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Right Ventricular Functional Reserve in Early-Stage Idiopathic Pulmonary Fibrosis
An Exercise Two-Dimensional Speckle Tracking Doppler Echocardiography Study

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BACKGROUND: The most important determinant of long-term survival in patients with idiopathic pulmonary fibrosis is the right ventricular (RV) adaptation to the increased pulmonary vascular resistance. Our aim was to explore RV contractile reserve during stress echocardiography in early-stage IPF.

METHODS: Fifty early-stage patients with IPF and 50 healthy control patients underwent rest and stress echocardiography, including RV two-dimensional speckle tracking echocardiography. At peak exertion, blood gas analysis and spirometry were also assessed.

RESULTS: At rest, RV diameters were mildly increased in IPF; however, although RV conventional systolic function indexes were similar between the IPF and control groups, RV global longitudinal strain and RV lateral wall longitudinal strain (LWLS) were significantly reduced in the IPF cohort. During physical exercise, patients with IPF showed a reduced exercise tolerance with lower maximal workload ($P < .01$), level of oxygen saturation ($P < .001$), and peak heart rate ($P < .01$). Systolic and diastolic BP values were similar in both groups. Systolic pulmonary artery pressure (PAPs) increase (ΔPAPs) during exertion was higher in IPF vs healthy subjects ($P < .0001$); RV LWLS increase (ΔRV LWLS) during exercise was lower in patients with IPF vs control patients ($P < .00001$). By multivariable analysis, RV LWLS at rest and ΔRV LWLS were directly related to peak exertion capacity, PAPs, and blood oxygen saturation level (Spo$_2$; $P < .0001$). Δ RV LWLS was directly related to diffusion lung carbon monoxide ($P < .0001$).

CONCLUSIONS: RV myocardial dysfunction is already present at rest in early-stage IPF and worsens during exertion as detected by two-dimensional speckle-tracking echocardiography. The RV altered contractile reserve appears to be related to reduced exercise tolerability and impaired pulmonary hemodynamic.   CHEST 2019; 155(2):297-306

KEY WORDS: 2D speckle tracking echocardiography; idiopathic pulmonary fibrosis; right ventricle; stress echocardiography

Idiopathic pulmonary fibrosis (IPF) is the most common type of chronic idiopathic interstitial pneumonia,[1] with rapid progression and a mean survival from diagnosis of 3 to 5 years.[2,3] The nonsurgical approach to therapy with antifibrotic medication slows the progression but cannot induce regression of this lung disease.[2] IPF can be complicated by precapillary pulmonary hypertension (PH),[4,5] which is present in 35% to 40% of patients at advanced stages of the disease. Patients with IPF referred to lung transplantation manifest a PH prevalence of about 85%.[6,7] The onset of PH as well as the decline of respiratory functional parameters including oxygen desaturation < 88% at 6-min walking test, diffusion lung carbon monoxide (DLCO) < 40% predicted, and a change in FVC > 10% percentage points,[8] are all unfavorable prognostic factors.[9–12] The most important determinant of long-term survival in these patients, however, is represented by the adaptation of the right ventricle to increased pulmonary vascular resistance (PVR).[13]

Most of the work in the scientific literature regarding the right ventricle in IPF has focused on the presence of PH at rest and the consequences of increased afterload on right ventricular (RV) function at the advanced stages of IPF.[4,5,14–23] RV global longitudinal strain (GLS) turned out to be an important determinant of outcome (right-sided heart failure, clinical deterioration, and mortality) in patients with PH.[24]

D'Andrea et al[25] have shown that in patients affected by IPF without evidence of PH, FVC, and mean pulmonary arterial pressure represent independent determinants of RV GLS, explaining about 70% of its variability; moreover, RV GLS has been demonstrated to be associated with 6-min walking test and is an independent predictor of functional capacity.[25]

Although transthoracic echocardiography is the standard practice for the evaluation of RV function in resting conditions, stress echocardiography (SE) should be considered as a diagnostic technique to assess pulmonary hemodynamic during exercise as well as RV contractile reserve.[26–29]

It has been already demonstrated that, in late stages of interstitial lung disease, RV dysfunction is more evident during physical exercise.[14-17] An inadequate increase of pulmonary blood flow during exertion may contribute to exercise intolerance. In these patients, the right ventricle adapts to an already increased afterload at rest during exercise, with further uncoupling of the RV contractile reserve in relation to the downstream pulmonary vascular afterload.[17-23] A paucity of data are available about RV dysfunction in early-stage IPF and its progression during the course of worsening disease.

