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Original Article

Right ventricular dysfunction in adolescents with mild cystic fibrosis

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Abstract

Background: In cystic fibrosis (CF) patients the right ventricle (RV) suffers a progressive deterioration, but it is not clear when these changes begin. The aim of this study was to analyze the RV function in CF patients with mild respiratory disease.
Methods: Color-Doppler-Echocardiographic studies were prospectively performed in CF adolescent patients and an age-matched control group. Findings were correlated with pulmonary function tests (PFT), genotype, chronic bacterial colonization, pancreatic status and clinical scores. Only patients with mild CF were selected.
Results: Thirty seven CF patients and 40 healthy controls were recruited. In CF patients all echocardiographic parameters were abnormal compared to controls. Doppler analysis showed slightly elevated pulmonary artery pressure values, and abnormal relaxation and systolic function for all indexes. No correlation was found with any of the features studied.
Conclusions: In CF patients, abnormalities in the structure and function of the RV may be present at early stages of the disease. These abnormalities are subclinical and do not correlate with clinical scores, PFT, genotype, chronic bacterial colonization or pancreatic insufficiency.
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Keywords: Cystic fibrosis; Echocardiography; Right ventricular function

1. Introduction

Cystic fibrosis (CF) represents the most common lethal genetic disease in Caucasians. It occurs in approximately 1 of every 3400 live births among Caucasians [1]. Technical advances and early referral to a specialist center with a better medical management have significantly extended life expectancy into adulthood [2].

In CF, progressive worsening in lung structure and function due to chronic infection and inflammation leads to an increasing morbidity and mortality rates. The right ventricle (RV) suffers a progressive deterioration parallel to the severity of the disease [3], but it is not clear whether these changes occur when clinical signals of pulmonary disease are mild or when they become severe. As in other chronic pulmonary diseases, cardiac involvement in CF has been associated with the progression of lung disease and the presence of hypoxia, but it is

Abbreviations: ACT, right ventricular acceleration time; AT-wave, tissue Doppler late diastolic tricuspid annular velocity; A-wave, tricuspid peak late diastolic filling velocity; BSA, body surface area; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ET-wave, tissue Doppler peak early diastolic tricuspid annular velocity; E-wave, tricuspid peak early diastolic filling velocity; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; PASP, pulmonary artery systolic pressure; PFT, pulmonary function tests; RPEP, right ventricular pre-ejection period; RV, right ventricle; RVAW, right ventricular anterior wall thickness; RVEDD, right ventricular end-diastolic dimension; RVET, right ventricular ejection time; RVFA, right ventricular fractional area change; SK, Shwachman–Kulczycki clinical score; ST-wave, tissue Doppler peak systolic tricuspid annular velocity; TAPSE, tricuspid annular plane systolic excursion; TDE, tissue Doppler echocardiography

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not known if there is a direct impairment of cardiac function related to cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction. Also, there are no studies evaluating cardiac function in CF patients with mild lung function impairment. Furthermore, cardiac findings have not yet been correlated with the presence of chronic bacterial colonization, pancreatic insufficiency, or with a specific genotype, at this range of age.

The aim of this study was to analyze the RV in a cohort of adolescents with mild CF, using M-mode, 2D, and Doppler echocardiography to evaluate the effects of the disease on RV anatomy (thickness and dimension) and function (systolic and diastolic). Also, to estimate the pulmonary artery systolic pressure (PASP) through the analysis of Doppler curves of tricuspid inflow and pulmonary forward flow. In addition, we aimed to compare these findings with the pulmonary function tests (PFT), genotype, pancreatic status, type of chronic bacterial colonization, and clinical scores of severity. We hypothesized that CF patients with mild lung disease have an alteration in cardiac function that is independent of the degree of pulmonary impairment.

2. Methods

2.1. Study subjects

A prospective study was conducted in our Institution that was approved by the Ethical Committee (R-0015/10). Thirty seven adolescent patients with cystic fibrosis (20 males and 17 females age range 12 to 18 years), were recruited from the outpatient clinic of the Cystic Fibrosis Unit, all of them clinically stable, with no respiratory exacerbation in the previous six month. All had genotype and sweat test confirmation, and only patients with mildly reduced FEV1 were selected [4]. Written consent was obtained from all the patients or their parents.

