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The Impact of Cystic Fibrosis- and Noncystic Fibrosis-Bronchiectasis on Pulmonary Artery Wall Thickness and Right Heart Functions Assessed by Speckle-Tracking Echocardiography

ABSTRACT

Background: Right heart functions are affected in patients with bronchiectasis as a result of pulmonary hypertension induced by chronic hypoxemia. Pulmonary artery wall thickness has recently been introduced as a sign of intensive and prolonged inflammation. The aim of this study was to analyze right ventricular and right atrial functions and to measure pulmonary artery wall thickness in patients with cystic fibrosis-bronchiectasis in comparison to those with noncystic fibrosis-bronchiectasis and healthy individuals.

Methods: We studied 36 patients with cystic fibrosis-bronchiectasis, 34 patients with noncystic fibrosis-bronchiectasis, and 32 age- and sex-matched control subjects. Lung function tests were performed. All subjects underwent comprehensive echocardiographic evaluation including conventional, tissue Doppler, speckle-tracking, and pulmonary artery wall thickness measurements.

Results: Right ventricular global longitudinal strain and global longitudinal right atrial strain during ventricular systole decreased in cystic fibrosis-bronchiectasis group compared with noncystic fibrosis-bronchiectasis and control groups ($P < .001$, both). Conversely, pulmonary artery wall thickness was increased in cystic fibrosis-bronchiectasis group in comparison to other groups ($P < .001$). Moreover, right ventricular global longitudinal strain was lower and pulmonary artery wall thickness was higher in patients with airflow obstruction ($P < .001$ and $P = .025$, respectively) than in those without. Only right ventricular global longitudinal strain was significantly correlated with pulmonary function test parameters. The negative effect of cystic fibrosis on right ventricular and right atrial functions was independent of age, gender, and disease duration.

Conclusion: Our study showed that right ventricular and right atrial functions were deteriorated and pulmonary artery wall was thickened in cystic fibrosis-bronchiectasis patients more than noncystic fibrosis-bronchiectasis patients. Right ventricular global longitudinal strain detected subclinical right ventricular dysfunction and was associated with the severity of pulmonary disease.

Keywords: Chronic diseases, echocardiography, pulmonary circulation and right ventricle

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INTRODUCTION

Bronchiectasis is a disease characterized by irreversible abnormal enlargement and anatomical distortion of the bronchial architecture resulting from chronic recurrent airway infections.[1,2] Long-term inflammatory response and pro-inflammatory vicious circle induced by activated immune cells trigger airway tissue breakdown in affected patients.[3] The key clinical symptoms are chronic productive cough, shortness of breath, and occasionally hemoptysis. Bronchiectasis represents a final common pathway of a large number of inherited and acquired disorders, such as pulmonary infections, connective tissue diseases, alpha 1-antitrypsin deficiency, primary immunodeficiencies, Kartagener's syndrome, primary ciliary dyskinesia, and cystic fibrosis (CF).[4] Despite extensive clinical, radiological, and immunological characterization, however, the etiology cannot be identified in nearly half of all cases (idiopathic bronchiectasis).[5]

Cystic fibrosis is a life-threatening autosomal recessive, multisystemic disease, mostly associated with a clinically significant bronchiectasis. It is caused by several mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, located on the seventh chromosome.[6] Persistent pulmonary infections exacerbated by abnormally thick mucus production and failure of normal mucociliary clearance in CF lead to a chronic, progressive inflammation, and destruction of the bronchial tree. In spite of high morbidity associated with the disease, prognosis of these patients has been significantly improved and lifetime has been extended due to great advances in the treatment during the last few decades.[7]

Pulmonary injury arising from chronic lung infections results in the development of cor-pulmonale secondary to the pulmonary hypertension which is the most frequent cardiac complication in both bronchiectasis due to cystic fibrosis (CF-BR) and bronchiectasis due to other conditions (non-CF-BR).[8,9] Studies with CF patients have demonstrated significant right heart remodeling and dysfunction by means of conventional and tissue Doppler echocardiography.[10-12] Recently, the introduction of modern speckle-tracking echocardiography has made the detection of subclinical right heart dysfunction possible in patients with CF.[13-16] Only 2 studies have been performed with non-CF-BR patients, indicating right ventricular (RV) systolic dysfunction by measuring tricuspid annular plane systolic excursion (TAPSE) and RV myocardial performance index (MPI).[9,17] However, to best of our knowledge, there is no comparative data about right heart dysfunction between CF-BR and non-CF-BR patient groups. A newly published study has also been showed that pulmonary artery (PA) wall thickness measured by echocardiography was increased in Behçet's disease (BD) compared to controls and that it may be a sign of severe disease with more intense and prolonged inflammation.[18] Accordingly, we hypothesized that PA wall may also be thickened in response to chronic inflammation in bronchiectasis.

The aim of our study was to evaluate RV and right atrial (RA) function parameters by conventional, tissue Doppler, and speckle-tracking echocardiography and to investigate whether PA wall thickness increases in adult patients with CF-BR in comparison to those with non-CF-BR and healthy controls.

HIGHLIGHTS

- Right heart functions are adversely affected in patients with bronchiectasis due to cystic fibrosis more than in those with bronchiectasis due to other conditions.
- Right ventricular global longitudinal strain is useful for the detection of subclinical right ventricular dysfunction and is associated with the severity of pulmonary disease in bronchiectasis.
- Pulmonary artery wall thickness is related to the presence of airflow obstruction in bronchiectasis.

