Internal and Emergency Medicine (2019) 14:1279–1285
https://doi.org/10.1007/s11739-019-02104-5

IM - ORIGINAL

Focus on echocardiographic right ventricular strain analysis in cystic fibrosis adults without cardiovascular risk factors: a case–control study

Edoardo Sciatti[1] · Enrico Vizzardi[1] · Ivano Bonadei[1] · Francesca Valentini[1] · Elisa Menotti[1] · Francesco Prati[1] · Lucia Dallapellegrina[1] · Marialma Berlendis[2] · Piercarlo Poli[3] · Rita Padoan[3] · Marco Metra[1]

Received: 14 February 2019 / Accepted: 3 May 2019 / Published online: 14 May 2019

Abstract

Strain echocardiography is able to detect subclinical ventricular systolic and diastolic dysfunction. Prolonged survival to cystic fibrosis favors heart and vessel involvement. The purpose of the present study was to compare clinically stable adult patients affected by cystic fibrosis without overt pulmonary hypertension with controls to evaluate right ventricular (RV) systolic and diastolic function by means of strain and tissue Doppler imaging (TDI), respectively. 22 adults affected by cystic fibrosis and 24 healthy volunteers matched for age and sex were enrolled. None had known cardiovascular risk factors or overt pulmonary hypertension. All people underwent blood pressure measurement and transthoracic echocardiography. Cystic fibrosis patients showed higher sPAP [median 25 (IQR 21–30) vs 22 (22–22) mmHg; $p=0.02$] and more frequent RV diastolic dysfunction ($p<0.001$). Among cases, some RV systolic parameters were significantly altered than controls, such as TAPSE [20 (18–24) vs. 23 (21–28) mm; $p=0.001$], FAC [34 (26–44) vs. 49 (48–50)%; $p<0.001$], midwall tissue strain [−25.0 (−31.3 to −22.8) vs. −30.5 (−31.8 to −29.3)%; $p=0.03$], apical tissue strain [−22 (−29.3 to −19.0) vs. −30.5 (−32.8 to −28.3)%; $p=0.001$] and 2D strain [−22.0 (−25.1 to −19.0) vs. −29.5 (−31.8 to −27.3)%; $p<0.001$]. Finally, 2D strain correlated with spirometric FEV1 ($\rho=-0.463$, $p=0.03$) and nearly with FEF25–75% ($\rho=-0.393$, $p=0.07$). Our study confirmed a RV subclinical systo-diastolic dysfunction in clinically stable patients affected by cystic fibrosis without overt pulmonary hypertension nor cardiovascular risk factors. This may be due to systemic inflammation and temporary recurrent pulmonary hypertension. We retain that RV 2D strain and TDI echocardiography could become an important tool in the follow-up of these patients.

Keywords Cystic fibrosis · Strain · Right ventricle · Echocardiography · Speckle tracking

Introduction

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disease in Caucasian race, involving approximately 1/2500 newborns. It is caused by more than 1900 different mutations of CF transmembrane conductance regulator (CFTR) gene, located on the 7th chromosome and codifying for a transmembrane chlorine channel. Typical symptoms regard the pulmonological and gastrointestinal systems. Despite the comorbidities and the severity of this pathology, survival is still increasing; in fact, today about 50% of patients join adulthood [1]. A prolonged survival, thus, favors the appearance of new complications and the involvement of other systems. In particular, the presence of chronic inflammation due to the pathophysiology of the transmembrane channel in the airways leads to particular

Edoardo Sciatti and Enrico Vizzardi contributed equally.

✉ Edoardo Sciatti
edoardo.sc@tin.it

[1] Section of Cardiovascular Diseases, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Piazzale Spedali Civili 1, 25123 Brescia, Italy

[2] Pulmonology Unit, ASST Spedali Civili of Brescia, Brescia, Italy

[3] Pediatric Department, Cystic Fibrosis Center, University of Brescia, ASST Spedali Civili of Brescia, Brescia, Italy

consequences in heart and blood vessels [2, 3]. Several studies have investigated heart morphology and function in this disease, by means of echocardiography, scintigraphy, and catheterization. In fact, cor pulmonale was the first heart involvement described; it is linked to pulmonary hypertension due to structural and functional lung disease [4, 5]. Afterwards, various authors demonstrated right ventricular (RV) dysfunction and abnormalities, while left ones remain longer normal [6-12]. Newer echocardiographic techniques allow to detect subclinical heart damage and dysfunction, in particular strain echocardiography. To our knowledge, only two studies have been carried out regarding left ventricular (LV) strain assessment, finding subclinical changes that were correlated with the degree of pulmonary involvement severity [13, 14]. Moreover, only two other works analyzed RV strain in pediatric patients affected by CF, revealing decreased systolic and diastolic properties [15, 16].