The control group consisted of 40 age-matched healthy adolescents (18 males and 22 females age range 12.1 to 17.5 years). They were recruited at the cardiology outpatient clinic where they were investigated for non-organic murmur or functional thoracic pain. Patients with previous history of cardiovascular or systemic disease were excluded. All had entirely normal physical findings and laboratory evaluations.

2.2. Echocardiographic studies

A comprehensive protocol was designed in our department to study the right ventricular anatomy and function, both systolic and diastolic. This included M-mode and 2D images, Doppler flow velocities of pulmonary and tricuspid valves, four-chamber view right ventricular area mapping, and tissue Doppler analysis of tricuspid annulus.

All the echocardiographic studies were performed by the same observer who was blinded to the clinical status of the patients. Analysis of the data was performed off-line by two researchers who were unaware of the physical conditions and grouping of the patients. Five consecutive cardiac cycles were obtained for each parameter and averaged.

M-mode, two-dimensional and Doppler echocardiography studies were performed by using an ultrasound system (model HD11-XE, Philips Medical Systems, Bothell, WA) and a S8-3 MHz transducer. Echocardiographic images were obtained from the parasternal and apical windows, with the patient in left lateral decubitus. Images were obtained at a rate of 50 mm/s and continuous 1-channel electrocardiographic monitoring was used throughout the study.

Echocardiographic M-mode measurements were obtained according to recommendations of the American Society of Echocardiography [5]. The RV anterior wall thickness (RVAW) and end-diastolic dimension (RVEDD) were measured at end diastole from the parasternal long-axis view, and corrected for body surface area (BSA).

The tricuspid annular plane systolic excursion (TAPSE) was measured on the M-mode tracing in the apical four-chamber window and was defined as the difference in the displacement of the RV base during diastole and systole. RV fractional area change (RVFA) was calculated by using the following formula: (end-diastolic area − end-systolic area)/end-diastolic area [6].

The right ventricular pre-ejection period (RPEP) was measured from the Q wave of the electrocardiogram to the onset of pulmonary forward flow. The acceleration time (ACT) and right ventricular ejection time (RVET) were measured from the onset of flow to the peak velocity of flow and the end of flow, respectively. The RPEP/RVET and ACT/RVET ratios were calculated. In the absence of a significant tricuspid regurgitation, these measurements allow to indirectly estimate the presence of elevated PASP.

RV diastolic indexes were assessed from the apical four-chamber view at end expiration. A 4-mm pulsed Doppler sample volume was positioned at the level of the tricuspid valve, just at the tips of the tricuspid leaflets during diastole. E-wave (early filling), A-wave (late filling), and E/A ratio indexes were obtained. Tricuspid regurgitation, when present, was used to estimate PASP, by adding 10 mm Hg to the tricuspid regurgitation gradient.

Tissue Doppler echocardiography (TDE) was performed in apical four-chamber view with the pulsed-wave sample volume (length = 4 mm) placed at the lateral tricuspid annulus. Measurements included the peak systolic annular velocity (ST-wave), peak early diastolic (ET-wave) and late diastolic (AT-wave) tricuspid annular velocity. The ET/AT ratio was calculated.

To test the homogeneity of the CF group, we also compared patients with FEV1% greater and less than 85% predicted values.

2.3. Pulmonary function tests

All cystic fibrosis patients underwent spirometry on the same day of the echocardiographic study. A Jaeger Masterscope Spirometer with Version 4.3 Jaeger Software (Jaeger, Hoechberg, Germany) was used to record inspiratory and expiratory flows. The tracings were obtained with the patients in the sitting position and the best of three tracings was used for analysis. Forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were expressed as percent predicted for the patient's age, height and weight according to prediction equations standardized in

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our laboratory [7]. Pulmonary disease was classified as mild for FEV1% values >70%, according to ATS/ERS guidelines [4].

2.4. Clinical studies

Genotype was defined based on the number of ΔF508 *CFTR* mutations carried by each individual as homozygous ΔF508/ΔF508, heterozygous ΔF508/other, or other/other. Pancreatic status was described as insufficient if the subject had diagnosed pancreatic insufficiency or was taking supplemental pancreatic enzymes.