METHODS

Study Population and Definitions

We prospectively recruited 36 patients with CF-BR and 40 patients with non-CF-BR referred from the outpatient clinic of our Pulmonology Department. Among those with non-CF-BR, 6 patients with dextrocardia as a part of Kartagener's syndrome were excluded. In the remaining 34 non-CF-BR patients, the underlying cause was unknown (idiopathic) in 19 (55%), primary immunodeficiencies in 8 (23%), measles in 3 (8%), tuberculosis in 2 (5%), and primary ciliary dyskinesia in 2 (5%). To obtain age-matched data, some of the patients with non-CF-BR were included from list of the patients previously followed by our pediatric pulmonology department. Diagnosis of CF was based on positive sweat chloride test with typical clinical findings and genotype confirmation. Diagnosis of bronchiectasis was also proven by physical examination and clinical history consistent with bronchiectasis in addition to high-resolution computed tomography (HRCT) scan of the chest for all consecutive patients. Further, 32 age- and sex-matched healthy control subjects were recruited among medical students and staff at our institution. None of the control subjects had any clinical evidence of cardiovascular (CV) or pulmonary disease. Patients with an age younger than 16 years, symptoms or signs of coronary artery disease, more than mild valvular disease, atrial fibrillation, congenital heart disease, chronic liver or kidney failure, hospitalization within the past 3 months, and acute exacerbation at the time of the study and patients on a lung transplantation waiting list were not included. The presence of CV risk factors, such as hypertension, diabetes mellitus, hyperlipidemia, and smoking was examined. Body mass index (BMI) and body surface area (BSA) were calculated from the measurement of height and weight. The presence of pancreatic involvement and bacterial pathogens identified in the culture of throat or sputum was recorded. Systolic (SBP) and diastolic blood pressure (DBP) were measured using a standard technique. Written informed consent was obtained from each subject involved. The Local Research Ethics Committee approved the study (No: 09.2021.173).

Assessment of Pulmonary Function Tests

Patients with CF-BR and non-CF-BR underwent spirometry (MIR Spirolab II, Medical International Research, Rome, Italy) to measure forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) in liters and as a percentage predicted for the patient's age, height, and sex. The tracings were obtained in sitting position and the best of 3 tracings was used for analysis. The airflow obstruction was defined as FEV1/FVC < 0.70 and was classified as mild for FEV1 $\geq 80\%$, moderate for $50\% \leq$ FEV1 $< 80\%$, severe for $30\% \leq$ FEV1 $< 50\%$, and very severe for FEV1 $< 30\%$ according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines.[19]

Conventional and Tissue Doppler Echocardiography

All subjects underwent comprehensive 2-dimensional (2D) transthoracic echocardiographic examination in a left lateral decubitus position, using a commercially available ultrasound system (EPIQ 7C; Philips Healthcare, Andover, Mass,

USA) by 3 experienced cardiologists who were blinded to all patient information. Data acquisition was performed with a 3.5-MHz transducer (S5-1 probe) in standard parasternal and apical views. The electrocardiogram was recorded continuously, and 3 consecutive cycles were obtained for further image analysis. Care was taken to achieve the highest possible frame rate with optimized sector and depth settings. All measurements were reported according to the American Society of Echocardiography Guidelines.[20] Pulmonary velocity was recorded with pulsed-wave Doppler from the parasternal short-axis view, placing the sample volume at the pulmonary valve level. Pulmonary velocity was used to calculate pulmonary acceleration time (AccT), defined as the time from the onset to maximal velocity. Pulmonary artery diameter was measured between pulmonary valve and PA bifurcation point. The simplified Bernoulli equation was used to calculate the systolic pulmonary artery pressure (sPAP) from the peak velocity of tricuspid regurgitant jet, and the RA pressure was added based on inferior vena cava collapsibility. The TAPSE was measured on the M-mode tracing in the apical 4-chamber view and was described as the difference in the displacement of the RV base during diastole and systole. Right ventricular outflow tract fractional shortening (RVOT fs) was measured by M-mode from parasternal short-axis view at aortic valve level while the cursor was aligned perpendicular to the anterior RVOT wall. Then RVOT fs was defined as 100 × (RVOT end-diastolic diameter – RVOT end-systolic diameter)/RVOT end-diastolic diameter. Tricuspid annulus systolic velocity (RV S') was recorded as the tissue Doppler imaging (TDI)-derived systolic velocity of RV annulus from the apical 4-chamber view. Right ventricular isovolumic acceleration (IVA) was obtained by dividing peak isovolumic contraction velocity by the time to reach it. Right ventricular end-diastolic and end-systolic areas were traced to obtain RV fractional area changes (FAC), calculated as (end-diastolic area – end-systolic area)/end-diastolic area. Right ventricular MPI was measured as the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time as described.