The purpose of the present study was to compare clinically stable adult patients affected by CF without overt pulmonary hypertension with controls to evaluate RV systolic and diastolic function by means of strain and tissue Doppler imaging (TDI), respectively.

Materials and methods

Subjects

We enrolled 22 patients affected by CF, followed up by the Cystic Fibrosis Center, Pediatric Department, University of Brescia and the Pulmonology Unit of ASST Spedali Civili of Brescia, Italy. They were compared with 24 healthy volunteers matched for age, sex and body mass index (BMI). Cases and controls were accurately selected without known cardiovascular risk factors or pulmonary hypertension. Everyone underwent blood pressure measurement and transthoracic echocardiography.

Blood pressure measurement

Blood pressure was assessed using a standard, calibrated sphygmomanometer. The mean of three sitting and standing blood pressure was recorded. The arm in which the highest sitting diastolic pressures was found was the arm used for all subsequent readings throughout the study. Every effort was made to have the same staff member obtain blood pressure measurements in each individual patient, at the same time of day, using the same equipment. Systolic blood pressure (SBP) was recorded when the initial sound is heard (phase I of the Korotkoff sound), while diastolic blood pressure (DBP) at the disappearance of the sound (phase V of the Korotkoff sound). The cuff was deflated at a rate not greater than 2 mmHg/s.

Spirometry test

Lung function was measured evaluating slow vital capacity (SVC), inspiratory capacity (IC), flow-volume curve with evaluation of forced expiratory volume (FEV1), forced vital capacity (FVC), Tiffeneau index (FEV1/SVC), mean forced expiratory flow (FEF25–75%), plethysmographic pulmonary volumes with calculus of total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV), carbon monoxide diffusing capacity (DLCO), respiratory muscle strength (maximal inspiratory and expiratory pressure: MIP and MEP).

Pulmonary function tests were obtained using V_{max} 22 pulmonary function analysis machines: spirometer with mass flow meter and Autobox 6200 (Sensormedics, Yorba Linda California). The American Thoracic Society guidelines were used to perform the tests of pulmonary function. The theoretical values used as reference were those reported by ATS/ERS [17] and Zapletal [18].

Transthoracic echocardiography

Echocardiographic examinations were performed using Vivid 7 machine (GE Healthcare, Milwaukee, Wisconsin, USA) with a 3.5 MHz transducer. Digital loops were stored on the hard disk of the echocardiograph for on-line and off-line analyses and transferred to a workstation EchoPac, Vingmed (GE Healthcare, Milwaukee, Wisconsin, USA) for off-line analysis. Participants were studied in the left lateral decubitus position and images acquired from standard parasternal and apical windows. All studies were read by two echocardiographers blinded to all patient information. The echocardiographic measurements of the LV internal dimension, interventricular septal and posterior wall diastolic thickness, left atrial area, peak *E* wave and A wave of mitral inflow, septal and lateral peak *E′* of mitral annulus and ascending aorta dimensions were performed off-line, according to the recommendations of the American Society of Echocardiography [19, 20]. LV volumes and ejection fraction were obtained by the modified biplane Simpson's method.

RV end-diastolic and end-systolic areas were traced to obtain RV fractional area change (FAC), calculated as follows: (end-diastolic area − end-systolic area)/end-diastolic area. Doppler of the tricuspid and mitral blood inflow velocities was measured according to echocardiographic guidelines [19, 21]. TDI analysis of the RV free wall at the level of the tricuspid valve annulus was performed, and the myocardial performance index (MPI) was calculated for each subject to measure the overall RV function [21]. *E′*, *A′* and *S′* waves were evaluated and *E*/*A* and

