Heart, Lung and Circulation (2015) **24,** 1002–1010
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2015.03.006

ORIGINAL ARTICLE

Heart Involvement in Children and Adults with Cystic Fibrosis: Correlation with Pulmonary Indexes and Inflammation Markers

Valentina Giacchi *, **Novella Rotolo, Barbara Amato, Giovanna Di Dio, Pasqua Betta, Mario La Rosa, Salvatore Leonardi, Pietro Sciacca**

Department of Medical and Paediatric Science, University of Catania, Catania, Italy

Received 24 February 2015; received in revised form 8 March 2015; accepted 12 March 2015; online published-ahead-of-print 24 March 2015

Background Cardiovascular involvement in Cystic Fibrosis (CF) is a not rare condition, although the prevalence of subclinical pulmonary hypertension (PH) and cardiac dysfunction is not known in the early stages of CF progression. The aim of our study was to assess cardiac involvement in children and adults affected by cystic fibrosis compared with healthy subjects of same age using echocardiography.

Methods Fifty-five patients, 25 adults and 30 children completed the study. We assessed FEV1 (Forced Expiratory Volume in one second), and carried out colour Doppler-echocardiography evaluating ejection fraction (EF) measurement of left ventricle, tricuspid annular plane systolic excursion (TAPSE) of right ventricle and pulmonary artery pressure (PAP). We compared the auxological, respiratory and cardiologic data with those of 16 adults and 34 children of the same age.

Results We discovered significantly different values of PAP between patients and controls in both children ($p = 0.0001$, $r = -0.62$) and adults ($p = 0.0001$, $r = -0.63$), whereas the EF and TAPSE showed significantly different values in only adults ($p = 0.0023$ and $p = 0.0194$ respectively).
We found in both children and adults with CF an inverse correlation between PAP and FEV1 ($p = 0.000$, $p = 0.001$), Erythrocyte Sedimentation Rate (ESR) and FEV 1 ($p = 0.015$, $r = -0.43$; $p = 0.009$, $r = -0.51$), and highly sensitive C-reactive protein (hs-CRP) and FEV 1 ($p = 0.007$, $r = -0.48$; $p = 0.001$, $r = -0.60$). In adults we also detected direct correlation between PAP and hs-CRP ($p = 0.008$, $r = 0.51$) and PAP and ESR ($p = 0.009$, $r = 0.51$).

Conclusions In paediatric-aged CF patients there are already early signs of potential heart impairment, represented by an increase of pulmonary blood pressure, and in adult age the systolic function of right ventricle may be impaired. We hypothesise that such cardiac impairments may gradually arise due to preceding chronic inflammation related to prior degeneration of lung function and thus it is very important to keep patients clinically stable and address chronic inflammation as early as possible in the progression of CF.

Keywords Cystic Fibrosis • Lung function • Cardiac impairment • Flogosis • Pulmonary hypertension.

Abbreviations: CF, Cystic Fibrosis; PH, pulmonary hypertension; FEV1, Forced Expiratory Volume in one second; EF, ejection fraction; TAPSE, tricuspid annular plane systolic excursion; PAP, pulmonary artery pressure; hs-CRP, highly sensitive C-reactive protein; ESR, Erythrocyte Sedimentation Rate.

*Corresponding author. Valentina Giacchi. Department of Pediatrics – University of Catania - ''Policlinico Hospital'' - Via Santa Sofia 78, 95123 - Catania, Italy. Tel.: +00393334126158; fax: +00390953782417, Email: valentina.giacchi@yahoo.it

Background

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disease seen in the Caucasian population [1]. The pathophysiology of CF lung disease is known to involve self-perpetuating cycles of airway obstruction, infection, and inflammation [2].

Cardiovascular impairment in CF is well-known, with cor pulmonale being the most serious cardiovascular complication [3]. The development of alveolar hypoxia (in hypoventilated areas) leads to hypoxic pulmonary vasoconstriction. When the hypoxic state is prolonged, the pulmonary circulation suffers structural alterations collectively known as remodelling, characterised by hypertrophy and hyperplasia of the arterial media, as well as by muscle fibres in the peripheral vessels [4]. These events have a strong impact on pulmonary arterial pressure (PAP) and right ventricle function [6–8], bearing a strongly negative prognostic value [5]. So, the evaluation of right ventricular (RV) function in this patient population is thus extremely important [3]. Although clinically apparent cor pulmonale is a preterminal event in many patients, the prevalence of subclinical PH and cardiac dysfunction in patients is not known [6]. Echocardiography allows us to identify and quantify PH, as well as to determine its variability and the repercussions for right heart chambers [4].

Aim of Study

The aim of our observational, cross-sectional, case-control study was to assess cardiac involvement in children and adults affected by cystic fibrosis compared with healthy subjects of the same age using echocardiography. In addition, we measured hs-CRP and ESR as markers of inflammation that may be associated with severity of CF and abnormal echocardiographic parameters.

Patients and Methods

This is an observational case-control study conducted in paediatric and adult subjects affected by cystic fibrosis regardless of the severity of the pulmonary disease, followed in our Cardiology and Cystic Fibrosis Clinic of Pediatric Department in University of Catania in Italy between September 2013 and May 2014. A total of 105 patients were enrolled, and 55, 25 adults (13 male and 12 female) and 30 children (23 male and seven female) completed the study. The main features of the paediatric and adult patients are reported in Table 1 and Table 2 respectively.