The aim of this study was to explore resting and exercise RV contractile reserve among early-stage patients with IPF. For this purpose, we applied two-dimensional speckle tracking echocardiography (2DSTE), which provides angle-independent information about segmental and global myocardial deformation.

Methods

Study Population

From June 2017 to December 2017, 50 patients affected by early-stage IPF referred to the Rare LungDiseases Unit – Cardiorespiratory Department, Monaldi Hospital, Naples, Italy, were enrolled. Echocardiography analysis was performed by our echocardiography laboratory, Division of Cardiology, Luigi Vanvitelli University - Naples, Monaldi Hospital. The diagnosis of IPF was made on the basis of the American Thoracic Society and European Respiratory Society 2011 Guidelines.[30,31] Patients with a history of pulmonary thromboembolism or other forms of diffuse parenchymal lung disease or coexisting rheumatologic disease were excluded. To form the control group, healthy subjects referred to our cardiology department for voluntary cardiovascular screening were assessed. In agreement with exclusion criteria, subjects affected by systemic hypertension, diabetes, dyslipidemia, and/or a history of cardiovascular disease were excluded. The final control group was represented by 50 sedentary healthy subjects.

All patients underwent comprehensive clinical assessment at rest and SE including RV 2DSTE; furthermore, at peak exertion, blood gas analysis and spirometry were also registered.

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The study was approved by the institution's ethics board and each participant provided informed consent.

Imaging Protocol and Measurements

Standard transthoracic echocardiography, Doppler evaluation, and strain analysis were performed at rest and at peak exertion using market available equipment (Vivid E9, GE Healthcare, Milwaukee, WI). All measurements were assessed, as an average of three consecutive beats, independently by two authors (A.D. and S.S.), cardiologists expert in echocardiography, according to the latest European and American guidelines and recommendations.[26,32-34] The following parameters were performed: basal RV diameter, mid-cavity RV diameter, and longitudinal diameter in the apical four-chamber view at the end-diastole; RV outflow tract (RVOT) at the subpulmonary region from the parasternal short-axis view. As an index of RV longitudinal systolic function, tricuspid annular plane systolic excursion (TAPSE) was determined in a standard apical four-chamber view.

Spectral Doppler Analysis

Tissue Doppler imaging (TDI) was used to determine RV peak systolic velocity (TDI systolic peak (Sm) wave) in an apical four-chamber view. In the parasternal short-axis or in the apical four-chamber views, the peak tricuspid regurgitant velocity (TRV), was measured. On the basis of the TRV, pulmonary artery systolic pressure (PAPs) was calculated as Bernoulli's principle: $(4 \times TRV^2) + RAP$, where RAP is the right atrial pressure. RV stroke volume was calculated as the product of RVOT area and RVOT time-velocity integral.[29] PVR was estimated using the following equation: $PVR = PAPm - PCWP/CO^{rif}$, where PAPm is the mean pulmonary artery pressure calculated as $PAPs \times 0.61 + 2$ mm Hg, according to Chemla et al,[35] CO is the cardiac output derived from the stroke volume, and PCWP is the pulmonary capillary wedge pressure, estimated for all cases of 10 mm Hg.

Regarding the left heart chambers, left ventricular (LV) involvement was estimated as expression of RV-LV interdependence in this setting; hence, LV diastolic parameters (E and A peak velocities and E/mean e′ ratio) and stroke volume were determined.[16,36]