E/*E*′ ratios calculated [21]. These parameters were used to grade RV diastolic dysfunction according to the guidelines [21]. Isovolumic acceleration (IVA) was obtained dividing isovolumic velocity by the time to reach it, as previously described [22]. Tricuspid annular plane systolic movement (TAPSE) was measured using M-mode acquisition in apical four-chamber view on the lateral tricuspid annulus. Systolic pulmonary artery pressure (sPAP) was obtained adding right atrial pressure estimate to Bernoulli's simplified equation on tricuspidal regurgitation jet velocity by means of continuous wave Doppler, after excluding pulmonary valve stenosis with the same Doppler technique. The forward velocity profile, obtained by pulsed Doppler in the RVOT close to the pulmonary valve, was used to calculate the acceleration time (AT), defined as the time from the onset to maximal velocity. Pulmonary hypertension was defined as sPAP > 35 mmHg and/or AT < 100 ms [21]. For tissue and longitudinal 2D strain, images were analyzed offline. The endocardial border of the RV was traced from the apical four-chamber view. Tracking was accepted only when the visual inspection and software indicated adequate tracking for all segments. 2D strain was measured manually for a six-segment RV model comprising basal, midwall, and apical segments of both the ventricular septum and the RV free wall. 2D global longitudinal ventricular strain also was obtained as the average strain of the six segments, complying with the last recommendations [23]. RV tissue strain (one dimensional) was evaluated by means of tissue strain imaging (TSI). From TDI apical four-chamber view, we placed three regions of interest along the free lateral wall at basal, midwall, and apical segments. The software elaborated the deformation curves and we derived the longitudinal peak systolic strain (LPSS) averaging five cardiac cycles.

Statistical analysis

All analyses were done using IBM SPSS Statistics 20 for Windows (SPSS, Inc., Chicago, IL, USA). Continuous variables were visually tested by Q–Q plots and represented by mean ± standard deviation or median (interquartile range), while categorical variables as frequency (*n*) and percentage of the sample. Independent samples Student's *t* test or Mann–Whitney *U* test was performed to analyze the difference between means for continuous variables and χ^2 test for the difference between proportions (Fisher's exact test for dichotomous variables). Spearman's bivariate correlation was run between every RV echocardiographic parameter and variables regarding pulmonary involvement (spirometric data and microbiological colonization) and inflammation (C-reactive protein). For all statistical tests, probability values < 0.05 were considered significant.

Results

Demographic and clinical characteristics are shown in Table 1. Patients and controls did not differ in age, BMI and sex distribution. 15 patients out of 22 were males (68.2%) while 17 healthy volunteers out of 24 were (70.8%; $p = 1$). No patient suffering from CF had secondary diabetes mellitus or any other CV risk factor. No patients were on CFTR potentiators or correctors, or taking diuretics. C-reactive protein was increased in the patient group (median 95 ng/L, interquartile range 16–243 ng/L).

All people in the study population were normotensive. Systolic blood pressure was not statistically different between the two groups, while diastolic blood pressure was slightly higher among patients than controls, as well as heart rate. On the contrary, pulse pressure was similar between the groups.

Spirometric data of the cases are displayed in Table 2 as percentage of theoretical values. They are typical of pulmonary obstructive diseases. In particular, 14 patients (63.6%) showed a FEF25–75% value < 60% and 13 (59.1%) a FEV1 < 80%. Of them, three patients (13.6%) had a value < 40%, four (18.2%) between 40 and 60%, and six (27.3%) between 60 and 80%. Regarding chronic airways microbiological colonization, in 11 patients (50.0%) *Pseudomonas aeruginosa* was found, in 3 (13.6%) methicillin-resistant *Staphylococcus aureus*, and in 5 (22.7%) both bacteria.

Left ventricular parameters are shown in Table 3. No difference between patients and controls was found in its dimensions except end-systolic diameter, which was significantly higher in CF group (despite similar end-systolic volume). Index LV mass was similar between the groups. All people had a normal LV systolic function. Diastolic function calculated by transmitral Doppler flow revealed a mild

Table 1 Demographic and clinical characteristics of the study population

Variable	Cystic fibrosis ($n = 22$)	Healthy controls ($n = 24$)	p
Age (years)	24 (21–30)	32 (23–37)	0.8
Male sex	15 (68.2%)	17 (70.8%)	1
BMI (kg/m^2)	22.0 (19.3–23.9)	22.2 (21.0–24.2)	0.5
BSA (m^2)	1.75 (1.56–1.89)	1.75 (1.68–1.88)	0.3
SBP (mmHg)	120 (111–130)	120 (110–130)	0.5
DBP (mmHg)	80 (70–80)	70 (60–75)	0.009
PP (mmHg)	50 (38–54)	50 (43–59)	0.3
HR (bpm)	81 (70–90)	68 (64–78)	0.01