Chronic bacterial colonization was described as more than 3 positive sputum cultures for at least 6 months. Patients were divided into three groups: those colonized by *Pseudomonas aeruginosa*, *Staphylococcus aureus*, or non-colonized.

Clinical scores were calculated according to the methods of Shwachman–Kulczycki (SK) [8], and Brasfield [9]. SK scores were calculated from a composite of four categories: general activity, physical examination, nutrition, and chest radiographic in clinically stable patients, free of pulmonary exacerbations. Chest radiographs were scored utilizing the Brasfield clinical scoring system based on five categories according to the chest roentgenogram: air trapping, linear markings, nodular-cystic lesions, large lesions, and overall severity.

2.5. Statistical analysis

SPSS 15.0 (SPSS Inc., Chicago, IL) was used for the statistical analysis. Data are expressed as mean value±SD. Student's *t* test was used to assess the significant differences of mean values between patients and controls. Pearson's correlation coefficient was used to assess statistically significant correlations. A p value<0.05 was considered statistically significant. Normal distribution of the continuous values was assessed by the Kolmogorov–Smirnov test. Regression lines were adjusted to explore potential correlations between PFT or clinical scores and echocardiographic findings.

3. Results

Clinical data of patients with CF are presented in Table 1. Baseline characteristics of study patients and controls are presented in Table 2. The interobserver reproducibility was good. Intraclass correlation coefficients (r value) between both observers for all echocardiographic parameters were above 0.7.

M-mode findings (RVAW, RVEDD, and corrected by BSA), and 2D findings (TAPSE and RVFA) in CF patients, were significantly different from healthy controls (Table 3).

Doppler echocardiography findings (tricuspid E-wave, A-wave, E/A ratio) were also different in CF patients compared with the controls, with an increased A-wave and decreased E-wave and E/A ratio for CF patients group. The acceleration time of pulmonary artery flow was shorter in patients with CF than in healthy subjects. RVET was also shorter in the CF group compared to the control group, with a significant increase in RPEP/RVET and a decrease in RVAT/RVET ratios (Table 3). Tricuspid regurgitation was present in 12 CF patients (32%), and for this subgroup PASP was 26±8 mm Hg (range 14 to 39 mm Hg), with three patients over 30 mm Hg.

Table 1
Lung function tests, clinical characteristics and scores in patients with cystic fibrosis (CF).

Variable	Value	Range
FEV1	2.6±0.7	1.41–4.07
FEV1%	93.2±14.7	70.32–123.61
FVC	3,2±0.8	1.70–4.75
FVC%	99.1±11.7	69.09–124.96
Shwachman (SK) score	88.4±6.4	74–98
Brasfield score	19.3±3.0	14–23
Genotype: ΔF508/ΔF508	10	
(No. cases) ΔF508/other	16	
Other/other	11	
Pancreatic status: sufficient	10	
(No. cases) insufficient	27	
Chronic infection: absent	6	
(No. cases) *P. aeruginosa*	5	
S. aureus	26	

Values are expressed as mean±SD (standard deviation).
FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 s.
(%) = percent of predicted value.

TDE revealed abnormal relaxation for all indexes in the CF group compared to the controls, with an increase in AT-wave, and decrease in ET-wave and ET/AT ratio. The ST-wave was also shorter in the CF group (Table 3).

When patients with FEV1% values greater and less than 85% predicted were compared, RVET and RPEP/RVET ratio showed significant differences, suggesting that mild elevation of PASP could be present in the second group, although ACT and ACT/RVET ratio values remained unchanged. No other changes in the rest of anatomic or functional parameters were found (Table 4).

Most of the CF subjects (73%) had pancreatic insufficiency. Individuals homozygous for the ΔF508 *CFTR* mutation represented 27%, the heterozygous comprised 43.2%, and the rest corresponded to 29.7%, of the entire study population. No correlation was found in any of the echocardiographic parameters with the status of the pancreas or specific genotype in the CF group. RVEDD values for individuals with pancreatic insufficiency were 22.8±4 mm, and for pancreatic sufficiency 21.2±4 (p

Table 2
Characteristics of CF patients and controls.