2D Echocardiographic RV Strain

For RV strain calculation, a region of interest, including the entire RV myocardial wall, was traced on the endocardial cavity interface of the RV-focused apical four-chamber view at peak systole by a point-and-click approach. Then, a second, larger region was automatically generated, which was near the epicardium with a width of 10 mm. The tracking algorithm followed the endocardium through the entire cardiac cycle. Myocardial thickening was represented with a negative value; myocardial thinning was represented with a positive value.[37,38] The software then automatically divided the image into six standard segments and provided an automated tracking-quality score as feedback of the stability of the regional speckle tracking, ranging from 1.0 (excellent tracking) to 3.0 (poor tracking) arbitrary units. A tracking score value < 2.5 was determined as acceptable. The tracking process and conversion to Lagrangian strains were performed offline using a dedicated software (EchoPAC PC 2D strain, GE Healthcare). Longitudinal strains for each segment were measured and averaged for RV septal and lateral walls. In addition, the software calculated RV GLS by averaging local strains along the entire right ventricle.[38,39] With the same procedure, LV longitudinal strain was evaluated in apical views. If RV and LV function are preserved, GLS is more negative (higher number numerically); alternatively, when RV or LV function deteriorates, GLS is less negative.[25,40,41]

Exercise SE

All participants recruited in the study, after the resting echocardiogram, underwent a supine bicycle exercise SE as a standard protocol characterized by incremental 2-min steps of 25 watts.[42-44] At peak exertion, functional parameters such as maximal oxygen desaturation, maximal heart rate, maximal systolic BP, and maximal workload (number of watts achieved by supine bicycle test) were evaluated.

Echocardiographic parameters evaluated at baseline and at peak exertion included RV end-diastolic chamber size, RV systolic parameters (TAPSE and TDI Sm wave), PAPs, RV stroke volume, LV diastolic parameters, LV stroke volume, and 2DSTE LV and RV analysis.[45]

Statistical Analysis

Statistical analyses were performed using a commercially available package (SPSS, Rel. 21.0. 2016, SPSS Inc., Chicago, IL). Variables are presented as mean $\pm$ SD. Two-tailed t test for paired and unpaired data was used to assess changes between groups. Linear regression analyses and partial correlation test by Pearson's method were used to assess univariate relations.

To identify significant independent determinants of RV myocardial strain in patients affected by IPF, their individual association with clinical, functional, and echocardiographic variables was assessed by multivariable Cox regression analysis. The following variables were included in the analysis: clinical peak exercise parameters (age, heart rate, oxygen saturation, systolic BP, diastolic BP, BMI); functional respiratory and metabolic parameters such as FVC, FEV_1, FEV_1/FVC, DLCO, DLCO/alveolar volume, pH, PCO_2, PO_2, bicarbonate, and lactate levels); standard echocardiographic parameters (RV diameters, TAPSE, PAPs, TDI Sm wave), RV stroke volume, LV stroke volume, Doppler mitral flow velocities, and the TDI E′ septal and lateral mitral annular diastolic velocities and the mean between the two values). These variables were selected according to their clinical relevance and potential effect on RV function, as demonstrated by previous studies.[4,11]

Variable selection was performed in the multivariable linear regression analysis using an interactive stepwise backward elimination method, each time excluding the variable with the highest P value according to Wald statistics. The assumption of linearity was tested graphically by studying the smoothed Martingale residuals from the null model plotted against the covariate variables. Linearity assumptions were satisfied. The Hosmer-Lemeshow goodness of fit test was used to check that the model adequately fit the data. The model also underwent bootstrap validation (200 runs).[2] To decrease the inflation of the type 1 error rate resulting from multiple testing, the statistical significance was defined as two-sided P value < .05. Receiver operating characteristic curve analysis was performed to select optimal cutoff values of echocardiographic parameters. Reproducibility of 2DSTE measurements was determined in all the subjects. Interobserver variability and intraobserver variability were evaluated using both Pearson's bivariate two-tailed correlations and Bland-Altman analysis. Relation coefficients, 95% confidence limits, and percent errors were reported.

Results

No statistically significant differences were noted between the two groups in age, BMI, heart rate, or systolic and diastolic BP. Oxygen saturation at rest was significantly lower in patients with IPF (Table 1).

Echocardiographic Findings of LV and RV Function at Rest in Early-Stage IPF

Left ventricular function was similar among the IPF and control cohorts (Table 2). RV diameters were mildly increased in IPF. RV conventional systolic function indexes (TAPSE and TDI Sm wave, RV stroke volume and PAPs) were similar among the IPF and control groups (Table 2; Fig 1).