BMI body mass index, *BSA* body surface area, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PP* pulse pressure, *HR* heart rate

Table 2 Spirometric data of the cystic fibrosis patients

Variable	Cystic fibrosis ($n=22$)
VC (%)	82 ± 22 (29–127)
FEV1 (%)	70 ± 27 (21–123)
FEF25–75 (%)	44 ± 27 (4–96)
FRC (%)	119 ± 23 (88–169)
TLC (%)	103 ± 13 (82–122)
RV (%)	161 ± 60 (88–287)
DLCO/VA adj (%)	109 ± 17 (72–137)
MIP (%)	98 ± 29 (28–157)
MEP (%)	65 ± 44 (24–243)

Data expressed as % of theoretical values; mean ± standard deviation (minimum–maximum)

VC vital capacity, *FEV1* forced expiratory volume in 1 s, *FEF25–75%* forced expiratory flow at 25–75% of the pulmonary volume, *FRC* functional residual capacity, *TLC* total lung capacity, *RV* residual volume, *DLCO/VA adj* diffusion capacity of the lung for CO divided by the alveolar volume, *MIP* maximal inspiratory pressure, *MEP* maximal expiratory pressure

impairment in the first group with ten patients (45.5%) having grade I and one (4.5%) grade II dysfunction ($p<0.001$), probably justifying a higher LV end-systolic diameter. Nevertheless, diastolic TDI waves on LV lateral wall found no differences between the groups and *E*/*E*′ ratio was similar. On the contrary, lateral *S*′ wave was higher in the first group.

Right chamber data are illustrated in Table 4. Several parameters were statistically different between patients and controls. Although without overt pulmonary hypertension, CF patients had higher sPAP and lower TAPSE and FAC. On the other hand, no difference was found in AT, MPI or IVA. RV diastolic function evaluation revealed a largely diffused dysfunction in CF patients: five (22.7%) patients had grade I and eight (36.4%) grade II diastolic dysfunction. Indeed diastolic *E*′ and *A*′ waves were statistically deeper in the same group, and *E*/*E*′ ratio was also higher. Apical *S*′ wave was reduced in CF patients, while basal and midwall were similar. RV strain revealed further differences between patients and controls: basal tissue strain was similar, while midwall tissue strain, apical tissue and 2D strain were impaired. Finally, end-systolic right atrial area was significantly larger in patients' group. RV diastolic dysfunction was globally present in about 40–60% of the patients, while RV systolic dysfunction in 14–55%.

Among all tested correlations, only 2D strain showed a significant association with FEV1 ($\rho=-0.463$, $p=0.03$) and nearly with FEF25–75% ($\rho=-0.393$, $p=0.07$). Indeed, 2D strain in patients who had FEV1 < 80% was -20.4 ± 3.9 with respect to -24.2 ± 2.5% in those with normal FEV1 values ($p=0.02$). Moreover, the group with FEF25–75% < 60% had -20.7 ± 4.0 and those with normal FEF25–75% -24.2 ± 2.7% ($p=0.04$). Finally, C-reactive protein correlated with FEV1 ($\rho=-0.452$, $p=0.035$), but not with RV parameters.

Discussion

The present study deals with adults affected by CF without cardiovascular risk factors, secondary diabetes or overt pulmonary hypertension. We found a preserved LV systolic