Characteristics	CF group	Controls	p value
Subjects n	37	40	
Sex male/female	20/17	18/22	
Age (yrs)	14.7±1.8	14.6±1.4	0.662
Height (cm)	157.4±10.2	163.3±8.2	0.006*
Body weight (kg)	49.1±11.5	54.0±8.8	0.040*
Body surface area (BSA) (m^2)	1.47±0.21	1.57±0.16	0.015*
Body mass index (kg/m^2)	19.6±2.9	20.1±1.9	0.319

Values are expressed as mean±SD; (*): significant.

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Table 3
Comparison of clinical and echocardiographic parameters between patients with cystic fibrosis (CF) and controls.

Variable	CF group	Controls	p value
Subjects n	37	40	
RV geometry			
RVAW (mm)	2.5±0.7	1.9±0.3	0.000*
RVAW/BSA	1.7±0.5	1.2±0.2	0.000*
RVEDD (mm)	22.3±4.0	19.7±3.5	0.003*
RVEDD/BSA	15.4±2.7	12.6±2.2	0.000*
RV systolic function			
RVFA (%)	0.34±0.05	0.40±0.06	0.000*
TAPSE (mm)	20.9±3.4	23.0±2.8	0.007*
ST-wave (cm/s)	12.6±2.0	14.0±2.9	0.016*
RV diastolic function			
E-wave (cm/s)	0.64±0.11	0.70±0.11	0.015*
A-wave (cm/s)	0.42±0.13	0.32±0.06	0.000*
E/A ratio	1.66±0.55	2.26±0.57	0.000*
ET-wave (cm/s)	14.7±3.2	17.9±2.9	0.000*
AT-wave (cm/s)	11.3±3.3	9.2±2.2	0.001*
ET/AT ratio	1.39±0.45	2.02±0.47	0.000*
PSAP estimation			
RPEP (ms)	68.1±13.7	64.0±11.4	0.175
ACT (ms)	118.8±29.1	145.1±24.2	0.000*
RVET (ms)	309.4±30.1	330.3±26.4	0.002*
Ratio RPEP/RVET	0.22±0.05	0.19±0.04	0.012*
Ratio ACT/RVET	0.38±0.08	0.44±0.08	0.002*

Values are expressed as mean±SD; (*): significant.
ACT = right ventricular acceleration time; AT-wave = tissue Doppler late diastolic tricuspid annular velocity; A-wave = tricuspid peak late diastolic filling velocity; ET-wave = tissue Doppler peak early diastolic tricuspid annular velocity; E-wave = tricuspid peak early diastolic filling velocity; RPEP = right ventricular pre-ejection period; RVAW = right ventricular anterior wall thickness; RVEDD = right ventricular end-diastolic dimension; RVET: right ventricular ejection time; RVFA = right ventricular fractional area change; ST-wave = tissue Doppler peak systolic tricuspid annular velocity; TAPSE = tricuspid annular plane systolic excursion.

Table 4
Comparison of clinical and echocardiographic parameters between CF patients with FEV1% values greater and less than 85% predicted.

Variable	>85%	<85%	p value
Subjects n	25	12	
Age (yrs)	14.8±1.8	14.5±1.9	0.664
Body surface area (BSA) (m^2)	1.49±0.21	1.41±0.19	0.255
RV geometry			
RVAW (mm)	2.4±0.6	2.6±0.7	0.436
RVAW/BSA	1.7±0.5	1.9±0.4	0.238
RVEDD (mm)	22.6±4.2	21.7±3.6	0.567
RVEDD/BSA	15.4±3	15.5±2.1	0.925
RV systolic function			
RVFA (%)	0.33±0.05	0.35±0.05	0.168
TAPSE (mm)	21.1±3.9	20.3±1.5	0.520
ST-wave (cm/s)	12.8±2.2	12.1±1.6	0.373
RV diastolic function			
E-wave (cm/s)	0.64±0.12	0.62±0.08	0.604
A-wave (cm/s)	0.43±0.14	0.39±0.07	0.345
E/A ratio	1.65±0.60	1.68±0.44	0.907
ET-wave (cm/s)	14.4±3.0	15.4±3.6	0.418
AT-wave (cm/s)	11.6±3.7	10.8±2.0	0.523
ET/AT ratio	1.36±0.46	1.47±0.44	0.536
PSAP estimation			
RPEP (ms)	65.6±11.9	73.1±16	0.125
ACT (ms)	118.4±31.6	119.8±24.3	0.888
RVET (ms)	316.6±31.1	294.6±22.4	0.036*
Ratio RPEP/RVET	0.21±0.05	0.25±0.06	0.029*
Ratio ACT/RVET	0.37±0.09	0.41±0.07	0.233

Values are expressed as mean±SD; (*): significant.
See Table 3 legend for expansion of abbreviations.