RV speckle tracking was obtainable at rest in 95% of the total analyzed segments. The remaining 5% segments

were not considered because of a suboptimal tracking score (> 2.5). Overall, the tracking score was < 2.0 for 83% of the analyzed segments. In patients with IPF, RV GLS and RV lateral wall longitudinal strain (LWLS) were significantly reduced. This variation was statistically significant in all the analyzed segments (Table 2; Fig 2).

As for left heart chambers, LV stroke volume, E/e′ ratio, and 2STDE strain were comparable between the two groups.

Echocardiographic and Spectral Doppler Evaluation During Exercise in Early-Stage IPF

During physical exertion, systolic function indexes such as TAPSE and TDI Sm wave and RV stroke volume were comparable between the two groups. PAPs increase

TABLE 1] Demographic and Functional Parameters at Rest and at Peak Exertion in the Overall Study Population

Variable	IPF (n = 50)	Control Patients (n = 50)	P
Rest parameters			
Age	61.2 ± 8.3	59.4 ± 6.3	NS
Sex (men/women)	35/15	34/16	NS
Smokers, %	...	...	31% vs 28%
BMI, kg/m^2	27.5 ± 3	28.3 ± 2	NS
Resting HR, beats/min	71.9 ± 9.1	73.5 ± 8.2	NS
SBP, mm Hg	128.3 ± 5.1	130.3 ± 6.1	NS
DBP, mm Hg	80.6 ± 5	79.5 ± 7.1	NS
Spo$_2$, %	83.4 ± 10.3	92.5 ± 5.1	<.001
6MWT distance, m	490 ± 13	...	...
Peak exertion parameters			
Watt achieved	100.3 ± 25	125.4 ± 50	<.01
Maximal SBP, mm Hg	165.3 ± 12	161. 4 ± 11	NS
Maximal DBP, mm Hg	88.4 ± 10	85 ± 16	NS
Maximal HR, beats/min	107.5 ± 26	115.3 ± 26	< 0.01
Spo$_2$, %	70.2 ± 16.3	89.4 ± 12	<0.001
Blood gas analysis			
pH	7.37 ± 4.5	...	...
Pco$_2$, mm Hg	36.5 ± 4	...	...
Po$_2$, mm Hg	80.7 ± 8.2	...	...
HCO$_3$, mEq/L	213,8 ± 27	...	...
Lactate, mmol/L	49.9 ± 24	...	...
FVC, %	75.9 ± 15	...	...
FEV$_1$, %	81.3 ± 16	...	...
FEV$_1$/FVC	85.9 ± 13	...	...
Dlco, %	53.6 ± 14	...	...
Dlco/AV	39.2 ± 18	...	...

6MWT = 6-min walking test; DBP, diastolic BP; Dlco = diffusion lung carbon monoxide; HR = heart rate; IPF = idiopathic pulmonary fibrosis; NS = not significant; SBP = systolic BP; Spo$_2$ = blood oxygen saturation level; VA = alveolar volume.

TABLE 2] RV and LV Standard Echo and 2DSTE Measurements at Baseline and Peak Exertion in the Overall Study Population