Table 3 Results from transthoracic echocardiography: left ventricle

Variable	Cystic fibrosis ($n=22$)	Healthy controls ($n=24$)	*p*
Mass index (g/m^2)	99 (83–119)	101 (74–111)	0.6
End-diastolic diameter (mm)	48 (43–51)	47 (44–50)	1
End-systolic diameter (mm)	31 (28–33)	23 (23–29)	< 0.001
Interventricular septum thickness (mm)	10 (9–11)	10 (9–10)	0.4
Posterior wall thickness (mm)	8 (8–9)	9 (8–9)	0.1
End-diastolic volume (mL)	65 (61–74)	65 (60–76)	0.9
End-systolic volume (mL)	23 (21–27)	23 (21–27)	0.9
Ejection fraction (%)	65 (60–65)	63 (60–67)	0.7
E wave (m/s)	0.72 (0.55–0.80)	0.61 (0.60–0.84)	0.8
A wave (m/s)	0.60 (0.45–0.77)	0.34 (0.33–0.44)	< 0.001
E/*A*	1.16 (0.84–1.63)	1.82 (0.58–2.07)	< 0.001
Deceleration time (ms)	208 (174–224)	170 (163–200)	0.09
Diastolic dysfunction	I: 10 (45.5%)	I: 0 (0.0%)	< 0.001
	II: 1 (4.5%)	II: 0 (0.0%)	
E′ wave (m/s)	0.11 (0.08–0.14)	0.11 (0.09–0.13)	0.7
A′ wave (m/s)	0.06 (0.05–0.08)	0.07 (0.04–0.08)	1
S′ wave (m/s)	0.09 (0.07–0.10)	0.06 (0.04–0.08)	< 0.001
E/*E*′	6.6 (4.6–8.6)	6.0 (4.8–8.1)	0.7

Table 4 Results from transthoracic echocardiography: right chambers

Variable	Cystic fibrosis ($n=22$)	Healthy controls ($n=24$)	p
sPAP (mmHg)	25 (21–30)	22 (22–22)	0.02
TAPSE (mm)	20 (18–24)	23 (21–28)	0.001
TAPSE < 17 mm	3 (13.6%)	0 (0.0%)	0.1
AT (ms)	120 (100–154)	140 (125–145)	0.3
MPI	0.40 (0.35–0.56)	0.42 (0.39–0.45)	0.7
IVA (cm/s^2)	3.9 (2.6–4.3)	3.9 (3.6–4.0)	0.7
FAC (%)	34 (26–44)	49 (48–50)	< 0.001
FAC < 35%	12 (54.5%)	0 (0.0%)	< 0.001
E wave (cm/s)	0.56 (0.43–0.59)	0.59 (0.53–0.75)	0.02
A wave (cm/s)	0.44 (0.37–0.53)	0.30 (0.21–0.36)	< 0.001
E/*A*	1.30 (0.97–1.47)	2.43 (1.44–2.88)	< 0.001
Deceleration time (ms)	227 (200–274)	178 (165–200)	< 0.001
Diastolic dysfunction	I: 5 (22.7%)	I: 0 (0.0%)	< 0.001
	II: 8 (36.4%)	II: 0 (0.0%)	
E′ wave (cm/s)	0.10 (0.08–0.14)	0.06 (0.04–0.11)	0.001
A′ wave (cm/s)	0.10 (0.08–0.12)	0.13 (0.12–014)	< 0.001
Basal *S*′ wave (cm/s)	0.13 (0.11–0.15)	0.14 (0.12–0.18)	0.2
Basal *S*′ wave < 9.5 cm/s	5 (22.7%)	0 (0.0%)	0.019
Midwall *S*′ wave (cm/s)	0.11 (0.09–0.13)	0.12 (0.10–0.16)	0.2
Apical *S*′ wave (cm/s)	0.08 (0.07–0.09)	0.12 (0.10–0.16)	< 0.001
E/*E*′	4.9 (3.6–7.0)	4.2 (3.1–5.8)	0.001
E/*E*′ > 6	9 (40.9%)	0 (0.0%)	< 0.001
Basal tissue strain (%)	− 25.5 (− 34.0 to − 21.0)	− 29.0 (− 30.0 to − 28.0)	0.2
Midwall tissue strain (%)	− 25.0 (− 31.3 to − 22.8)	− 30.5 (− 31.8 to − 29.3)	0.03
Apical tissue strain (%)	− 22.0 (− 29.3 to − 19.0)	− 30.5 (− 32.8 to − 28.3)	0.001
2D strain (%)	− 22.0 (− 25.1 to − 19.0)	− 29.5 (− 31.8 to − 27.3)	< 0.001
2D strain > − 20%	7 (31.8%)	0 (0.0%)	0.003
Right atrial area (cm^2)	15 (14–15)	11 (9–12)	< 0.001