Speckle-Tracking Echocardiography

Two-dimensional speckle-tracking echocardiography (2D-STE) analysis was performed in standard 2D grayscale images, using the same echocardiography system. Echocardiographic measurements were performed offline by a single cardiologist on a workstation using Qlab advanced quantification software version 8.1 (Philips, Eindhoven, The Netherlands). The RV endocardial borders were manually traced in apical 4-chamber view at the end-systolic frame. A second larger concentric circle was then automatically generated near the epicardium and manually adjusted if necessary. An automated tracking algorithm followed speckles throughout the cardiac cycle. Strain was calculated by measuring the change in the position of speckles within myocardial segments. Right ventricular global longitudinal strain (GLS) was derived from the average of the 6 segmental (basal, mid, and apical segments) peak systolic longitudinal strain values of both the ventricular septum and the RV free wall (Figure 1). The same analysis was also performed in apical 4-chamber grayscale images for RA. Longitudinal RA strain during ventricular systole (or reservoir phase) was obtained just before tricuspid valve opening; strain during late diastole (or pump phase) was obtained at the onset of the P-wave on electrocardiography. Global longitudinal RA strain during ventricular systole (GRAs-res) and late diastole (GRAs-pump) were calculated by averaging values observed in all 6 RA segments (Figure 1). Right ventricular maximum volume (before tricuspid valve opening, RAV-max), RA preA volume (onset of the P-wave, RAV-preA), and RA minimum volume (after the atrial contraction, RAV-min) were measured from the volume curve generated by the software. Volumetric parameters were indexed to BSA (RAVi-max, RAVi-preA, RAVi-min, respectively).

Pulmonary Artery Wall Thickness

Two-dimensional parasternal aortic short-axis images were obtained during a breath-hold, stored in a cine-loop format from 3 consecutive beats, and transferred to a workstation

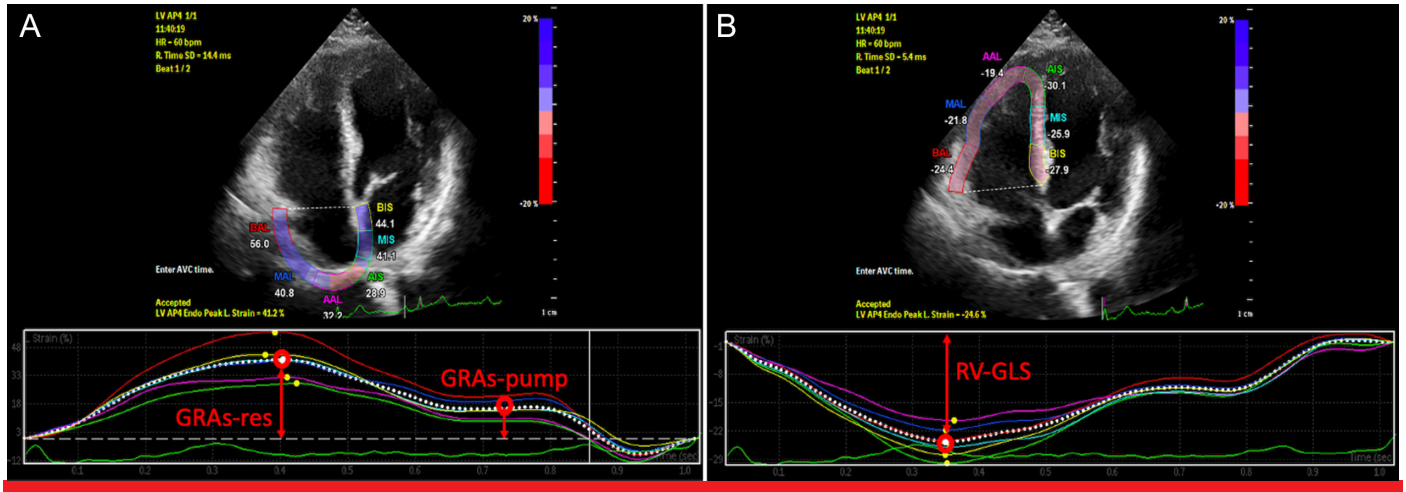

Figure 1. Right ventricular global longitudinal strain (RV GLS), global longitudinal right atrial strain during ventricular systole (GRAs-res), and global longitudinal right atrial strain during late diastole (GRAs-pump) were measured by speckle-tracking echocardiography analysis of 6 consecutive myocardial segments in the RV and the RA.

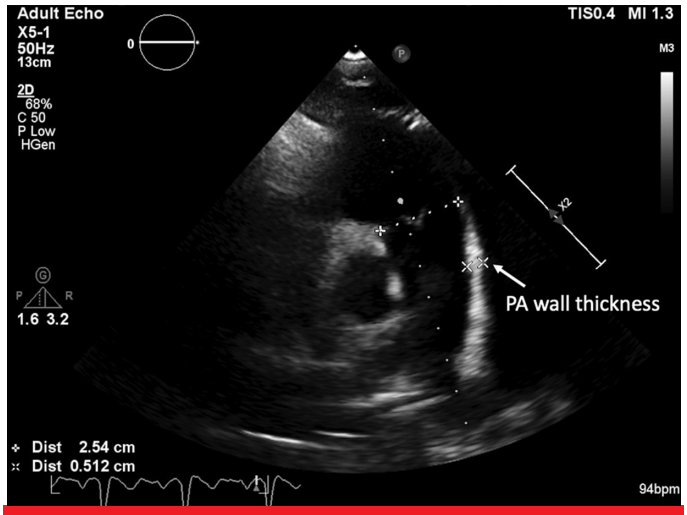

Figure 2. Measurement of pulmonary artery wall thickness in parasternal short axis view at the level of aortic valve.