Variable	IPF	Control Patients	P
Rest measurements			
RVD1, mm	34.4 ± 2.3	28 ± 3.4	<.01
RVD2, mm	27.3 ± 28	29 ± 3.2	NS
RVD3, mm	64.4 ± 4.6	69.9 ± 5.5	<.05
RVOT diameter, mm	22.9 ± 3.2	26 ± 3.1	<.01
PAPs, mm Hg	18.6 ± 8.8	15.3 ± 6	<.05
PVR, WU	3.4 ± 1.9	1.8 ± 0.7	<.01
TAPSE, mm	20.3 ± 3.3	21 ± 3.1	NS
TDI RV peak systolic velocity Sm, cm/s	13.9 ± 4	12.8 ± 0.3	NS
RV stroke volume, mL	86.3 ± 18	89.4 ± 6	NS
RV lateral wall longitudinal strain 2DSTE, %	-9.4 ± 4.8	-17.6 ± 3.3	<.001
RV GLS, %	-14.5 ± 4,6	-18.4 ± 2.8	<.01
PW mitral peak E velocity, cm/s	62.3 ± 10	68.4 ± 13	NS
TDI septal E', cm/s	10.5 ± 11	11.3 ± 1 3	NS
TDI lateral E', cm/s	16.6 ± 14	15.8 ± 16	NS
Mitral E/E' ratio	8.3 ± 2.2	6.4 ± 3.1	NS
LV stroke volume, mL	88.5 ± 25	90.4 ± 12	NS
LV strain 4 CH, %	-19.4 ± 3.2	-19.3 ± 4	NS
LV strain 5 CH, %	-19.3 ± 3.1	-19.6 ± 3.3	NS
LV strain 2 CH, %	-18.2 ± 3.3	-19.2 ± 3.6	NS
LV GLS	-18.4 ± 3.3	-19.4 ± 4.1	NS
Peak exertion measurements			
RVD1, mm	36.6 ± 3.6	30.3 ± 3.1	<.01
RVD2, mm	29.1 ± 3.3	31 ± 3.1	NS
RVD3, mm	68.4 ± 9.5	70 ± 3.1	NS
RVOT diameter, mm	23.1 ± 3.3	24 ± 3.1	NS
PAPs, mm Hg	40.7 ± 18.6	32.5 ± 5	<.001
TAPSE, mm	24.3 ± 5.5	25.3 ± 6	NS
TDI RV peak systolic velocity Sm, cm/s	19.5 ± 5.6	21.2 ± 6.1	NS
RV stroke volume, mL	109.4 ± 6.6	112.3 ± 10.3	NS
RV lateral wall longitudinal strain 2DSTE, %	-11.4 ± 9.3	-22.4 ± 4.2	<.0001
RV GLS, %	-15.3 ± 5.5	-23-9 ± 4.9	<.0001
PW mitral peak E velocity, cm/s	99.1 ± 12.3	90.3 ± 14.3	NS
TDI septal E', cm/s	10.8 ± 12.3	18.9 ± 13.1	NS
TDI lateral E', cm/s	12.5 ± 13.3	19.4 ± 16	<.01
Mitral E/E' ratio	9.2 ± 2.4	8.3 ± 3.1	NS
LV stroke volume, mL	110.4 ± 10.1	116.3 ± 13.6	NS
LV Strain 4CH, %	-22.3 ± 3.2	-24.3 ± 5.3	NS
LV Strain 5CH, %	-21.4 ± 3.3	-23.6 ± 4.2	NS
LV Strain 2CH, %	-20.5 ± 3.9	-22.4 ± 4.5	NS