The patients, if of age, or at least one parent or legal guardian of the child if underage, gave their written, informed consent before the patient's inclusion in the study. The study was conducted in accordance with the Helsinki

Table 1 Demographic, clinical and echocardiographic features of pediatric patients.

P	Age (ys)	Gender	Weight (Kg)	Height (cm)	FEV1 (%)	SpO2 (%)	ESR (mm/h)	CRP (mg/dl)	EF (%)	TAPSE (mm)	Z-SCORE	PAP (mmHg)	Antibiotics History
1	6	M	18.4	114.0	88.0	98	6	0.10	70.8	16.0	-2.00	25	Ciprofloxacin Tobramycin
2	14	M	31.5	143.5	54.0	97	17	0.58	75.0	22.0	0	14	Meropenem Amikacin
3	5	F	17.7	108.0	38.0	100	14	3.30	69.8	20.0	+1.38	48	Ceftazidime Amikacin
4	9	F	23.7	124.0	76.3	99	5	1.50	62.7	23.0	+2.20	35	Ceftazidime Amikacin Cotrimoxazole
5	14	M	41.2	147.5	50.5	96	50	2.27	59.3	22.4	+0.23	52	Meropenem Amikacin
6	11	M	36.0	136.0	100.7	98	33	3.20	75.0	24.0	+2.69	14	Aztreonam Colistin
7	18	F	53.6	148.0	32.9	96	49	3.80	70.0	19.0	-2.68	49	Meropenem Colistin
8	9	M	25.5	123.7	86.5	98	57	3.60	71.0	28.0	+5.53	28	Ceftazidime Amikacin Cotrimoxazole
9	6	M	15.0	101.0	65.0	96	15	0.21	63.0	17.0	-1.26	35	Ciprofloxacin Tobramycin
10	7	M	18.5	112.5	33.9	97	29	2.90	62.0	17.0	-1.43	42	Meropenem Amikacin Cotrimoxazole
11	13	M	52.8	161.0	139.5	97	8	0.11	62.0	24.0	+1.73	25	Ciprofloxacin Tobramycin

Table 1. (continued)

P	Age (ys)	Gender	Weight (Kg)	Height (cm)	FEV1 (%)	SpO2 (%)	ESR (mm/h)	CRP (mg/dl)	EF (%)	TAPSE (mm)	Z-SCORE	PAP (mmHg)	Antibiotics History
12	6	F	20.0	106.0	75.0	99	2	2.50	59.0	13.1	-4.15	42	Meropenem Cotromoxazole
13	15	F	24.0	138.0	22.0	96	94	0.62	68.0	15.0	-3.90	39	Ceftazidime Amikacin
14	8	M	23.6	128.0	86.1	97	15	1.54	69.4	14.4	-3.33	28	Ciprofloxacin Tobramycin
15	16	M	47.0	163.0	130.0	97	21	0.24	64.0	20.0	-1.65	11	Meropenem Amikacin
16	18	M	55.5	171.0	52.2	97	18	4.80	72.0	17.0	-3.66	17	Meropenem Cotromoxazole
17	9	M	24.0	118.0	22.6	90	43	5.13	70.0	16.0	-2.47	62	Aztreonam Colistin Cotrimoxazole
18	5	M	16.3	104.5	83.0	98	5	1.20	68.8	21.0	+2.15	22	Ceftazidime Amikacin
19	14	M	34.3	151.0	58.6	98	71	7.40	61.0	16.0	-3.43	23	Meropenem Amikacin Cotrimoxazole
20	9	M	50.0	142.0	71.0	99	12	0.34	79.0	25.0	+3.53	38	Ceftazidime Cotrimoxazole
21	6	M	19.0	110.0	86.0	98	5	1.10	69.0	13.0	-4.22	21	Meropenem Cotromoxazole
22	6	M	17.0	104.0	65.0	98	24	2.50	68.0	17.0	-1.26	40	Meropenem Amikacin Cotrimoxazole
23	6	F	19.5	111.0	60.0	98	24	2.40	74.0	17.0	-1.26	44	Ceftazidime Cotrimoxazole
24	14	M	41.7	150.0	112.5	98	29	1.40	74.0	24.0	+1.14	25	Ceftazidime Amikacin Cotrimoxazole
25	5	M	22.0	112.5	97.0	99	4	1.30	61.0	22.4	+3,23	23	Ceftazidime Cotrimoxazole
26	5	M	15.0	102.0	80.0	97	37	3.20	62.0	21.0	+2.15	25	Meropenem Amikacin Cotrimoxazole
27	13	M	90.5	165.0	81.0	99	45	3.00	77.3	30.0	+5.73	26	Meropenem Amikacin Cotrimoxazole
28	6	M	15.4	103.0	84.0	96	3	0.10	67.5	19.0	+0.22	31	Ciprofloxacin Tobramycin
29	5	M	18.0	115.5	67.0	99	40	1.60	77.0	20.0	+1.38	40	Ceftazidime Cotrimoxazole
30	16	F	55.0	163.0	101.2	99	4	0.10	74.0	14.0	-4.65	23	Meropenem Amikacin

Declaration, and the study protocol was approved by the (local) Ethics Committee of the Medical University of Catania.

Scheduled examination contemplates anamnestic assessment including age, clinical examination with measurement of height and weight and oxygen saturation measurement, history of antibiotics therapy in the last three months, blood testing including highly sensitive C-reactive protein (hs-CRP), erythrosedimentation velocity (ESV), spirometry, colour Doppler-echocardiography.