for further offline analysis. Pulmonary artery wall thickness was measured from the external wall (opposite to the wall neighboring the aorta) in the mid-portion of main PA (approximately 1 to 2 cm distal to the pulmonary valve), as described previously (Figure 2).[18] The average of 3 consecutive measurements was recorded.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 26.0 (IBM Statistics for Windows, Armonk, NY, USA). Continuous variables were checked for normal distribution by the Kolmogorov–Smirnov test and presented as mean ± standard deviation (SD), while categorical variables were expressed as frequencies (number of cases) or percentages. Continuous variables were compared using Student's *t*-test or analysis of variance (ANOVA) test for normal distribution and Mann–Whitney *U*-test or Kruskal–Wallis test for non-normal distribution. For comparing categorical data, Chi-square (χ^2) test was performed. Pearson's or Spearman's correlation analysis was performed to explore the relationship between the studied parameters. Linear regression analysis was also performed to further explore the associations, with RV GLS as dependent variable and age, gender, disease duration, and the presence of CF-BR as independent variables. Ten randomly selected datasets were re-analyzed by the same observer 1 day later and by the second observer to determine the intra-observer and inter-observer variability of RV GLS, GRAs-res, and PA wall thickness measurements by means of Bland–Altman analysis. A value of $P < .05$ was considered statistically significant.

RESULTS

Study Population

Study population of our study consisted of 36 patients (mean age, 26.1 ± 4.6 years; 47% men) with CF-BR, 34 patients (mean age, 29.0 ± 9.9; 44% men) with non-CF-BR, and 32 healthy controls (mean age, 26.8 ± 5.4; 43% men). Demographic, clinical, and microbiological characteristics for each group were given in Table 1. There were no significant differences in age, gender, heart rate, BMI, and BSA among CF-BR, non-CF-BR, and control groups. Duration of the disease in CF-BR was comparable to those in non-CF-BR groups. Two patients (5%) with CF-BR and 4 patients (11%) with non-CF-BR had hypertension, but mean SBP and mean DBP were not statistically different among groups. The frequency of other CV risk factors such as hyperlipidemia, smoking, and diabetes mellitus did also not differ significantly between 2 bronchiectasis groups. Testing for gene mutation and sweat test were positive for all patients (n = 36, 100%) and 28 patients (77%) had pancreatic involvement in CF-BR group. The most frequent microbial agent was *Pseudomonas aeruginosa* (n = 28, 77%) for patients with CF-BR and *Haemophilus influenzae* (n = 16, 47%) for patients with non-CF-BR.

Table 1. Demographic, Clinical, and Microbiological Characteristics of the Study Population

	CF-BR (n = 36)	Non-CF-BR (n = 34)	Controls (n = 32)	*P*
Age (years)	26.1 ± 4.6	29.0 ± 9.9	26.8 ± 5.4	.220
Male gender, n (%)	17 (47)	15 (44)	14 (43)	.926
Disease duration (years)	15.1 ± 7.2	18.4 ± 6.3	-	.764
BMI (kg/m^2)	21.8 ± 3.1	23.5 ± 4.9	22.5 ± 3.3	.823
BSA (m^2)	1.65 ± 0.2	1.70 ± 0.2	1.68 ± 0.1	.535
Heart rate	86.0 ± 8.7	83.0 ± 11.7	82.0 ± 8.0	.202
SBP (mm Hg)	114.0 ± 14.0	119.6 ± 19.8	118.3 ± 17.5	.446
DBP (mm Hg)	71.8 ± 10.1	75.4 ± 12.3	76.4 ± 13.4	.312
Hypertension, n (%)	2 (5)	4 (11)	-	.347
Hyperlipidemia, n (%)	2 (5)	1 (2)	-	.751
Smoking, n (%)	2 (5)	4 (11)	-	.362
Diabetes mellitus, n (%)	8 (22)	2 (5)	-	.081
Pancreatic disease, n (%)	28 (78)	0 (0)	-	<.001
Microbiology				
Pseudomonas aeruginosa	28 (78)	7 (21)	-	<.001
Staphylococcus aureus	27 (75)	2 (6)	-	<.001
Achromobacter	2 (6)	0 (0)	-	.493
Haemophilus influenza	0 (0)	16 (47)	-	<.001
Streptococcus pneumonia	0 (0)	4 (12)	-	.051

BMI, body mass index; BSA, body-surface area; CF-BR, bronchiectasis due to cystic fibrosis; DBP, diastolic blood pressure; non-CF-BR, bronchiectasis due to other conditions than cystic fibrosis; SBP, systolic blood pressure.

Reproducibility

Reproducibility of data readings performed by experienced cardiologists was tested. For intra-observer and inter-observer variability analysis, repeated readings for RV GLS,

GRAs-res, and PA wall thickness correlated well ($r=0.93$ and 0.83, $r=0.84$ and 0.77, $r=0.94$ and 0.95, respectively). Bland–Altman analysis revealed only minor differences (mean ± SD); -1.2 ± 0.7% and -2.1 ± 1.2%, 0.7 ± 3.0% and 0.9 ± 3.6%, 0.025 ± 0.064 mm and 0.023 ± 0.065 mm, respectively.

Pulmonary Function Tests

Spirometry results were demonstrated in Table 2. Forced expiratory volume in 1 second (%, predicted) and FVC (%, predicted) values in CF-BR group were significantly lower when compared with values in non-CF-BR group. The airflow obstruction was observed in 14 patients (38%) with CF-BR and 11 patients (32%) with non-CF-BR ($P=.135$). Among those, 7 patients (19%) with CF-BR and 5 patients (14%) with non-CF-BR had severe, while 4 patient (11%) with CF-BR and 1 patient with non-CF-BR (3%) had very severe airflow obstruction.