sPAP systolic pulmonary artery pressure, *TAPSE* tricuspid annular plane systolic excursion, *MPI* myocardial performance index, *IVA* isovolumic acceleration, *FAC* fractional area change

function and morphology and a slight diastolic dysfunction, thus confirming previous studies' results [6-8]. Vice versa, we demonstrated a subclinical involvement of the right chambers. In particular, sPAP was significantly higher (albeit these patients had no pulmonary hypertension) and diastolic function frequently impaired (40–60%), as measured by transtricuspidal Doppler flow and TDI on RV free wall. Moreover, RV systolic function parameters were more altered in patients than controls (14–55%), such as TAPSE, FAC (apical) *S*′ wave and strain parameters, thus confirming the aforementioned studies [9, 10, 12, 15, 16]. Some variables were not different between cases and controls, in part because of the small number of patients enrolled and in part because of the heterogeneity of CF manifestations in some of them.

According to the cited studies, we hypothesize that right heart involvement in CF patients without overt pulmonary hypertension could be explained by two mechanisms. First, systemic inflammation along with hypoxemia, oxidative stress and consequent endothelial dysfunction are able to affect ventricular contractility and relaxing properties, thus altering the examined parameters [8]. Interestingly, CF patients had higher DBP and heart rate. It is conceivable that chronic inflammation causing oxidative stress on the arterial wall and endothelial dysfunction is the cause of a slightly higher blood pressure; as a consequence, heart rate may increase in parallel with myocardial work. Second, subclinical, recurrent and temporary pulmonary hypertension due to lung pathology progression could progressively damage RV properties even in well-controlled patients. It is possible that both mechanisms coexist and potentiate each other [24]. Since the increasing life expectancy, it becomes necessary to discover and assess early signs of myocardial involvement through echocardiography. Therefore, we retain that RV TDI and 2D strain echocardiography could become an important tool in the follow-up of these patients. In particular, 2D strain overcomes most of the limitations inherent in conventional echocardiography, given that it

is independent of cardiac translation; also it is angle and load independent, thus allowing accurate quantification of regional and global myocardial functions, being potentially useful to better refine the systo-diastolic RV dysfunction. Myocardial remodeling is a process not yet fully understood which leads to loss of function and fibrous tissue deposition. Early subclinical ventricular fibrosis is the initial sign of myocardial damage in cardiovascular disease. Other diagnostic tools can be useful in this regard. Echocardiography may be completed by means of integrated backscatter (IBS) imaging, which is able to study myocardial fibrosis [25]. In addition, contrast-enhanced cardiac magnetic resonance imaging (CMR) is considered the non-invasive gold standard to detect myocardial fibrosis, but is less widely available and expensive [26]. Several biomarkers can also help to detect myocardial fibrosis, such as miRNA-21 [27], ST2 and galectin-3 [28]. Although no therapies are able to reverse this process, the myocardial interstitium as a site of fibrosis is the focus of research efforts [29]. More in general, right heart dysfunction has a negative prognostic impact, but to date no specific therapies have been developed [30]. Indeed, we can only suggest that patients showing altered systolic and/or diastolic RV parameters could undergo more frequent controls and prevent a more rapid clinical worsening. Nevertheless, further studies are needed to explore the pathologic significance and implications of these findings.

Strength of our study is the careful selection of adult patients without cardiovascular risk factors nor overt pulmonary hypertension. In this way, we have been able to identify RV echocardiographic alterations linked to CF itself. Nevertheless, our cohort was characterized by a great damage in expiratory flows at low level of pulmonary filling, as expressed by FEF25–75%, meaning peripheral airways largely involved in lung remodeling. Minimum value is 4% of theoretical one and indicates a severe lung damage. Moreover, FEV1 is the "gold standard" parameter in the follow-up and in the prognosis estimation of CF patients. It represents the patency to airflow of the larger airways. Again, minimum value is 21% and suggests a severe impairment. For the first time we demonstrated a correlation between FEV1 and RV 2D strain and a tendency to association between FEF25–75% and RV 2D strain. We retain that these results are very important because 2D strain is an important tool to globally appreciate RV systolic performances and nearly approximates its contractility. On the one hand, these associations confirm the RV subclinical impairment during the disease, but on the other hand, they are able to suggest that RV 2D strain could be a very useful tool to identify patients with a worse prognosis in a pre-clinical phase of RV failure. Future larger studies regarding RV 2D strain ability to predict CF prognosis are needed.