We performed spirometry by Care Fusion, Master Screen Pediatric – Viasys Healthcare device and assessed FEV1 (Forced Expiratory Volume in one second) as percentage of the value for gender, age, weight and height. We carried out colour Doppler-echocardiography with Philips E 33 echocardiography with multi-frequency S8-3 probe, and we evaluated systolic function of left ventricle by ejection fraction (EF) measurement, systolic function of right ventricle by tricuspid annular plane systolic excursion (TAPSE) and

Table 2 Demographic, clinical and echocardiographic features of adult patients.

P	Age (ys)	Gender	Weight (Kg)	Height (cm)	FEV1 (%)	SpO2 (%)	ESR (mm/h)	CRP (mg/dl)	EF (%)	TAPSE (mm)	PAP (mmHg)	Antibiotics History
1	21	M	58.0	167	95.0	97	17	0.40	63.0	20.0	17	Meropenem Amikacin
2	31	M	50.0	175	29.0	98	89	7.63	56.0	17.0	31	Ciprofloxacin Tobramycin
3	33	M	74.3	169	102.0	100	9	0.36	73.0	24.0	18	Ceftazidime Cotrimoxazole
4	40	M	56.0	180	26.2	95	111	3.59	60.0	23.2	15	Meropenem Amikacin Cotrimoxazole
5	25	F	40.1	155	36.8	97	15	0.21	72.8	19.0	23	Ceftazidime Amikacin Cotrimoxazole
6	24	F	47.0	155	56.2	96	115	1.14	58.0	19.0	22	Ceftazidime Cotrimoxazole
7	24	F	50.0	157	79.3	98	30	0.46	64.0	19.0	27	Ceftazidime Amikacin
8	24	F	47.7	161	73.3	98	15	0.50	75.0	22.0	14	Ceftazidime Cotrimoxazole
9	33	F	38.2	148	58.0	99	22	0.22	71.9	18.0	24	Ceftazidime Amikacin Cotrimoxazole
10	49	M	79.0	168	130.5	99	25	0.17	63.0	12.0	9	Ceftazidime Amikacin Cotrimoxazole
11	29	M	71.5	166	103.8	97	22	0.12	65.0	21.0	10	Ciprofloxacin Tobramycin
12	50	F	62.2	159	81.7	97	43	0.90	62.0	25.0	34	Ceftazidime Amikacin Cotrimoxazole
13	23	M	60.0	170	19.1	85	48	3.65	66.0	17.0	54	Ceftazidime Amikacin
14	22	F	41.0	146	78.1	100	23	0.64	71.0	20.0	27	Ceftazidime Amikacin
15	27	M	73.0	172	34.4	93	24	0.55	68.0	25.0	42	Meropenem Amikacin Cotrimoxazole
16	23	F	42.0	160	29.3	94	76	9.39	64.0	23.0	47	Ceftazidime Amikacin
17	35	M	45.5	163	13.0	88	58	0.16	69.0	18.0	44	Meropenem Amikacin Cotrimoxazole
18	21	M	47.0	164	53.5	98	41	1.40	73.0	20.2	31	Ceftazidime Amikacin
19	23	F	53.0	158	99.0	98	23	0.24	65.0	26.0	15	Ciprofloxacin Tobramycin
20	23	F	53.0	155	106.2	98	14	0.14	67.0	20.0	25	Ceftazidime Amikacin Cotrimoxazole
21	29	M	65.0	165	46.3	98	69	2.10	56.0	17.0	42	Ceftazidime Amikacin Cotrimoxazole
22	22	F	44.0	157	60.7	99	17	0.18	60.0	22.0	27	Ceftazidime Amikacin
23	23	M	68.6	168	92.4	97	115	0.47	66.9	23.0	29	Ceftazidime Amikacin

Table 2. (continued)

P	Age (ys)	Gender	Weight (Kg)	Height (cm)	FEV1 (%)	SpO2 (%)	ESR (mm/h)	CRP (mg/dl)	EF (%)	TAPSE (mm)	PAP (mmHg)	Antibiotics History
24	25	M	56.5	178	39.0	95	38	2.74	61.6	21.0	31	Ceftazidime Amikacin
25	49	F	42.0	151	48.2	93	116	1.32	75.0	17.0	43	Meropenem Cotrimoxazole

Table 3 Comparison between patients and healthy controls.

Variable	Paediatric patients	Paediatric controls	*P value*	Adults patients	Adults controls	*P value*
Age (years)	9 *(5-18)*	7.5 *(5-18)*	0.451	25 *(21-50)*	30 *(19-35)*	0.303
M/F (n)	23/7	24/10	0.777	13/12	10/6	0.540
Weight (Kg)	23.85 *(15-90.5)*	26.9 *(14-68)*	0.804	53 *(38.2-79)*	65.5 *(51-78)*	**0.0062**
Height (cm)	123.85 *(101-171)*	127.5 *(106.5-173)*	0.824	163 *(146-180)*	170 *(160-178)*	**0.0150**
SpO2 (%)	98 *(90-100)*	-	-	97 *(85-100)*	-	**-**
ESR (mm/h)	19.5 *(2-94)*	-	-	30 *(9-116)*	-	**-**
CRP (mg/dl)	1.57 *(0.10-7.4)*	-	-	0.50 *(0.12-9.39)*	-	**-**
EF	69.2 *(59-79)*	69.9 *(60.3-80.3)*	0.297	65 *(56-75)*	71 *(66.9-77)*	**0.0023**
TAPSE	19.5 *(13-30)*	20 *(11.8-27)*	0.834	20 *(12-26)*	22.5 *(20-25)*	**0.0194**
PAP	28 *(11-62)*	20 *(5-43)*	**0.0001**	27 *(9-54)*	12.5 *(5-21)*	**0.0001**
FEV1	75.65 *(22-139.5)*	99.5 *(95-107)*	**0.0000**	58 *(13-130)*	99.5 *(96-104)*	**0.0004**

pulmonary artery pressure (PAP) according to the American Society of Echocardiography [7–9].