Echocardiography

Table 3 presents the conventional, tissue Doppler and STE results of each group. The major determinants of right heart function (RV GLS, GRAs-res, RV S′ and TAPSE) were significantly decreased in CF-BR group when compared to nonCF-BR group and controls. RVOT fs values in patients with CF-BR also differed significantly to those in controls, but were identical to those in patients with nonCF-BR. CF-BR group demonstrated significantly lower pulmonary AccT and significantly higher PA wall thickness and RAVi-max values in comparison to nonCF-BR group and controls. Tricuspid regurgitation was present in 28 CF (77%) and 29 nonCF-BR (85%) patients, and sPAP estimations were also significantly different between these subgroups (43.7±7.5 mm Hg and 35.0±10.8 mm Hg, respectively, P < .001). However, analysis of variance showed no significant differences in pulmonary velocity, RV IVA, RV FAC and RV MPI among groups.

The main clinical and echocardiographic parameters were also compared between bronchiectasis patients (CF-BR group plus non-CF-BR group) with airflow obstruction (FEV1/FVC<70%, n=25) and without airflow obstruction (FEV1/FVC>70%, n=45) (Table 4). Patients with airflow obstruction appeared to have significantly increased PA wall thickness and significantly decreased RV GLS compared to the patients without airflow obstruction. However, those with and without airflow obstruction did not differ significantly in terms of age, gender, disease duration, and remaining echocardiographic parameters.

Among all tested variables, only RV GLS was significantly correlated with lung function test results [$r=0.55$ for FEV1 (%, predicted) and $r=0.39$ for FEV1/FVC, $P<.001$ and $P=.001$, respectively] (Figure 3). Linear regression analysis showed that CF-BR is still a significant risk factor negatively affecting the RV GLS and GRAs-res when adjusted by age, gender, and disease duration. The CF-BR patients on the average had 3.558% lower RV GLS and 4.966% lower GRAs-res compared to non-CF-BR and healthy controls (Table 5A and 5B).

Table 2. Pulmonary Function Test Results for the Patients with CF- and non-CF-Bronchiectasis

	CF-BR (n=36)	Non-CF-BR (n=34)	P
FEV1 (L)	1.85 ± 0.86	2.26 ± 0.83	.062
FEV1 (%, predicted)	52.3 ± 22.1	68.2 ± 21.3	.003
FVC (L)	2.65 ± 1.08	3.06 ± 0.91	.124
FVC (%, predicted)	63.8 ± 22.6	78.5 ± 16.4	.002
FEV1/FVC (%)	70.5 ± 12.1	73.4 ± 15.2	.345
FEV1/FVC < 70%, n (%)	14 (38)	11 (32)	.135
Mild AO, n (%)	0 (0)	1 (2)	.547
Moderate AO, n (%)	3 (8)	4 (12)	
Severe AO, n (%)	7 (19)	5 (14)	
Very severe AO, n (%)	4 (11)	1 (3)	

AO, airflow obstruction; CF-BR, bronchiectasis due to cystic fibrosis; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; non-CF-BR, bronchiectasis due to other conditions than cystic fibrosis.

Table 3. Conventional, Tissue Doppler, and Speckle-Tracking Echocardiography Findings Among Groups

	CF-BR (n=36)	Non-CF-BR (n=34)	Controls (n=32)	P
Pulmonary velocity (m/s)	0.88 ± 0.13	0.90 ± 0.12	0.85 ± 0.10	.277
Pulmonary AccT (ms)	109.9 ± 17.9[a,b]	123.6 ± 19.5[b]	146.53 ± 19.8	<.001
Pulmonary artery diameter (cm)	18.6 ± 3.2[b]	18.3 ± 2.8[b]	15.7 ± 3.1	<.001
PA wall thickness (cm)	0.529 ± 0.13[a,b]	0.450 ± 0.10[b]	0.354 ± 0.03	<.001
TAPSE (mm)	17.5 ± 3.3[a,b]	19.9 ± 2.4[b]	24.7 ± 3.2	<.001
RVOT fs (%)	32.8 ± 7.5[b]	32.4 ± 6.7[b]	46.7 ± 12.4	<.001
RV S′ (cm/s)	11.4 ± 2.0[a,b]	13.0 ± 2.3[b]	14.5 ± 2.1	<.001
RV IVA (cm/s^2)	282.7 ± 86.0	275.4 ± 78.0	279 ± 84.1	.724
RV FAC (%)	45.9 ± 10.3	48.3 ± 7.0	51.2 ± 12.4	.112
RV MPI	34.0 ± 5.2	33.7 ± 5.1	32.1 ± 5.8	.857
RV GLS (%)	-21.1 ± 5.7[a,b]	-24.2 ± 3.7	-26.4 ± 3.5	<.001
GRAs-res (%)	24.9 ± 5.8[a,b]	29.6 ± 9.2[b]	36.9 ± 8.8	<.001
GRAs-pump (%)	7.4 ± 3.6	8.7 ± 4.5	9.0 ± 3.1	.201
RAVi-max (mL/m^2)	31.1 ± 7.0[a,b]	25.8 ± 5.9	25.6 ± 4.7	<.001
RAVi-min (mL/m^2)	13.3 ± 5.7	12.6 ± 4.6	13.3 ± 4.9	.807
RAVi-preA (mL/m^2)	19.1 ± 7.0	18.0 ± 6.0	18.6±5.7	.732