0.288); and RVFA% values were 0.34±0.05, and 0.34±0.06, respectively. "Homozygous", "heterozygous", and "Other" genotype groups showed values for RVEDD of 22.3±3.5; 21.6±4.7; and 23.5±3.5 mm; with no differences among them. The same results were obtained for RVFA%, with values of 0.33±0.05; 0.34±0.05; and 0.33±0.06; respectively.

Five patients (13.5%) were chronically colonized by *P. aeruginosa,* 26 (70.3%) by *methicillin sensitive S. aureus,* while the other 6 (16.2%) showed no colonization. When these three groups were compared among them, no statistically differences were found (values for RVEDD were 25.2±5.8 mm for *P. aeruginosa* colonized patients; 21.4±3.5 mm for *S. aureus* colonized patients; and 24.2±3.5 mm for non-colonized. Also values for RVFA% were 0.35±0.07, 0.33±0.05, and 0.34±0.05; respectively).

Linear regression analysis revealed no correlation between any echocardiographic parameters and FEV1, FVC, SK or Brasfield scores (Table 5).

4. Discussion

In this study we have found abnormalities in RV anatomy, systolic and diastolic function during adolescence, even before significant changes in PFT appeared. In addition, these changes are not related to a specific genotype or type of chronic colonization.

The RV disease in CF is thought to be secondary to raised pulmonary artery pressure due to chronic hypoxia from the progressive lung destruction [10]. As a result, cor pulmonale defined as right ventricular enlargement and dysfunction, develops, which may progress to right heart failure [11]. The incidence and prognosis of clinical cor pulmonale failure in infancy are not exactly known, but there are clinical [12], echocardiographic [13], and autopsy studies [14] that have found a high prevalence of RV hypertrophy and dilatation in patients with CF. Finally, occurrence of RV failure secondary to cor pulmonale is a poor prognostic sign.

Right ventricular dimension has been classically considered to reflect the severity of cor pulmonale in CF [13,15]. Previously published studies have reported an increase in size and thickness of the right ventricle in children and young adults with moderate to severe CF [13,16], suggesting that these values could represent the early stages of development and progression of long-term cardiac changes in patients with CF. In our

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Table 5
Linear correlation coefficients between PFT, clinical scores, and echo findings.

Variable	FEV1%*	FVC%*	SK*	Brasfield*
RVAW (mm)	−0.192	0.049	−0.295	−0.088
RVAW/BSA	−0.217	−0.031	−0.311	−0.052
RVEDD (mm)	0.055	0.260	−0.066	−0.156
RVEDD/BSA	0.071	0.227	−0.271	−0.041
RVFA (%)	−0.097	−0.016	−0.168	−0.055
TAPSE (mm)	−0.029	0.178	0.150	−0.093
E-wave (cm/s)	−0.028	−0.039	−0.007	0.028
A-wave (cm/s)	0.156	0.180	−0.231	−0.161
E/A ratio	−0.054	−0.064	0.205	0.151
RPEP (ms)	−0.311	−0.312	−0.192	−0.171
ACT (ms)	0.057	−0.080	0.125	0.108
RVET (ms)	0.235	0.196	0.375	0.299
Ratio RPEP/RVET	−0.292	−0.234	−0.276	−0.284
Ratio ACT/RVET	−0.104	−0.184	−0.019	−0.063
ST-wave (cm/s)	0.000	0.045	0.215	0.218
ET-wave (cm/s)	−0.172	0.057	0.180	0.077
AT-wave (cm/s)	0.103	0.266	0.092	−0.080
ET/AT ratio	−0.091	−0.151	0.124	0.205

FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity; (%) = percent of predicted value; SK = Shwachman score.
See Table 3 legend for expansion of abbreviations.
* $p > 0.05$ for all values.

study, statistically significant differences were also found in the thickness and size of the right ventricle between CF patients and controls ($p < 0.001$ and $p < 0.003$ respectively), and also between CF patients and published normal ranges for RV dimensions (22.3±4 vs. 14.6±1.6; $p < 0.001$) [17], but in contrast our patients had mild respiratory symptoms, with minor lung deterioration and almost normal pulmonary function tests.

