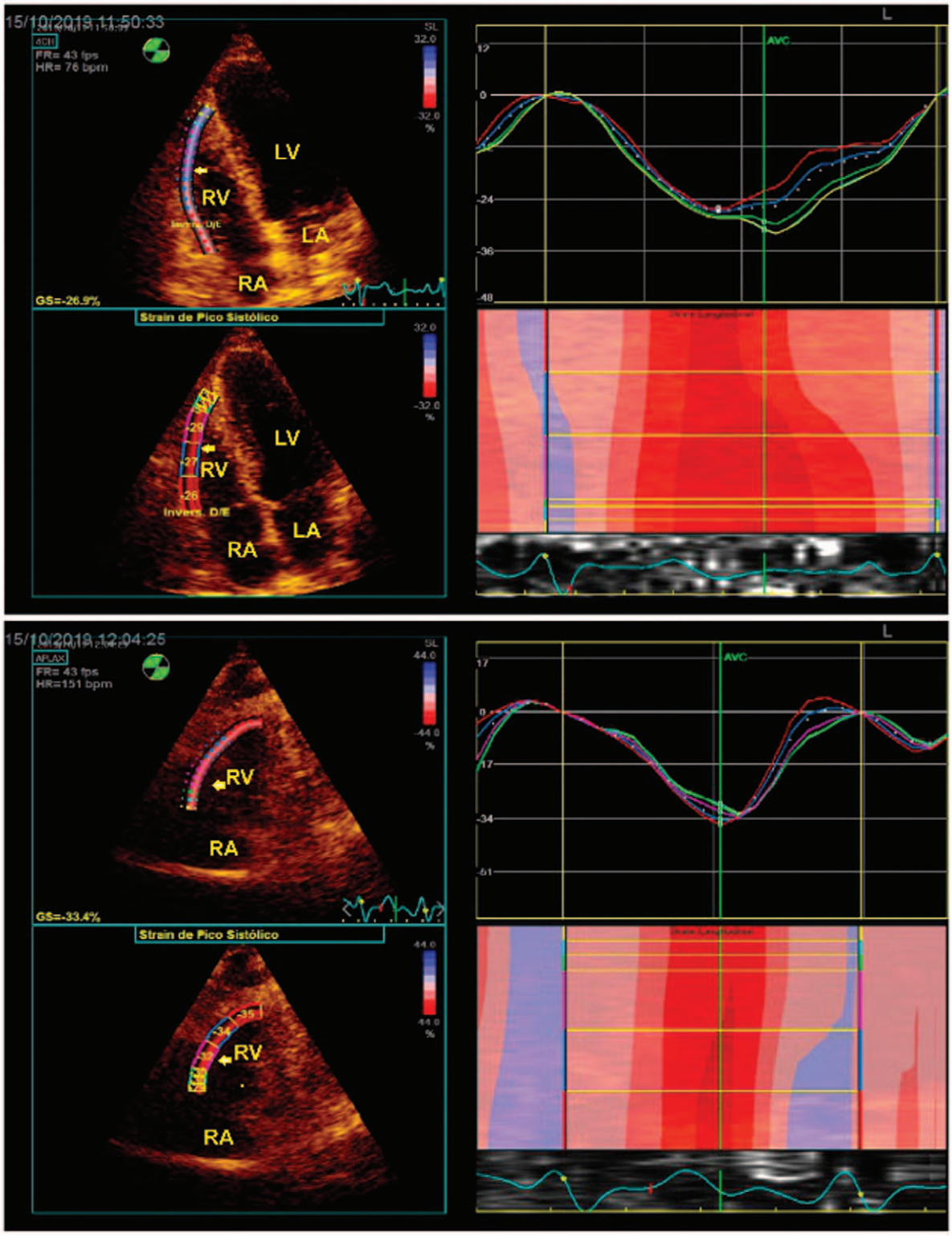

Figure 3. Normal RVLS% obtained at rest and at peak of exercise in the control group. IPF = idiopathic pulmonary fibrosis, RVLS = right ventricle longitudinal strain.

from −21.1 ± 3.8% at rest to −17.0 ± 4.5% at peak exercise (95% CI: 2.1–6.1, $P < .001$), which indicates that the RV contractility mean had decreased. During exercise, only 3 IPF patients presented slightly improved RV contractility; from rest to peak exercise, their values changed as follows: −14.5 to −19.6, −16.0 to −18.0, and −16.8 to −18.0.