2DSTE = 2-dimensional speckle tracking echocardiography; CH = chambers; GLS = global longitudinal strain; LV = left ventricular; PAPs = systolic pulmonary artery pressure; PVR = pulmonary vascular resistance; PW = pulsed wave, RVD1 = basal right ventricle diameter; RVD2 = mid-cavity RVD; RVD3 = longitudinal RVD; RVOT = right ventricular outflow tract; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging.
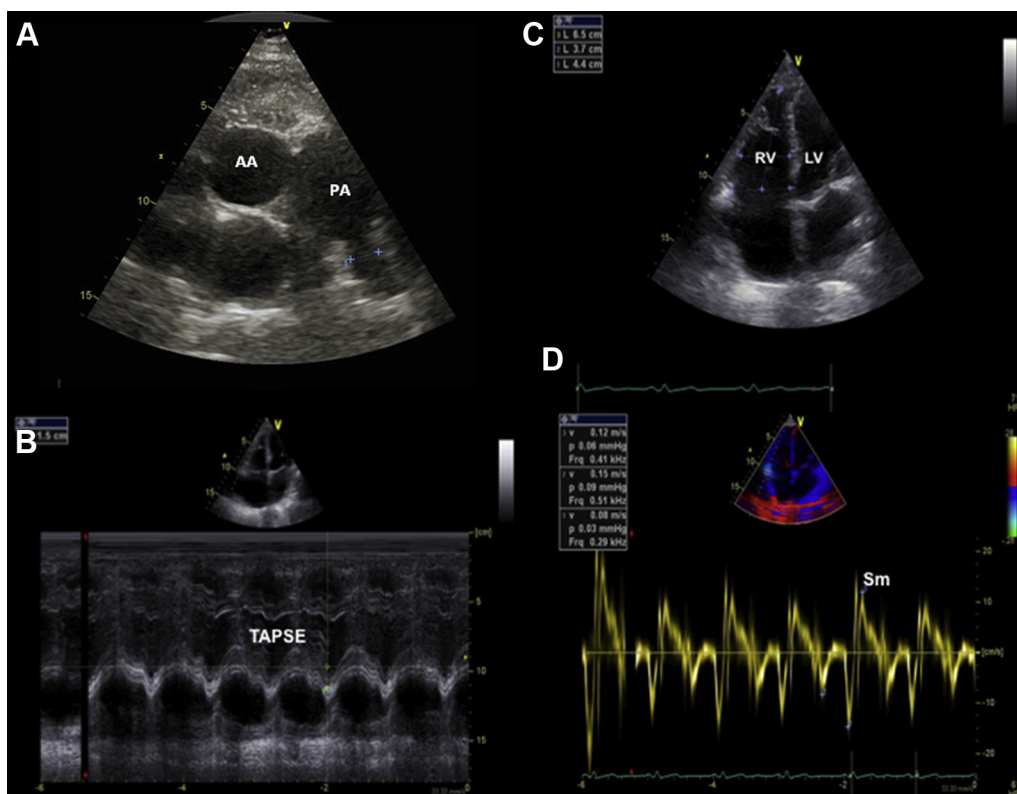
Figure 1 – *Standard echocardiography. A, Mild pulmonary artery enlargement. B, Right ventricular enlargement, with normal function by (C) tricuspid annular plane systolic excursion and (D) tissue Doppler analysis.*

(ΔPAPs) during exertion, calculated as the difference between PAPs at peak exertion and PAPs at rest, was higher in patients with IPF (Table 3).

RV Deformation (Strain) Analysis During Exercise in Early-Stage IPF

RV GLS and RV LWLS increase (Δ RV GLS and Δ RV LWLS, respectively) were lower compared with healthy subjects (Table 3).

Exercise Tolerance and Vital Parameters at Peak Exertion in Early-Stage IPF

During physical exercise, patients with IPF showed a reduced exercise tolerance with a lower maximal workload, level of oxygen saturation, and peak heart rate. Systolic and diastolic BP values were similar in both groups (Table 1).

Regression Analysis of Variables

On univariate analysis, RV LWLS at rest was directly related to peak exertion capacity expressed in watts ($r = -0.58$, $P < .0001$), and to PAPs and blood oxygen saturation level (SpO$_2$) at peak exertion ($r = 0.55$, $P < .0001$; and $r = -0.44$, $P < .0001$, respectively). Moreover, during exercise, Δ RV LWLS was directly

related to ΔPAPs ($r = -0.51$, $P < .0001$), to lactate ($r = -0.49$, $P < .0001$) and to DLCO ($r = 0.53$, $P < .0001$).

Multivariable analyses confirmed that RV LWLS at rest was directly related to peak exertion expressed in watt, peak PAPs, and SpO$_2$ (Table 4), whereas Δ RV LWLS was significantly and independently associated with ΔPAPs, lactate, and DLCO.