[a]Significantly different compared to "Non-CF-BR" group.
[b]Significantly different compared to "Controls" group.
CF-BR, bronchiectasis due to cystic fibrosis; GRAs-res, global longitudinal right atrial strain during ventricular systole; GRAs-pump, global longitudinal right atrial strain during late diastole; non-CF-BR: bronchiectasis due to other conditions than cystic fibrosis; PA, pulmonary artery; pulmonary AccT, pulmonary acceleration time; RAVi-max, right atrium maximum volume index; RAVi-min, right atrium minimum volume index; RAVi-preA, right atrium preA volume index; RV FAC, right ventricular fractional area change; RV GLS: right ventricular global longitudinal strain; RV IVA, right ventricular isovolumic acceleration; RV MPI, right ventricular myocardial performance index; RVOT fs, right ventricular outflow tract fractional shortening; RV S′, tricuspid annulus systolic velocity; TAPSE, tricuspid annular plane systolic excursion.

Table 4. Characteristics of the Patients with CF- and non-CF-Bronchiectasis Based on Airflow Obstruction (FEV1/FVC < 70%)

	Patients with Airflow Obstruction (n = 25)	Patients Without Airflow Obstruction (n = 45)	*P*
CF-BR, n (%)	14 (56)	22 (48)	.072
Age (years)	27.0 ± 7.7	28.0 ± 7.8	.524
Male gender, n (%)	19 (50)	13 (40)	.148
Disease duration (years)	16.1 ± 7.4	17.6 ± 7.9	.362
Pulmonary velocity (m/s)	0.88 ± 0.13	0.90 ± 0.11	.343
Pulmonary AccT (ms)	113.1 ± 16.7	120.6 ± 22.6	.136
Pulmonary artery diameter (cm)	1.89 ± 0.3	1.80 ± 0.2	.204
PA wall thickness (cm)	0.520 ± 0.13	0.456 ± 0.10	.025
TAPSE (mm)	18.1 ± 3.6	18.8 ± 2.6	.979
RVOT fs (%)	32.6 ± 6.8	33.0 ± 7.4	.874
RV S′ (cm/s)	12.0 ± 2.5	12.9 ± 1.9	.886
RV IVA (cm/s^2)	280.2 ± 83.3	277.4 ± 80.1	.763
RV FAC (%)	46.0 ± 8.6	48.2 ± 9.2	.613
RV MPI	33.9 ± 5.1	33.8 ± 5.0	.985
RV GLS (%)	-20.4 ± 3.9	-25.3 ± 5.0	<.001
GRAs-res (%)	26.3 ± 7.2	28.2 ± 8.7	.312
GRAs-pump (%)	7.9 ± 3.8	8.3 ± 4.5	.653
RAVi-max (mL/m^2)	29.7 ± 7.3	27.1 ± 6.5	.126
RAVi-min (mL/m^2)	13.9 ± 5.5	11.8 ± 4.5	.084
RAVi-preA (mL/m^2)	19.2 ± 6.4	17.7 ± 6.6	.323

CF-BR, bronchiectasis due to cystic fibrosis; GRAs-res, global longitudinal right atrial strain during ventricular systole; GRAs-pump, global longitudinal right atrial strain during late diastole; non-CF-BR, bronchiectasis due to other conditions than cystic fibrosis; PA, pulmonary artery; pulmonary AccT, pulmonary acceleration time; RAVi-max, right atrium maximum volume index; RAVi-min, right atrium minimum volume index; RAVi-preA, right atrium preA volume index; RV FAC, right ventricular fractional area change; RV GLS: right ventricular global longitudinal strain; RV IVA, right ventricular isovolumic acceleration; RV MPI, right ventricular myocardial performance index; RVOT fs, right ventricular outflow tract fractional shortening; RV S′, tricuspid annulus systolic velocity; TAPSE, tricuspid annular plane systolic excursion.

DISCUSSION

In this prospective study, we investigated the possible impairment in right heart functions and the thickening of PA wall in patients with CF-bronchiectasis in relation to those in patients with non-CF-bronchiectasis. Our main findings were as follows:

- Cystic fibrosis-bronchiectasis causes detrimental effect on contractile function measures of the RA and the RV such as RV GLS, GRAs-res, RV S′, and TAPSE and leads to a thickening in PA wall more than non-CF-bronchiectasis.
- The negative impact of CF on RA and RV function assessed by STE was independent of age, gender, and disease duration in our patient population.
- The presence of airflow obstruction results in a depressed RV GLS and a thickened PA wall in all patients with bronchiectasis. We observed that RV GLS was also correlated with the parameters of airflow obstruction severity (FEV1/FVC and FEV1, % predicted; both).
- Volumetric measures show a higher RA volume in patients with CF-BR than those in patients with non-CF-BR and healthy controls.