We compared the auxological, respiratory and cardiologic data with those of 16 adults and 34 children of the same age.

Statistical Analysis

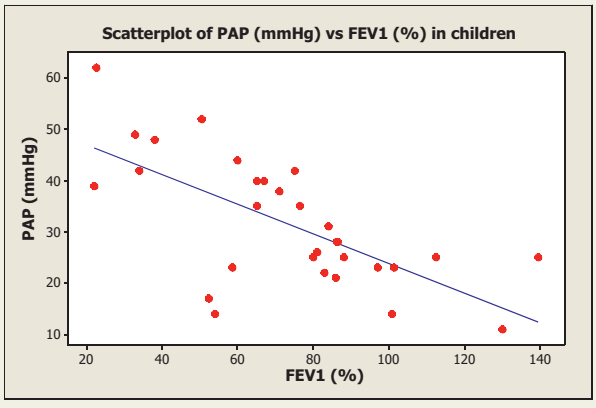
Descriptive statistics were calculated for all clinical variables. For each dataset we calculated the median. For the evaluation of statistically significant parameter differences within the whole sample, we used the independent two-sample Mann-Whitney test for quantitative measures, and Fisher's test for nominal characteristics. The correlation between numerical variables was calculated through Spearman's correlation coefficient. The relationship between quantitative outcome measures and their relative significance was determined using linear regression by univariate analysis. Statistical significance was set at levels of P<0.05, P<0.01, and P<0.001.

Results

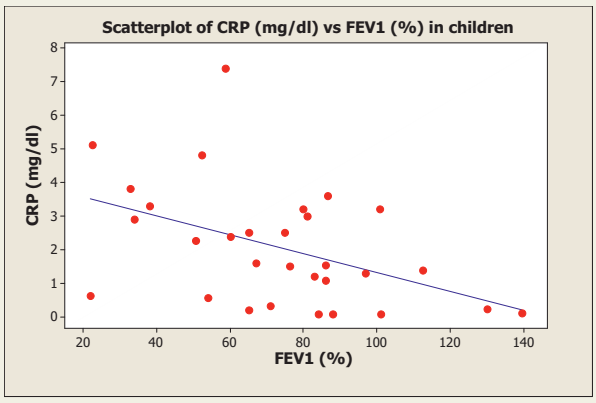
The results are illustrated in Table 3 and Graphs (1-8). We did not detect significant difference in age, between both adults and paediatric patients and their respective controls. The groups of adults differentiated in both weight ($p < 0.01$) and height ($p < 0.05$), whereas the groups of children did not show significant difference in any auxological parameter.

Both children and adults showed different values of FEV1. Regarding cardiopulmonary parameters, we discovered significantly different values of PAP between patients and controls in both children ($p = 0.0001$) and adults ($p = 0.0001$), whereas the EF and TAPSE showed significantly different values in only adults ($p = 0.0023$ and $p = 0.0194$ respectively).

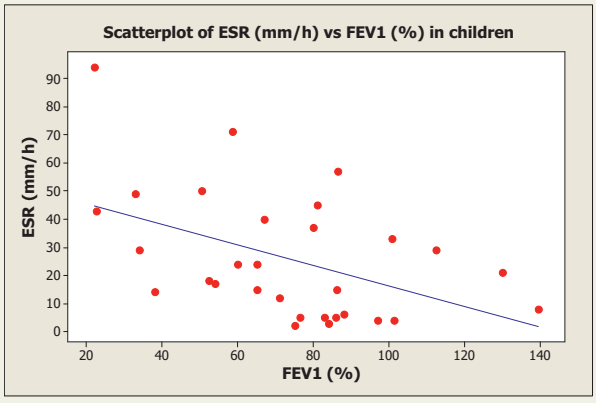
We found in both children and adults with CF an inverse correlation between PAP and FEV1 ($p = 0.000$, $p = 0.001$),



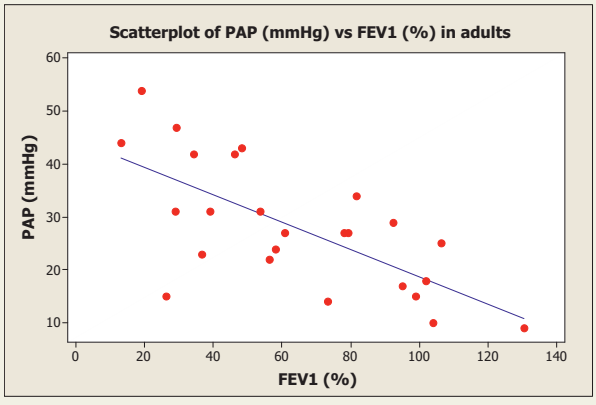
Graph 1 Spearman correlation of PAP (mmHg) and FEV1 (%) in children = -0,620.
P-Value = 0,000
S = 9,36044 R-Sq = 45,0% R-Sq(adj) = 43,0%