IPF patients could be divided into 2 groups: (1) normal RVLS at rest and (2) abnormal RVLS at rest. In this first subgroup, the

Table 1

Demographic and echocardiographic data of the IPF and control groups at rest.

Variable	IPF* (n = 20)	Control (n = 10)	95% CI of difference	P
Age (year)	72.3 ± 8.6	68.5 ± 5.2	−9.8 to 2.3	.219
Sex (Female/male)	10/10	6/4		.619
BMI (Kg/m^2)	24.7 ± 3.4	25.3 ± 2.4	−2.3 to 3.5	.668
SBP (mmHg)	139.0 ± 23.3	124.0 ± 15.0	−34.5 to 4.5	.127
DBP (mmHg)	82.0 ± 10.0	76.5 ± 10.7	−14.6 to 3.8	.238
SpO_2 rest (%)	93.2 ± 1.6	94.1 ± 1.4	−0.03 to 2.43	.056
FVC%	67.1 ± 15.2	–		–
FEV_1%	74.3 ± 11.7	–		–
D_LCO%	53.9 ± 19.0	–		–
LA (mL/m^2)	20.8 ± 6.2	14.7 ± 4.4	−10.5 to −1.4	.011
RA (mL/m^2)	15.5 ± 5.8	12.5 ± 5.6	−7.5 to 1.6	.199
RV FAC (%)	46.8 ± 9.9	62.0 ± 7.6	7.8 to 22.4	<.001
RV TAPSE (mm)	20 ± 3	22 ± 2	0.4 to 5.1	.012
TDI RV Sm peak (cm/s)	12 ± 2	13 ± 2	1.0 to 1.6	.695
sPAP (mmHg)	33.4 ± 10.8	22.8 ± 7.1	−18.4 to −2.8	.009
mPAP (mmHg)	21.8 ± 6.2	15.4 ± 4.5	−10.9 to −1.7	.008
E/E′ average	7.7 ± 1.9	7.2 ± 1.3	−1.9 to 0.8	.458

BMI = body mass index, DBP = diastolic blood pressure, D_LCO% = carbon monoxide diffusing capacity of the lung, *E/E′* = mitral *E/E′* ratio, FEV_1% = forced expiratory volume in 1 s as a percentage of the predicted value, FVC% = forced vital capacity as a percentage of the predicted value, IPF = idiopathic pulmonary fibrosis, LA = left atrium, mPAP = mean PA pressure, RA = right atrium, RV FAC = right ventricle fractional area change, SBP = systolic blood pressure, sPAP = systolic PA pressure, SpO_2 = peripheral oxyhemoglobin saturation, TAPSE = tricuspid annular plane systolic excursion, TDI RV Sm peak = tissue Doppler imaging of lateral tricuspid systolic annulus velocity

* Data are presented as the mean ± standard deviation.

Table 2

Echocardiographic data at rest and their corresponding exercise parameters.

Variable	IPF* (n = 20)	Control* (n = 10)	95% CI of difference	P
mPAP (at rest, mmHg)	21.8 ± 6.2	15.4 ± 4.5	−10.9 to −1.7	.008
mPAP (peak exercise, mmHg)	42.4 ± 16.0	28.0 ± 9.8	−25.7 to −2.9	.015
mPAP (peak − rest, mmHg)	20.6 ± 11.8	12.6 ± 7.6	−16.4 to 0.4	.001
RVLS % (at rest)	−21.1 ± 3.8	−23.6 ± 2.1	−5.1 to 0.2	.068
RVLS % (peak)	−17.0 ± 4.5	−26.8 ± 3.1	−13.1 to −6.5	<.001
RVLS % (peak) − GLS% (at rest)	4.1	−3.2	−10.2 to −4.4	<.001

IPF = idiopathic pulmonary fibrosis, mPAP = mean PA pressure, RVLS = right ventricle longitudinal strain.