Discussion

Resting RV Function

In the present study, RV GLS and RV LWLS were significantly reduced in IPF despite preserved RV systolic function assessed by "conventional" echo-Doppler indices (TAPSE and TDI Sm wave). These data confirm a subclinical impairment of RV myocardial function even in the early stages of IPF. Of note, a prognostic effect of RV regional myocardial deformation in IPF has been previously demonstrated, with an RV LWLS $\leq$ -12% as the only independent predictor of cardiovascular events, including sudden cardiac death, during the follow-up.[40] As a result, a full cardiac work-p of the patient affected by early-stage IPF should include the assessment of RV function through 2DSTE to detect
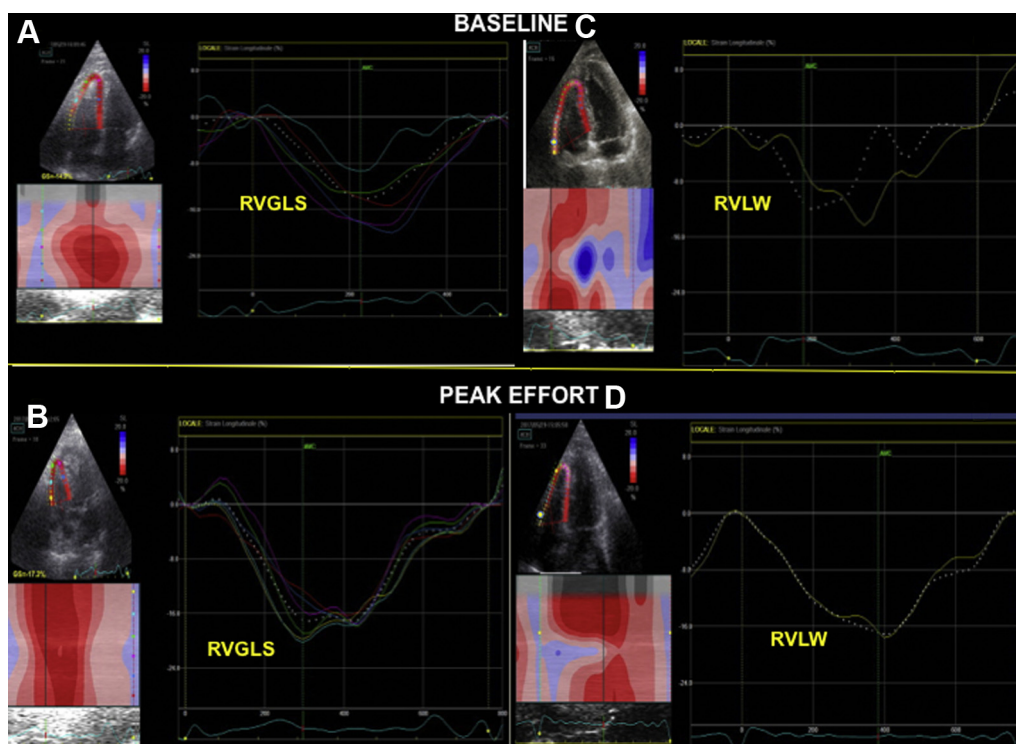
Figure 2 – RVGLS and RVLW strain. A-C, at rest and at (B-D) peak exertion in the same patient affected by IPF, with significant RV contractile reserve as detected by two-dimensional strain improvement. IPF, idiopathic pulmonary fibrosis; RVGLS = right ventricular global longitudinal strain; RVLW = right ventricular lateral wall.

a subclinical impairment, stratify the risk, and timely start the appropriate therapy.

RV Function During Exercise

The present study represents the first report exploring both pulmonary pressures and RV contractile reserve during stress tests in early-stage IPF, demonstrating RV dysfunction during physical exertion along with impaired exercise tolerance. The reduced functional capacity in patients was highlighted by a lower maximal workload, an impaired chronotropic response, and a reduced peak SpO_2 level.

In particular, during physical exertion, the ΔPAPs from resting state to peak exercise significantly increased in the IPF group compared with the healthy control patients. Such dynamic increase in pulmonary pressure may be due to an impairment of the physiologic vasodilatory response of pulmonary vascular bed along with hypoxia-induced generalized pulmonary vasoconstriction during exercise stress. In addition, ΔRV GLS and ΔRV LWLS were both significantly reduced in patients with IPF compared with the control group. The lower ΔRV GLS and ΔRV LWLS in patients with confirm the early RV myocardial involvement, with impaired contractile reserve despite traditional indices of

TABLE 3] Echocardiographic Parameters Reaching Statistic Significance: Difference Between Basal Value and Peak Exertion in IPF Population and Healthy Control Patients

Variable	IPF	Control Patients	P
ΔPAPs, mm Hg	23.1 ± 2.2	16.9 ± 3.3	<.001
ΔPAPs, %	122.1 ± 12.2	109.2 ± 8.3	<.0001
ΔRV lateral wall longitudinal strain 2DSTE	2.1 ± 0.9	5.3 ± 2.2	<.001
ΔRV lateral wall longitudinal strain 2DSTE, %	22.2 ± 0.9	31.3 ± 2.2	<.0001
ΔRV GLS 2DSTE	1.2 ± 0.6	5.9 ± 2.4	<.00001
ΔRV GLS 2DSTE, %	8.2 ± 2.6	33.6 ± 9.4	<.00001

See Table 1 and 2 legends for expansion of abbreviations.