Finally, we think that some of these clinically stable patients with normal sPAP could show exercise-induced pulmonary hypertension, as it was recently demonstrated in systemic sclerosis [31]. In this way, echocardiographic registration during exercise could be an interesting test to investigate the second mechanism cited above and to be used to prevent unfavorable evolutions of this pathology. At the time of enrolling patients with normal echocardiography and no heart failure symptoms did not routinely undergo exercise echocardiography. A targeted study is needed to test this hypothesis.

Our study suffers from some limitations. First, the small number of patients in the cohort, which prevent us from finding important correlations regarding, for example, microbiological colonization and RV echocardiographic parameters. Second, we lack a direct correlation between RV echocardiographic parameters and disease outcome. Third, biomarkers related to RV or LV dysfunction (e.g., natriuretic peptides) are not available in this study to confirm our results.

Concluding, we demonstrated in a small cohort the wide presence of RV echocardiographic alterations in both systolic and diastolic functions in CF patients. Moreover, we found an inverse correlation between RV 2D strain and FEV1, suggesting another tool to discover those patients who may benefit from a closer follow-up.

Acknowledgements The authors are grateful to "Lega Italiana Fibrosi Cistica-onlus Lombardia" for its interest in helping these patients.

Author contributions EV, ES, MB, RP wrote the paper; ES analyzed data; ES, IB, FV, EM, FP, LD, PP collected data; MB, RP, MM revised the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statements on human and animal rights This was a prospective single-center case-control study in compliance with the Declaration of Helsinki and approved by the local ethical committee.

Informed consent Every patient gave his/her informed consent.

References

1. Cystic Fibrosis Foundation Patient Registry (2017) Annual data report. Cystic Fibrosis Foundation, Bethesda, MD
2. Ionescu AA, Nixon LS, Evans WD et al (2002) Bone density, body composition and inflammatory status in cystic fibrosis. Am J Respir Crit Care Med 162:789–794
3. MacNee W, Maclay J, McAllister D (2008) Cardiovascular injury and repair in chronic obstructive pulmonary disease. Proc Am Thorac Soc 5:824–833
4. Wiglesworth FW (1946) Fibrocystic disease of pancreas. Am J Med Sci 212(3):351–365
5. Royce SW (1951) Cor pulmonale in infancy and early childhood; report on 34 patients, with special reference to the occurrence of