* Data are presented as the mean ± standard deviation.

12 IPF patients (60%) with normal RVLS values at rest (−23.49 ± 2.91%) declined during exercise (−18.23 ± 4.62%, 95% CI: 3.5 to 6.9, $P < .001$). In this second subgroup, 8 IPF patients (40%) had abnormal RVLS mean value at rest (−17.70 ± 1.85%) that worsened at peak exercise (−15.27 ± 4.14%, 95% CI: −2.3 to 7.1, $P = .266$), however, this difference did not achieve statistical significance. All 12 IPF patients in the first subgroup decreased RVLS values, while only 5 of 8 IPF patients in the second subgroup also did the same.

Comparing IPF patients with controls, RVLS values were only significantly different at peak exercise (controls: −17.0 ± 4.5%, IPF: −26.8 ± 3.1%, 95% CI: −13.1 to −6.5, $P < .001$; Table 2). The difference in GLS at rest between IPF patients and controls was not statistically significant (−21.1 ± 3.8% and −23.6 ± 2.1%, respectively, 95% CI: −5.1 to 0.2, $P < .068$). Importantly, the mean RVLS values of the 2 groups moved in opposite directions during exercise (Fig. 4). On STE analyses, RV contractility worsened in IPF patients and improved in controls. RVLS differences between the 2 groups were also more apparent at peak exercise.

Multiple linear regression was performed, and the only echocardiographic variable that stayed in the model was mPAP at rest. It pointed mPAP at rest as the main variable to predict ΔRVLS. Indeed, this bivariate model showed statistical significance ($P = 0{,}002$), and mPAP at rest was responsible for 28% of ΔRVLS total variance.

We also performed a correlation analysis between the main CPET variables and RVLS values at rest and at peak exercise. Most Pearson correlation coefficients demonstrated a weak-to-moderate correlation (Table 3); mainly those that referred to RVLS at peak exercise were statistically significant. All patients and all subjects in the control group were made to exercise until exertion. IPF patients achieved lower $V'O_2$ peak compared to controls (16.4 ± 3.2 and 24.6 ± 7.5 mL/Kg/min, respectively, 95% CI: 2.7–13.7, $P = .007$); lower O_2 pulse (8.4 ± 2.3 and 12.0 ± 4.2 mL/Kg/min/beat, respectively, 95% CI: 0.3–6.6, $P = .031$); and lower maximal heart rate (125 ± 15 and 143 ± 11 beats/min, respectively, 95% CI: 6.5–29.5, $P = .003$).

4. Discussion

CPET in combination with STE was suitable for studying RV function in IPF patients. Our findings demonstrated that RVLS measured by STE during exercise was capable of unveiling