Right heart dysfunction in patients with CF and those with non-CF-BR has been documented by previous studies. Three of those studies demonstrated RV systolic dysfunction using conventional and tissue Doppler echocardiography parameters such as RV FAC, TAPSE, and peak systolic tricuspid annular velocity in CF patients compared with healthy controls.[10-12] However, these methods are often insufficient to demonstrate subclinical myocardial dysfunction in the early stage. Two-dimensional speckle-tracking echocardiography is a newer imaging technique for the assessment of myocardial function by means of strain measurements. These measurements are not affected by translational motion of the heart and not angle dependent, allowing more accurate analysis of regional myocardial function.[21-23] Further, STE is helpful to detect the presence of myocardial dysfunction in subclinical phase. Previous studies indicated the presence of subclinical RV dysfunction using tissue Doppler and 2D-STE

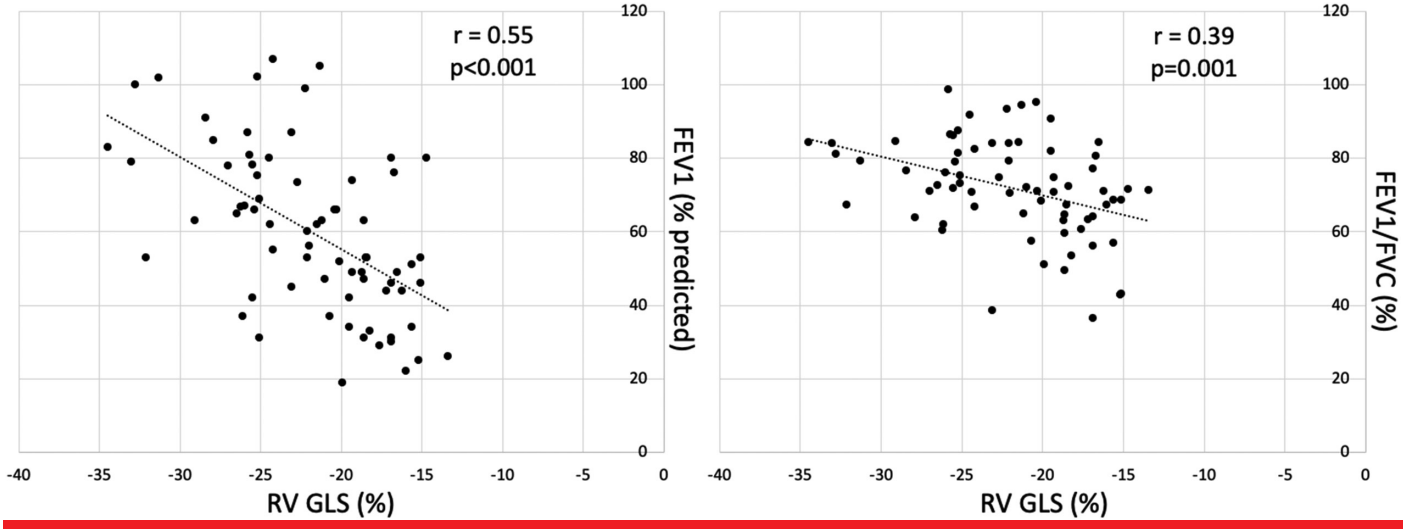

Figure 3. Correlation analysis between right ventricular global longitudinal strain and pulmonary function test parameters.

Table 5. Linear Regression Analysis Showing the Independent Risk Factors Affecting RVGLS (A) and GRAs-res (B)

	Unstandardized β	Standardized β	*t*	95% CI	*P*
		(A)			
Age	0.005	0.007	0.062	(−0.152)-0.162	.951
Gender (male)	1.302	0.129	1.106	(−1.049)-3.653	.273
Disease duration	0.071	0.108	0.803	(−0.106)-0.249	.425
CF-BR	−3.558	−0.353	−2.59	(−6.301)-(−0.814)	**.012**
		(B)			
	Unstandardized β	**Standardized β**	***t***	**95% CI**	***P***
Age	−0.077	−0.075	−0.614	(−0.328)-0.174	.541
Gender (male)	0.886	0.056	0.471	(−2.870)-4.642	.639
Disease duration	0.012	0.012	0.087	(−0.272)-0.296	.931
CF-BR	−4.966	−0.313	−2.263	(−9.349)-(−0.583)	**.027**

CF-BR, bronchiectasis due to cystic fibrosis.

analysis in both adult and pediatric CF patients when compared to the controls.[13,15,16] Dordevic et al[14] investigated RA phasic functions using STE and showed that there was an obvious trend of RA function impairment from controls to CF patients although difference was not statistically significant. Additionally, studies with non-CF-BR patients revealed RV dysfunction using only conventional and tissue Doppler measurements such as TAPSE and RV MPI.[9,17] However in none of these studies, the presence of bronchiectasis was confirmed by HRCT scan in CF patients. Besides, echocardiographic measurements in the patients with CF and non-CF-BR in former investigations were compared with only healthy individuals and there is no data currently exist comparing RV and RA functions between specifically CF-BR and non-CF-BR patients.

Our study demonstrated no significant differences in conventional and tissue Doppler-based RV function measures between patients with CF-BR, non-CF-BR, and controls including RV IVA, RV FAC, and RV MPI. Right ventricular outflow tract fractional shortening was lower in CF-BR patients compared to controls but comparable to non-CF-BR patients. Some of these results were not consistent with previous data.[10-12,15] This might be due to the presence of highly specific and a larger patient population in this study and due to the fact that these measurements were limited for comprehensive assessment of RV's complex structure. On the other hand, novel measurements of the RV and the RA functions such as RV GLS, GRAs-res, RV S', and TAPSE were significantly reduced in CF-BR patients, even more than those in non-CF-BR patients compared to healthy controls. Although the impairment on RA function assessed by STE was not significant in a previous report[14], we found significant decrease in GRAs-res in CF-BR patients in comparison to non-CF-BR and controls. RVGLS also showed lower values in patients with airflow obstruction than without airflow obstruction (-20.4±3.9 vs. -25.3±5.0, <0.001) and positive correlation was determined with the parameters of pulmonary function test (FEV1/FVC and FEV1, % predicted; both). These results suggested that RVGLS was closely related with the severity of pulmonary disease. Previously, Sciatti et al[13] indicated significant correlation of RV strain measurements with only FEV1 in CF patients similar to our study. Decreased RV and RA myocardial contractility in our CF-BR patients based on these measurements is consistent with former studies.[13-16] But in contrast to the study performed by Gencer et al.[17] we found significantly decreased TAPSE and similar RV MPI in non-CF-BR patients compared to controls.