pulmonary heart disease in cystic fibrosis of the pancreas. Pediatrics 8(2):255–274
6. Florea VG, Florea ND, Sharma R et al (2000) Right ventricular dysfunction in adult severe cystic fibrosis. Chest 118(4):1063–1068
7. Rovedder PM, Ziegler B, Pinotti AF, Menna Barreto SS, Dalcin Pde T (2008) Prevalence of pulmonary hypertension evaluated by Doppler echocardiography in a population of adolescent and adult patients with cystic fibrosis. J Bras Pneumol 34(2):83–90
8. Ionescu AA, Ionescu AA, Payne N, Obieta-Fresnedo I, Fraser AG, Shale DJ (2001) Subclinical right ventricular dysfunction in cystic fibrosis. A study using tissue Doppler echocardiography. Am J Respir Crit Care Med 163(5):1212–1218
9. Baño-Rodrigo A, Salcedo-Posadas A, Villa-Asensi JR, Tamariz-Martel A, Lopez-Neyra A, Blanco-Iglesias E (2012) Right ventricular dysfunction in adolescents with mild cystic fibrosis. J Cyst Fibros 11(4):274–280
10. Giacchi V, Rotolo N, Amato B, Di Dio G, Betta P, La Rosa M, Leonardi S, Sciacca P (2015) Heart involvement in children and adults with cystic fibrosis: correlation with pulmonary indexes and inflammation markers. Heart Lung Circ 24(10):1002–1010
11. Koelling TM, Dec GW, Ginns LC, Semigran MJ (2003) Left ventricular diastolic function in patients with advanced cystic fibrosis. Chest 123(5):1488–1494
12. Koestenberger M, Ravekes W (2013) Tricuspid annular peak systolic velocity (s') in pediatric patients with mild cystic fibrosis. Pediatr Cardiol 34(2):483
13. Labombarda F, Pellissier A, Ellafi M, Creveuil C, Ribault V, Laurans M, Guillot M, Bergot E, Grollier G, Milliez P, Zalcman G, Saloux E (2011) Myocardial strain assessment in cystic fibrosis. J Am Soc Echocardiogr 24(9):1037–1045
14. Sellers ZM, McGlocklin L, Brasch A (2015) Strain rate echocardiography uncovers subclinical left ventricular dysfunction in cystic fibrosis. J Cyst Fibros 14(5):654–660
15. Ozcelik N, Shell R, Holtzlander M, Cua C (2013) Decreased right ventricular function in healthy pediatric cystic fibrosis patients versus non-cystic fibrosis patients. Pediatr Cardiol 34(1):159–164
16. Eising JB, van der Ent CK, Teske AJ, Vanderschuren MM, Uiterwaal CSPM, Meijboom FJ (2018) Young patients with cystic fibrosis demonstrate subtle alterations of the cardiovascular system. J Cyst Fibros 1:643–649
17. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J (2005) Interpretative strategies for lung function tests. Eur Respir J 26(5):948–968
18. Zapletal A, Paul T, Samánek M (1977) Significance of contemporary methods of lung function testing for the detection of airway obstruction in children and adolescents (author's transl). Z Erkr Atmungsorgane 149(3):343–371
19. Nagueh SF, Appleton CP, Gillebert TC et al (2009) Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 22(2):107–133
20. Lang RM, Bierig M, Devereux RB et al (2005) Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 18(12):1440–1463
21. Rudski LG, Lai WW, Afilalo J, Hua L et al (2010) Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 23(7):685–713 **(quiz 786–788)**
22. Vogel M, Cheung MM, Li J, Kristiansen SB, Schmidt MR, White PA, Sorensen K, Redington AN (2003) Noninvasive assessment of LV force-frequency relationships using tissue Doppler-derived isovolumic acceleration: validation in an animal model. Circulation 107(12):1647–1652
23. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, Pedri S, Ito Y, Abe Y, Metz S, Song JH, Hamilton J, Sengupta PP, Kolias TJ, d'Hooge J, Aurigemma GP, Thomas JD, Badano LP (2015) Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. J Am Soc Echocardiogr 28:183–193
24. Labombarda F, Saloux E, Brourd J, Bergot E, Milliez P (2016) Heart involvement in cystic fibrosis: a specific cystic fibrosis-related myocardial changes? Respir Med 118:31–38
25. Orabona R, Sciatti E, Vizzardi E, Bonadei I, Prefumo F, Valcamonico A, Metra M, Frusca T (2018) Ultrasound evaluation of left ventricular and aortic fibrosis after pre-eclampsia. Ultrasound Obstet Gynecol 52:648–653
26. Iles L, Pfluger H, Phrommintikul A, Cherayath J, Aksit P, Gupta SN, Kaye DM, Taylor AJ (2008) Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. J Am Coll Cardiol. 52:1574–1580
27. Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Bussen M, Bauersachs J, Engelhardt S (2008) MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. Nature 456:980–984
28. de Boer RA, Daniels LB, Maisel AS, Januzzi JL Jr (2015) State of the art: newer biomarkers in heart failure. Eur J Heart Fail 17:559–569
29. Schelbert EB, Fonarow GC, Bonow RO, Butler J, Gheorghiade M (2014) Therapeutic targets in heart failure: refocusing on the myocardial interstitium. J Am Coll Cardiol 63:2188–2198
30. Gorter TM, van Veldhuisen DJ, Bauersachs J, Borlaug BA, Celutkiene J, Coats AJS, Crespo-Leiro MG, Guazzi M, Harjola VP, Heymans S, Hill L, Lainscak M, Lam CSP, Lund LH, Lyon AR, Mebazaa A, Mueller C, Paulus WJ, Pieske B, Piepoli MF, Ruschitzka F, Rutten FH, Seferovic PM, Solomon SD, Shah SJ, Triposkiadis F, Wachter R, Tschöpe C, de Boer RA (2018) Right heart dysfunction and failure in heart failure with preserved ejection fraction: mechanisms and management. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 20:16–37
31. Gargani L, Pignone A, Agoston G et al (2013) Clinical and echocardiographic correlations of exercise-induced pulmonary hypertension in systemic sclerosis: a multicenter study. Am Heart J 165(2):200–207