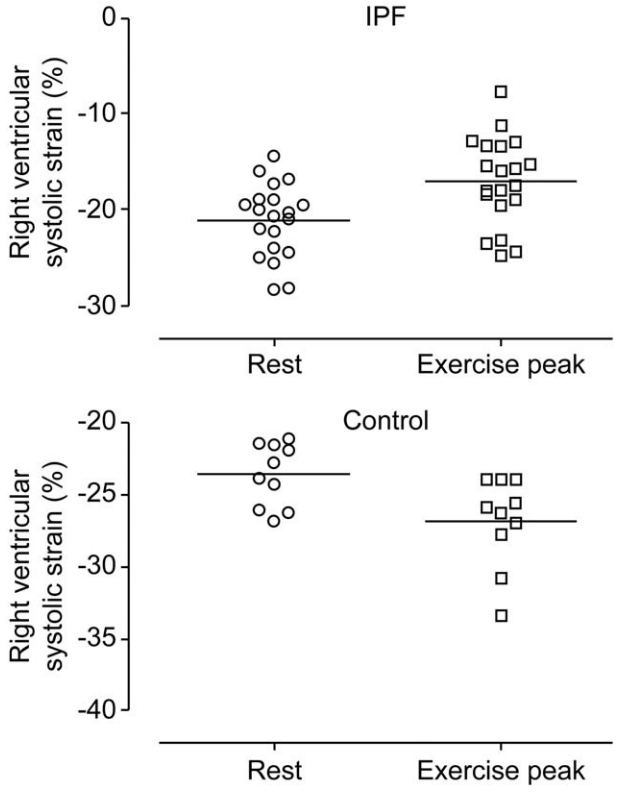

Figure 4. Right ventricular systolic strain shifts from rest to peak exercise in control participants and patients with IPF. IPF = idiopathic pulmonary fibrosis.

systolic RV dysfunction in non-advanced IPF patients, although RV function measurements at rest by conventional echocardiography were similar between IPF and control groups. Exercise-induced changes in STE may provide an early index for suspected PH in non-advanced IPF stages.

In a previous study, it was found that abnormal RVLS at rest was already detected in part of non-severe IPF patients.[26] In this study, however, we went forward to find that, as measured by STE, the RV function in IPF patients failed to increase appropriately during exercise. In contrast, the RV contractility in controls improved to more negative RVLS values. Exercise results in pulmonary hemodynamic changes, elevating the PA pressure due to an increase in cardiac output.[27] In healthy subjects, passive distension of the pulmonary circulation and vasodilation-mediated flow changes accommodate this cardiac output with modest mPAP increases and decreased pulmonary vascular resistance.[28] Thus, the RV adapts to increased afterload by increasing contractility.

Our main finding is that IPF patients at non-advanced stages already have an impaired RV contractile reserve. The failure to improve RV contractility in response to a progressive rise in afterload probably results from poor RV-PA coupling at peak exercise. We speculate that RVLS values at rest do not predict the success or failure to improve RV contractility during exertion, that is, to uncover contractility changes, it must be measured during exercise. RV dysfunction appears in the early stages of the disease and its detection may also be early.

Unmasking pulmonary vascular disease by raising the cardiac output to demonstrate an increase in pulmonary resistance is a logical idea. In contrast to left ventricular fibers, the predominant longitudinal orientation of RV fibers may minimize the mechanisms that preserve RV systolic function during increased afterload.[8] Furthermore, a thinner RV wall is capable of accommodating an increased preload; however, it is inadequate for greatly increased PA pressures.[28] This may explain the RV dysfunction at peak exercise detected by RVLS in non-advanced IPF patients.

Additionally, we observed a lack of correlation between CPET parameters and STE measurements at rest in the IPF group. However, we found a moderate correlation between STE RV functions and most parameters at peak exercise, supporting the importance of STE measurements during exercise for under-

Table 3

Pearson correlation coefficients between CPET data and RVLS values.

Variable	RVLS% at rest	*P*	RVLS% at peak exercise	*P*
$V'O_2$ peak	−0.164	.388	−0.458	.011*
$V'O_2$ peak (%)	−0.205	.277	−0.462	.010*
$V'O_2$ AT	−0.283	.130	−0.470	.009*
$V'O_2AT/V'O_2$ predicted	−0.176	.352	−0.345	.062
O_2 pulse ($V'O_2/HR$)	−0.339	.067	−0.419	.021*
$V'E/V'CO_2$ (peak)	0.234	.213	0.412	.024*
$V'E/V'CO_2$ (slope)	0.122	.520	0.372	.043*
$V'E/V'CO_2$ (AT)	0.277	.139	0.480	.007*
$PETCO_2$ (peak)	−0.231	.220	−0.369	.045*
$PETCO_2$ (AT)	−0.183	.332	−0.389	.034*
V'E maximal (L/min)	−0.167	.378	−0.353	.056
V'E/MVV	−0.125	.510	−0.071	.709
SpO_2 (rest)	−0.144	.448	−0.154	.416
SpO_2 (peak)	−0.233	.215	−0.501	.005*
BORG (dyspnea)	0.042	.827	0.322	.089
BORG (leg fatigue)	0.140	.470	0.019	.923