The abnormal RV and RA functions in bronchiectasis are thought to be secondary to increased PA pressure due to chronic hypoxemia resulting from progressive lung damage.[24] The development of cardiomyopathy as a consequence of diabetes and myocardial fibrosis and inflammation due to long-standing hypoxemia may also be other potential mechanisms in CF-BR.[25] The acceleration time of PA flow was significantly lower and sPAP as measured based on the tricuspid regurgitation jet was significantly greater in patients with CF-BR in comparison to non-CF-BR patients and controls in our study. Baño-Rodrigo et al[12] found lower sPAP values than our study population with CF, but this may be due to the selection of only patients with mildly reduced FEV1 in their study. Our study showed dilation of the RA in CF-BR patients and that RA volumes (RAVi) were significantly higher than those in non-CF-BR patients and controls. A previous study investigating RA phasic functions in CF patients compared to healthy individuals also indicated increased RA volume.[14] Pulmonary hypertension could be one of the reasons for RA dilation in these patients.

Recently, PA wall thickness has emerged as a marker of inflammation in BD.[18] They investigated whether PA wall thickness increases in response to systemic inflammation in BD and demonstrated higher values in severe disease compared to those in non-severe disease. They suggested that PA wall thickness is a simple and reliable parameter assessed by transthoracic echocardiography and that it may be a sign of severe inflammation in BD. Similarly, we demonstrated thickened PA wall in our bronchiectasis patients possibly due to chronic inflammation and hypoxemia. Thickening in CF-BR patients was more than in non-CF-BR patients. Furthermore, patients with airflow obstruction (FEV/FVC < 70%) showed even more thickening in PA wall compared to the patients

without airflow obstruction (FEV1/FVC >70%), but no significant correlation of PA wall thickness was observed with FEV1 (%, predicted) and/or FEV1/FVC. With these results, simple measurement of PA wall thickness may indicate the presence of airflow obstruction but is not related to the severity of pulmonary disease.

Clinical Implications

To our knowledge, this is the first prospective study investigating both RV and RA functions using modern speckle tracking technique in a highly specific patient population including bronchiectasis due to CF and non-CF-bronchiectasis. We demonstrated that CF-BR dramatically impaired RA and RV functions more than non-CF-BR. Since life expectancy is increasing due to the new treatment options in patients with CF-BR, detecting early signs of myocardial involvement is crucial. In our study, conventional parameters such as RV S', RVOT fs, and TAPSE were in normal range in CF-BR patients, although significantly lower in comparison to controls. Thus, assessing RV GLS has a critical importance and this parameter may be used for the detection of subclinical myocardial dysfunction in patients with CF-BR. We also showed that RV GLS was lower in bronchiectasis patients with airflow obstruction when compared to those without, and that it was correlated to the parameters of pulmonary function test. With these findings, RV GLS may be a parameter in the follow-up of the patients with CF-BR. Additionally, we studied PA wall thickness for the first time and found significant thickening in CF-BR patients and in patients with airflow obstruction. Therefore, PA wall thickness may be a parameter of the presence of airflow obstruction in bronchiectasis patients.

Study Limitations

There are some limitations in this study. Sample size was relatively small due to our highly selective patient population. Right heart functions were not evaluated by advanced imaging modalities such as cardiac magnetic resonance imaging, 3D echocardiography. We did not investigate any inflammatory or neurohormonal biomarkers related to right heart dysfunction and/or pulmonary disease to confirm our results (natriuretic peptides, procalcitonin, etc.). We did not have follow-up data to determine the relationship between RV function and prognosis in patients with bronchiectasis. Our patients with airflow obstruction had mostly moderate, severe, and very severe disease based on FEV1 (% predicted) and FEV1/FVC. Therefore, the impact of mild airflow obstruction on right heart function was missing in this study. Because of the difference in pulmonary function tests [FEV1 (%, predicted) and FVC (%, predicted)] between CF-BR and non-CF-BR groups, we could not demonstrate whether right heart dysfunction was directly related to CF or that CF impaired respiratory functions and caused right heart dysfunction indirectly. Lastly, measurements of PA wall thickness were highly dependent on the image quality and small deviations on the image during acquisitions might cause the thickness to be measured more or less than actual size. Although we recorded the average of 3 consecutive measurements, this situation might affect our results.

CONCLUSIONS

We demonstrated for the first time the impairment of RA and RV functions and thickened PA wall in CF-bronchiectasis more than non-CF-bronchiectasis using modern speckle-tracking echocardiography. Right ventricular GLS was closely related to the severity of pulmonary disease. It can also detect subclinical RV dysfunction in spite of normal conventional echocardiographic measures and may be useful parameter for clinical follow-up of patients with bronchiectasis. Pulmonary artery wall thickness seems a new and promising indicator of the presence of airflow obstruction. Further studies are needed to evaluate the prognostic value of these echocardiographic indices in this specific patient population.

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