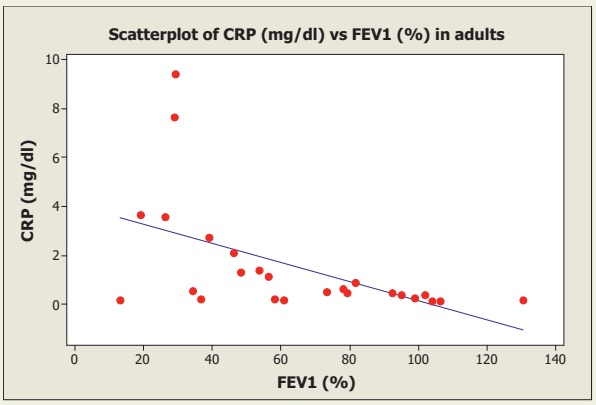
Graph 2 Spearman correlation of CRP (mg/dl) and FEV1 (%) in children = -0,481
P-Value = 0,007
S = 1,59277 R-Sq = 21,0% R-Sq(adj) = 18,1%



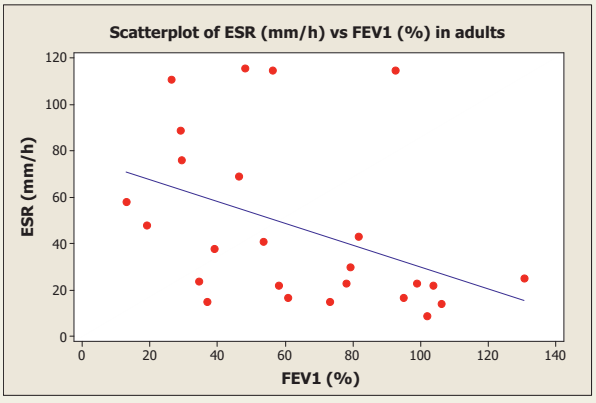
Graph 3 Spearman correlation of ESR (mm/h) and FEV1 (%) in children = -0,439
P-Value = 0,015
S = 20,2295 R-Sq = 21,7% R-Sq(adj) = 18,9%



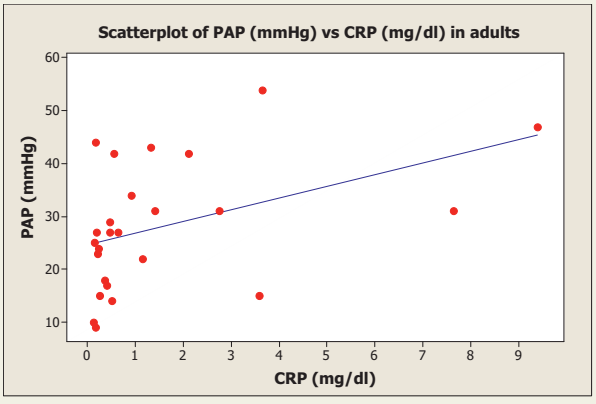
Graph 4 Spearman correlation of PAP (mmHg) _1 and FEV1 (%) in adults = -0,635
P-Value = 0,001
S = 8,98263 R-Sq = 47,0% R-Sq(adj) = 44,7%



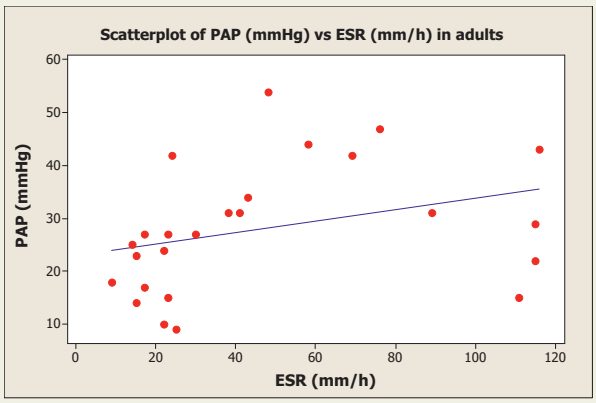
Graph 5 Spearman correlation of CRP (mg/dl) and FEV1 (%)in adults = -0,605
P-Value = 0,001
S = 2,03604 R-Sq = 28,0% R-Sq(adj) = 24,9%



Graph 6 Spearman correlation of ESV (mm/h) and FEV1 (%) in adults = -0,513
P-Value = 0,009
S = 33,7027 R-Sq = 17,2% R-Sq(adj) = 13,6%



Graph 7 Spearman correlation of PAP (mmHg) and CRP (mg/dl) in adults = 0,518
P-Value = 0,008
S = 11,1516 R-Sq = 18,3% R-Sq(adj) = 14,8%



Graph 8 Spearman correlation of PAP (mmHg) and ESR (mm/h) in adults = 0,513
P-Value = 0,009
S = 11,6666 R-Sq = 10,6% R-Sq(adj) = 6,7%

ESR and FEV 1 ($p = 0.015$, $r = -0.43$; $p = 0.009$, $r = -0.51$), and hs-CRP and FEV 1 ($p = 0.007$, $r = -0.48$; $p = 0.001$, $r = -0.60$). In adults we also detected a direct correlation between PAP and hs-CRP ($p = 0.008$, $r = 0.51$) and PAP and ESR ($p = 0.009$, $r = 0.51$).