AT = anaerobic threshold, BORG = BORG scale score, CPET = cardiopulmonary exercise test, HR = heart rate, $PETCO_2$ = end-expiratory CO_2 partial pressure, RVLS = right ventricle longitudinal strain, SpO_2 = oxyhemoglobin saturation, V'E maximal = maximal volume expired per minute, V'E/MVV = volume expired per minute/maximum voluntary ventilation, $V'E/V'CO_2$ = volume expired per minute/CO_2 ventilation, $V'O_2$ AT = oxygen consumption anaerobic threshold, $V'O_2$ peak = peak exercise oxygen consumption, $V'O_2AT/V'O_2$ predicted = oxygen consumption anaerobic threshold/oxygen consumption predicted.
* Statistically significant.

standing patients' physiological changes. A notable and significant correlation was detected between RVLS and SpO_2 during exercise. This indicates subclinical hypoxia as a possible cause for PH and RV dysfunction, even in non-advanced, non-hypoxemic patients at rest, and may be due to SpO_2 decreases during exercise and/or sleep.[30]

Several studies attempted to uncover pulmonary vascular disease by redistributing the flow or increasing the cardiac output utilizing echocardiography with exercise stress[31] or dobutamine administration.[32] Nowadays, these approaches have poor applicability and low reliability. D'Andrea et al[13] also evaluated right ventricular contractility during exercise in patients with IPF, however, in this sample there were patients with severely impaired SpO_2 levels at rest, which may represent an advanced stage of the disease. The present study suggests that non-advanced IPF patients have associated RV dysfunction with increased mPAP during exercise. As PH progresses, RV synchrony is lost. Intraventricular asynchrony may be present even in early disease stages.[33] Thus, RV function can be temporarily suppressed at peak exercise, returning to baseline values at rest and STE stress test could be a tool to identify IPF patients with subclinical RV dysfunction.

We also compared RV function and pulmonary hemodynamic responses in control subjects and found that exercise stress was associated with a lower mPAP slope, and improved RV contractility. Only a few studies assessed changes in RV function during exercise in healthy subjects. Exercise echocardiography was compared with exercise cardiac magnetic resonance imaging and invasive pressure measurements. They suggested that echocardiography during exercise represents an efficient screening tool to identify RV function changes and pulmonary vascular disease.[10]

The current study has some limitations.[29] First, 2D TTE was used to non-invasively assess intracardiac pressure instead of direct measurements using catheterization; however, hemodynamic invasive measurements are not appropriate for patients without advanced IPF. Second, at present there is no specific software for RV STE analysis, and, for this study, we used the software that measures LV function. Finally, the number of patients recruited was small, and this study does not include a follow-up data.

There are also questions regarding the interpretation of our findings. First, RVLS during exercise may offer an early warning marker of global RV dysfunction and may predict the outcome or functional capacity in IPF patients better than RVLS at rest. Second, as abnormalities in RV functions and PH are present at early disease stages, and are not exclusively caused by hypoxia, other factors may contribute to the development of PH and RV dysfunction.

In future directions, the early occurrence of RV dysfunction highlights the need to establish its cause. If associated with intermittent hypoxia, consider reevaluating the criteria for oxygen therapy. If associated with another pathogenic pathway independent of hypoxia, the development of new drugs that may act in the early stage of the disease should be considered, minimizing PH and RV dysfunction.

5. Conclusion

Exercise echocardiography may assess RV function in non-advanced IPF patients. Exercise unmasks RV dysfunction, which decreases when an acute overload likely promotes RV-PA uncoupling. Patients with impaired RV function should receive greater attention as this parameter may be an early index of suspected PH and may indicate a poorer prognosis.

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Author contributions

SBC analyzed and interpreted patient data and was a major contributor to the manuscript preparation. MPR reviewed all data and made substantial contributions to the conception and design of the work. FXM acquired and analyzed CPET data. NMCF selected all patients. CAMS acquired and analyzed the data and revised the work. All authors have read and approved the final manuscript.

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