TABLE 4] Multivariate Analysis Model: Correlation Between RV Lateral Wall Longitudinal Strain and ΔRV Lateral Wall Longitudinal Strain With Univariate Clinical Parameters

Variable	HR	P
RV lateral wall longitudinal strain (at rest)		
Watt (peak)	-0.50	<.001
PAPs (peak)	0.98	<.001
Spo_2	0.36	<.01
Δ RV lateral wall longitudinal strain (at peak exercise)		
ΔPAPs	-0.48	<.001
Lactate	-0.41	<.01
D_{LCO}	0.51	<.001

See Table 1 legend for expansion of abbreviations.

RV systolic function remaining within the normal reference ranges. This finding could be in part also due to the dependence of the peak systolic strain from the afterload. It is possible that PVR increases more in the patients with IPF than in healthy control patients during exercise, thus leading to a lower ΔRV GLS and ΔRV LWLS.

Of note, our study has clearly underlined a direct relationship between ΔPAPs and ΔRV LWLS in patients with IPF. This direct correlation may further reflect the interdependence, during physical stress, between the increasing pressure workload represented by the "sick pulmonary circulation" and the inability of the right ventricle to adapt its contractile function to the increased metabolic demand.

This uncoupling between pulmonary pressures and RV function in IPF can lead to a self-sustaining maladaptive process, in which the alteration of pulmonary hemodynamic worsens RV contractile dysfunction, which in its turn is responsible for the insufficient increase of pulmonary blood flow, with further impairment of pulmonary gas exchange that finally results in a reduced tolerance to exercise. This pathologic mechanism is further confirmed in our study by the statistically significant correlation between RV LWLS at rest and both peak workload and Spo_2 nadir at peak exertion, and by the associations between ΔRV LWLS and blood lactate, which is considered a marker of inadequate tissue perfusion and prolonged tissue hypoxia.

Finally, ΔRV LWLS also resulted significantly related to D_{LCO}, which is an important independent predictor of

mortality within 2 years of IPF diagnosis.[44] In this perspective, an SE including the evaluation of both pulmonary pressures and RV contractile reserve through 2DSTE could be useful during the follow-up of IPF to identify sooner those patients who are at greater risk for developing clinical cardiac dysfunction and therefore require appropriate therapy.

Study Limitations

MRI and right heart catheterization represent the gold standard for right heart function and hemodynamic respectively. On the other hand, echo-Doppler echocardiography has been demonstrated to be an accurate tool in the evaluation of right heart structure, function, and pressure.[41,46] They also are noninvasive, have no radiation burden, and are easier to perform in nearly every clinical setting; there also are few limitations intrinsic to right heart strain analysis. Because there is no currently available 2DSTE-dedicated software for RV strain analysis, we applied a software package (EchoPAC PC, GE Healthcare) designed for the strain analysis of the left ventricle to the right ventricle. For global RV deformation analysis, the 2DSTE software is not able to discriminate between LV and RV septal components; this influences > 50% of the resulting GLS of the right ventricle assessed in apical four-chamber views.

Next, although the RV-focused apical four-chamber view was believed to provide accurate assessment on RV longitudinal deformation, it would be desirable to obtain information about the whole deformation of RV chamber. Circumferential RV strain was not measured from parasternal long-axis and short-axis views because the right ventricle in these views shows an insufficient wall thickness.

Finally, this is a single-center study with a small sample dimension that does not allow for definitive general conclusions regarding the myocardial deformation index in patients with IPF.

Conclusions

RV myocardial dysfunction is already "silently" present at rest in early-stage IPF and it worsens during exertion, as detected by 2DSTE. The RV altered contractile reserve appears to be related in these patients to reduced exertion tolerability and impaired pulmonary hemodynamic.

Further investigation by use of resting and exercise 2DSTE are needed.

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