Discussion

Our study highlights that subjects with cystic fibrosis present a higher risk of heart involvement than healthy controls of same age.

According to other studies [4,6], our patients presented higher values of PAP than healthy controls in childhood, with a percentage of high PAP equal to 46.6% in the paediatric population and 40% in adults.

Previously, several investigators examined heart function in CF patients, (however, with the prominent pulmonary disturbances in CF patients) and the majority of these studies focussed on the right ventricle. Increased pulmonary pressures in individuals with lung disease can cause cor pulmonale and right ventricular overload [10].

PH is observed in 20–65% of adult CF patients with severe disease [11], and occurs in some patients with end-stage pulmonary diseases [5], being significantly correlated with declining pulmonary function (FEV1) [6]. However, data on its frequency and impact among patients with milder disease are limited [5].

It was demonstrated that subclinical PH develops in a substantial proportion of patients with CF and stable lung disease and that it correlates with the frequency and severity of episodes of arterial oxygen desaturation and with FEV1 [4,12]. In fact both intermittent and sustained hypoxaemia have been implicated in the pathogenesis of PH in animal models and in human studies [4]. Baño-Rodrigo et al. found evidence of mild elevation of PASP in the group with FEV1% values < 85% predicted [13].

While some authors showed that RV systolic function seems to be preserved [6,14], others have found RV dysfunction in up to 60% of the cases in the adult population with severe CF using echocardiography [15], radionuclide angiography techniques [16], and magnetic resonance imaging [17]. The degree of dysfunction seems to parallel the severity of the disease, especially when a concomitant PH is present [16].

We evaluated RV systolic function by measurement of TAPSE, a 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 [18,19]. In our patients, TAPSE values showed a significant difference between patients and controls only among adults, suggesting that right ventricular systolic dysfunction does not seem to occur at very early stages of the disease process.

In contrast to studies focussed on the right ventricle, evidence for the primary left ventricular dysfunction in CF has been scarce [20]. We detected normal systolic function of the left ventricle in both children and adult patients, although the latter presented values of EF lower than healthy controls of same age. One possible reason for this finding was that the most patients studied were young, in a stable condition, and carrying on with normal daily living activities.

Several studies have documented preserved LV function in the presence of normal or severely impaired RV function. However, one group reported a reduced LV ejection fraction with a diffusely hypokinetic ventricle in 19% of CF patients (four of 17) [30], although most previous reports suggest that LV dysfunction is rare even in patients with severe pulmonary disease [21,22]. We assessed LVEF in resting subjects by 2D-echocardiography and our results indicate that LV involvement seems to occur when a massive right ventricular enlargement is present [23] because of abnormal septal motion and absence of a severe impairment of right ventricle. Potentially, LV involvement may also be due to myocardial fibrosis or hypoxaemia [21].

In our study PAP and FEV 1 showed an inverse correlation in both children and adults, confirming the statements of other authors [4,6,24], indicating that the increase of pulmonary resistance has as a substrate the reduction in function of pulmonary oxygenation [25,26].

The regression analysis revealed, in addition to other studies, that higher values of inflammatory markers are correlated with a poorer pulmonary function already in childhood and also with higher values of PAP in adult age. In a previous study Bright-Thomas et al. identified an association between the systemic inflammatory marker hs-CRP and PAP [12] in adults with CF but, to our knowledge, this is the first study of CF patients performed on both children and adults at the same time.

It is unclear if systemic inflammation contributes to any of our results, but it is clear that in addition to cardiac function, it is important to clarify the role of large vessel reactivity and haemodynamics in CF to determine the cardiovascular risk for these patients.

Endothelial dysfunction is thought to precede the structural changes known as ''vascular remodelling'' which in

turn lead to the increase in vascular resistance and ultimately to irreversible PH. This occurs possibly through an imbalance between the production of vasoconstrictive and vasodilative factors [5].

Although hypoxia is a mechanism for altered vascular structure in this disease, chronic inflammation could also be responsible for some degree of remodelling 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 [27]. Any direct involvement of the CF on the heart would be masked in advanced stages of the disease, when changes secondary to PH and hypoxia would predominate [13].

A predictive relationship between circulating highly sensitive C-reactive protein (hs-CRP) and haemodynamic alterations, suggests that systemic inflammation may be relevant [28], although not demonstrating causation. An acute pro-inflammatory stimulus could be associated with heightened vessel stiffness [29], whereas, anti-inflammatory therapy may favourably alter large artery haemodynamics [30].

We propose that pulmonary-localised and systemic inflammation due to the adverse alterations in pulmonary function and structure during early CF progression may subsequently lead to overt changes in right ventricle function. Although we measured hs-CRP and ESR in the present study, additional markers and more direct evidence of cardiac inflammation and cardiac remodelling was not investigated.

The adult stage of CF is characterised by the presence of persistent systemic inflammation that may increase periodically at times of 'exacerbation', i.e. in association with clinical deterioration. In CF, intervention with intravenous (iv) antibiotics is recognised to attenuate circulating markers of inflammation and results in parallel improvements in clinical characteristics; including pulmonary function, body mass [31–33] as well as reduction in energy expenditure, circulating catecholamine levels and catabolic metabolism [32–34]. It is apparent that an acute pro-inflammatory stimulus can promote haemodynamic changes indicative of increased loading on the central systemic vasculature [29]. Studies concerning the treatment with iv antibiotics in the CF population detail a reduction in heart rate [33,35,36]. In addition Hull et al. demonstrated a response in haemodynamics to a therapy recognised to favourably modulate systemic inflammation [30].