Raised pulmonary artery pressure is an independent prognostic factor for a bad outcome. Prevalence of pulmonary hypertension in CF patients with severe obstructive lung disease is about 20% to 40%, and survival in this group is reduced; whereas patients with better pulmonary function have a much lower incidence of pulmonary hypertension and a higher survival rate [3]. However, it has also been observed that the presence of pulmonary hypertension is not always followed by clinical evidence of cor pulmonale [3].

Doppler analysis of pulmonary blood flow has proven to be a useful technique in the diagnosis of pulmonary artery hypertension. Shortening of ACT < 100 ms and values of RPEP/RVET over normal or ACT/RVET below normal, are highly suggestive of elevated PASP [15,18]. In our group of patients, ACT, RVET and ACT/RVET ratio where shorter than in the control group, while the RPEP/RVET ratio was increased, suggesting slightly elevated PASP. Also, in the small subgroup in which the pulmonary artery systolic pressure could be determined from tricuspid regurgitation, findings were consistent with normal or slightly elevated PASP. Although evidence of mild elevation of PASP was found in the group with FEV1% values <85% predicted, no changes on geometry or function of the right ventricle were observed, compared with the >85% predicted group.

RVFA has been demonstrated to be a clinically feasible diagnostic tool for monitoring RV function in patients with lung disease [19]. Published studies of RV function by echocardiography in CF patients with several degrees of lung disease are contradictory. While there are authors showing that RV systolic function seems to be preserved [3,20], others have found RV dysfunction in up to 60% of the cases in the adult population with severe CF using echocardiography [21], radionuclide angiography techniques [22], and magnetic resonance imaging [19]. The degree of dysfunction seems to parallel the severity of the disease, especially when a concomitant pulmonary hypertension is present [22]. Reported values for normal young adults are 0.40±0.03 [6] and 0.41±0.15 [23] in two different papers. Our adolescent control group had similar values 0.40±0.06, in contrast with those of the CF group of 0.34±0.08, showing that RVFA is mildly depressed in patients with CF. We suggest that a mild degree of RV dysfunction is present in clinically stable CF adolescent patients.

TAPSE is another geometry independent parameter that has proven to be a rapid and non-invasive method of evaluating right ventricular systolic function, with a close correlation with RV ejection fraction as measured by radionuclide angiography [6,24]. TAPSE has been found to be depressed in adult CF patients with severe disease [21]. In our patients, TAPSE values were decreased compared to controls, and also when they were compared with published normal values (20.9±3.4 vs. 23.0±1.1; $p < 0.001$) [25], suggesting that right ventricular systolic dysfunction may occur at very early stages of the disease process.

Abnormalities of diastolic function are an early feature of myocardial disease. Diastolic function of the RV in CF has been shown to be abnormal in several studies [26] and correlation between RV diastolic parameters and PASP has also been reported in various chronic obstructive lung diseases [27]. In our study we also found abnormalities in RV diastolic filling, characterized by decreased peak velocity E, increased peak velocity A, and low E/A ratio. All these values showed significant differences with our controls, and also with published normal values [28].

TDE allows quantitative assessment of RV systolic and diastolic function by means of measurement of myocardial velocities. The advantages of TDE variables are that they appear to be more sensitive indicators of RV myocardial diastolic dysfunction than Doppler RV variables, as they are less load dependent. Early studies in adults have found that such abnormalities comprised low ET, high AT, and low ET/AT values [29]. Our findings confirm this hypothesis. In adults, peak systolic velocity (ST) <11.5 cm/s identifies the presence of RV systolic dysfunction with a high sensitivity and specificity [30]. In our group of patients the tricuspid peak systolic velocity was also low and significantly different from healthy individual (12.6±2.0 vs. 14.0±2.9; $p < 0.05$) and from published normal values in adolescents (12.6±2.0 vs. 13.6±0.5; $p < 0.005$) [31], suggesting RV systolic dysfunction. Our results are similar to others, who found RV dysfunction in patients with CF but with a more severe degree of lung disease [23].