The present study is an observational study and should be followed up with larger, hypothesis-testing designed studies. Some longitudinal studies of patients from the earliest diagnosis of CF could better highlight the mechanisms between systemic inflammation and cardiovascular impairment. Moreover a more specific, larger set of molecular markers may need to be also considered with cardiac and pulmonary parameters also to separate what is pulmonary inflammation and what is related to chronic rise in the vascular and cardiac factors contributing to PH.

Conclusions

Patients with CF may show signs of potential heart impairment such as an increase of pulmonary pressure in paediatric age, and an impaired systolic function of right ventricle in adult age, while a poor pulmonary function (FEV 1) is logically a risk factor for the development of PH as seen by an increase in PAP.

Whether the relative hypoxia seen in patients with mild lung disease is the cause of the higher PAP measurements than controls warrants future detail investigation. Focus on other factors is also needed including investigation of systemic inflammation and therapeutic interventions.

Increased inflammation markers seem to be related to an impairment of pulmonary function in childhood and also to higher values of PAP in adult age. We hypothesise that this is a common process linked to chronic inflammation characterised by degeneration of lung function before and heart involvement later, also considering that the alteration of RV systolic function in CF patients may be preceded by the increase of PAP. On this basis it would be very important to keep patients clinically stable and correct and early antibiotic therapy may play a role in the preservation of heart function.

Further studies are necessary to confirm our data and to evaluate with prospective studies the clinical evolution of patients since childhood.

Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contributions

Conception and design: Pietro Sciacca, Valentina Giacchi, Pasqua Betta

Collection and assembly of data: Valentina Giacchi, Barbara Amato, Giovanna Di Dio

Analysis and interpretation of data: Valentina Giacchi, Novella Rotolo

Draft of the manuscript: Valentina Giacchi, Novella Rotolo, Pietro Sciacca

Critical revision of the manuscript and important intellectual content: Pietro Sciacca, Salvatore Leonardi

Final approval: Pietro Sciacca, Salvatore Leonardi, Mario La Rosa

Acknowledgement

We acknowledge the excellent technical assistance of Nicola Bonanno of the Department of Pediatrics of the University of Catania, Italy. We also acknowledge our secretary Concetta Scuderi for her collaboration in collecting data.

References

[1] Abraham TP, Dimaano VL, Liang HY. Role of tissue Doppler and strain echocardiography in current clinical practice. Circulation 2007;116:2597–609.

[2] Hoffman LR, Ramsey BW. Cystic Fibrosis Therapeutics. The Road Ahead. CHEST 2013;143(1):207–13.

[3] Ozcelik N, Shell R, Holtzlander M, Cua C. Decreased right ventricular function in healthy pediatric cystic fibrosis patients versus non-cystic fibrosis patients. Pediatr Cardiol 2013;34:159–64. http://dx.doi.org/10.1007/s00246-012-0407-4.

[4] Eidt Rovedder PM, Ziegler B, Furlan Pinotti AF, Menna Barreto SS, de Tarso Roth Dalcin P. Prevalence of pulmonary hypertension evaluated by Doppler echocardiography in a population of adolescent and adult patients with cystic fibrosis. J Bras Pneumol 2008;34(2):83–90.

[5] Henno P, Maurey C, Danel C, Bonnette P, Souilamas R, Stern M, et al. Pulmonary vascular dysfunction in endstage cystic fibrosis: role of NF-kB and endothelin-1. Eur Respir J 2009;34:1329–37. http://dx.doi.org/10.1183/09031936.00186908.

[6] Fraser KL, Tullis DE, Sasso Z, Hylan RH, Thornley KS, Hanly PJ. Pulmonary Hypertension and Cardiac Function in Adult Cystic Fibrosis. Role of Hypoxemia. Chest 1999;115:1321–8.

[7] Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr 2010;23(5):465–95.

[8] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography, European Society of Cardiology. Eur J Echocardiogr 2006;7(2):79–88.

[9] Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr 2002;15(2):167–84.

[10] Bright-Thomas RJ, Webb AK. The heart in cystic fibrosis. J R Soc Med 2002;95(Suppl. 41):2–10.

[11] Manika K, Pitsiou GG, Boutou AK, Tsaoussis V, Chavouzis N, Antoniou M, et al. The Impact of Pulmonary Arterial Pressure on Exercise Capacity in Mild-to-Moderate Cystic Fibrosis:A Case Control Study. Pulmonary Medicine 2012;6. http://dx.doi.org/10.1155/2012/252345. Article ID 252345.

[12] Bright-Thomas RJ, Ray SG, Webb AK. Pulmonary artery pressure in cystic fibrosis adults: Characteristics, clinical correlates and long-term follow-up. Journal of Cystic Fibrosis 2012;11:532–8.

[13] Baño-Rodrigo A, Salcedo-Posadas A, Villa-Asensi JR, Tamariz-Martel A, Lopez-Neyra A, Blanco-Iglesias E. Right ventricular dysfunction in adolescents with mild cystic fibrosis. Journal of Cystic Fibrosis 2012;11:274–80.