Previous studies have found that PFT correlate well with the presence of pulmonary hypertension and RV abnormalities in patients with severe CF [13]. In clinical practice, FEV1 and the annual fall in FEV1 percentage predicted have been classically

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used as marker of the degree of pulmonary involvement and to predict survival [32]. These parameters are reported to correlate with genotype, sex, pancreatic and nutritional status, and colonization by *P. aeruginosa* [33]. In our group of patients their pulmonary disease was best classified as mild, with FEV1% and FVC% nearly normal (means 93.2 and 99.1 respectively). In contrast with published papers [13,23], we did not find any correlation between the RV echocardiographic parameters and the FEV1 or FVC percent predicted values. We postulate that as the diseases progresses thorough adolescence and adult life and PFT deteriorates, correlation with RV abnormalities would be closer.

Correlation between genotype and severity of pulmonary disease is contradictory. Published data suggest that ΔF508 mutation has traditionally been related to more severe pulmonary deterioration [34], while other mutations have been related to milder forms of the disease [35]. In our study we were unable to show differences between RV dysfunction and mutations in the disease-causing gene in this age range.

In CF, impairment of mucociliary clearance and innate defense mechanisms leads to susceptibility to chronic infections by opportunistic bacteria. Most patients are initially colonized by *S. aureus* and/or *Haemophilus influenzae;* however, by adulthood *P. aeruginosa* emerges as the most prevalent CF pathogen. Chronic colonization for *P. aeruginosa* is strongly associated with respiratory deterioration and mortality [36], for which patients colonized by *P. aeruginosa* would be more prone to develop RV dysfunction, as lung diseases progress more rapidly in this group than in non-colonized patients. In our group of patients we were unable to demonstrate a statistically significant association between the presence of chronic lung colonization and right ventricular abnormalities. We suggest that this association may need some time to develop and to prove any further correlation a longer time of exposition to the pathogen, beyond adolescence would be required. Nevertheless, the limited number of patients for each subgroup did not allow us to establish definitive conclusions on this particular issue.

Significant correlations between cor pulmonale and SK clinical score have been found by some authors [13]. We were unable to confirm this hypothesis. SK score was only mildly depressed in our patients, and such correlation would probably need a longer period of evolution and more clinical severity to be present.

A limitation of this study is the relatively small sample size. Although we have been able to show statistically significant differences between CF patients and healthy controls, the sample size was insufficient to find differences in the subgroup analysis.

Our findings show incipient alterations of cardiac function in CF patients with mild disease. Since lung function in these patients was almost normal, these findings cannot be explained by the progression of pulmonary disease. Classically, the deterioration of cardiac function in CF patients has been associated, as in other progressive lung diseases, with the presence of hypoxia. This explanation is not valid in this case as hypoxia is unlikely to be present in these patients. Although hypoxia is not a major mechanism for altered vascular structure at this stage of the disease, chronic inflammation could also be responsible for some degree of remodeling of pulmonary resistance vessels and hence provoking mild elevations of PASP that secondarily could influence the right heart. Another possible mechanism is that, as occurs in other organs affected by CF, there is a direct involvement of the disease on the heart. Recently, it has been demonstrated that CFTR is involved in the regulation of cardiomyocyte contraction, and it has also been postulated that loss of CFTR function might leave CF patients at increased risk of heart dysfunction and disease [37]. Any direct involvement of the CF on the heart would be masked in advanced stages of the disease, when changes secondary to pulmonary hypertension and hypoxia would predominate. Further investigation in this field is necessary to determine the possibility that CF directly affect cardiac function.

In conclusion, our findings suggest that abnormalities in the structure and function of the RV may be present during adolescence at very early stages of the disease, when respiratory manifestations are mild. These abnormalities are subclinical, and do not correlate with the clinical scores, PFT, genotype, chronic colonization, genotype, or pancreatic status. Whether those changes are secondary to mild elevations of PASP, or from direct involvement of cardiomyocytes in CF have to be elucidated.

Conflict of interest statement

Authors of the manuscript have no conflicts of interest to disclose.

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