[14] Burghuber OC, Salzer-Muhar U, Gotz M. Right ventricular contractility is preserved in patients with cystic fibrosis and pulmonary artery hypertension. Scand J Gastroenterol Suppl 1988;143:93–8.

[15] Florea VG, Florea ND, Sharma R, Coats AJ, Gibson DG, Hodson ME, et al. Right ventricular dysfunction in adult severe cystic fibrosis. Chest 2000;118(4):1063–8.

[16] Matthay RA, Berger HJ, Loke J, Dolan TF, Fagenholz SA, Gottschalk A, et al. Right and left ventricular performance in ambulatory young adults with cystic fibrosis. Br Heart J 1980;43(4):474–80.

[17] Schenk P, Globits S, Koller J, Brunner C, Artemiou O, Klepetko W, et al. Accuracy of echocardiographic right ventricular parameters in patients with different end-stage lung diseases prior to lung transplantation. J Heart Lung Transplant 2000;19(2):145–54.

[18] Kaul S, Tei C, Hopkins JM, Shah PM. Assessment of right ventricular function using two-dimensional echocardiography. Am Heart J 1984;107(3):526–31.

[19] Ueti OM, Camargo EE, Ueti AA, Lima-Filho EC, Nogueira EA. Assessment of right ventricular function with Doppler echocardiographic indices derived from tricuspid annular motion: comparison with radionuclide angiography. Heart 2002;88(3):244–8.

[20] Sellers ZM, Kovacs A, Weinheimer CJ, Best PM. Left ventricular and aortic dysfunction in cystic fibrosis mice. Journal of Cystic Fibrosis 2013;12:517–24.

[21] Panidis IP, Ren JF, Holsclaw DS, Kotler MN, Mintz GS, Ross J. Cardiac function in patients with cystic fibrosis: evaluation by two-dimensional and Doppler echocardiography. J Am Coll Cardiol 1985;6:701–6.

[22] Matthay RA, Berger HJ, Loke J, Dolan TF, Fagenholz SA, Gottschalk A, et al. Right and left ventricular performance in ambulatory young adults with cystic fibrosis. Br Heart J 1980;43:474–80.

[23] Jacobstein MD, Hirschfeld SS, Winnie G, Doershuk C, Liebman J. Ventricular interdependence in severe cystic fibrosis. A two-dimensional echocardiographic study. Chest 1981;80(4 Oct):399–404.

[24] Goldring RM, Fishman AP, Turino GM, Cohen HI, Denning CR, Anderson DH. Pulmonary hypertension and cor pulmonale in cystic fibrosis of the pancreas. J Pediatr 1964;65:501–24.

[25] Stern RC, Borkat G, Hirschfeld SS, Boat TF, Matthews LW, Liebman J, et al. Heart failure in cystic fibrosis. Treatment and prognosis of cor pulmonale with failure of the right side of the heart. Am J Dis Child 1980;134:267–72.

[26] Siassi B, Moss AJ, Dooley RR. Clinical recognition of cor pulmonale in cystic fibrosis. J Pediatr 1971;78:794–805.

[27] Sellers ZM, De Arcangelis V, Xiang Y, Best PM. Cardiomyocytes with disrupted CFTR function require CaMKII and Ca(2+)-activated Cl(−) channel activity to maintain contraction rate. J Physiol 2010;588(Pt 13):2417–29.

[28] Hull JH, Garrod R, Ho TB, Knight RK, Cockcroft JR, Shale DJ, et al. Increased augmentation index in patients with cystic fibrosis. Eur Respir J 2009;34:1322–8.

[29] Vlachopoulos C, Dima I, Aznaouridis K, Vasiliadou C, Ioakeimidis N, Aggeli C, et al. Acute systemic inflammation increases arterial stiffness and decreases wave reflections in healthy individuals. Circulation 2005;112:2193–200.

[30] Hull JH, Garrod R, Ho TB, Knight RK, Cockcroft JR, Shale DJ, et al. Dynamic vascular changes following intravenous antibiotics in patients with cystic fibrosis. Journal of Cystic Fibrosis 2013;12:125–9.

[31] Nixon LS, Yung B, Bell SC, Elborn JS, Shale DJ. Circulating immunoreactive interleukin-6 in cystic fibrosis. Am J Respir Crit Care Med 1998;157:1764–9.

[32] Ionescu AA, Nixon LS, Evans WD, Stone MD, Lewis-Jenkins V, Chatham K, et al. Bone density, body composition, and inflammatory status in cystic fibrosis. Am J Respir Crit Care Med 2000;162:789–94.

[33] Bell SC, Bowerman AM, Nixon LE, Macdonald IA, Elborn JS, Shale DJ. Metabolic and inflammatory responses to pulmonary exacerbation in adults with cystic fibrosis. Eur J Clin Invest 2000;30:553–9.

[34] Ionescu AA, Nixon LS, Shale DJ. Cellular proteolysis and systemic inflammation during exacerbation in cystic fibrosis. J Cyst Fibros 2004;3:253–8.

[35] McCloskey M, Redmond AO, Pyper S, McCabe C, Westerterp KR, Elborn SJ. Total energy expenditure in stable patients with cystic fibrosis. Clin Nutr 2001;20:235–41.

[36] Pike SE, Prasad SA, Balfour-Lynn IM. Effect of intravenous antibiotics on exercise tolerance (3-min step test)) in cystic fibrosis. Pediatr Pulmonol 2001;32:38–43.