



Proinflammatory indicators and the relevance of echocardiography in children with cystic fibrosis

Original Article

Cite this article: Yagci OO, Sulu A, Kosger P, Yildirim GK, Anil H, Ucar B, and Harmanci K (2024) Proinflammatory indicators and the relevance of echocardiography in children with cystic fibrosis. *Cardiology in the Young* **34**: 73–78. doi: [10.1017/S1047951123001178](https://doi.org/10.1017/S1047951123001178)

Received: 2 October 2022

Revised: 3 April 2023

Accepted: 27 April 2023

First published online: 19 May 2023

Keywords:

Cystic fibrosis; echocardiography; proinflammatory indicators; neurohormones; children

Corresponding author: Dr O. Ozenli Yagci;

Email: ozenliovgu@gmail.com

Ovgu Ozenli Yagci¹ , Ayşe Sulu² , Pelin Kosger² , Gonca Kilic Yildirim³, Hulya Anil⁴, Birsen Ucar² and Koray Harmanci⁴

¹Department of Pediatrics, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey; ²Department of Pediatric Cardiology, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey; ³Department of Pediatric Nutrition and Metabolism, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey and ⁴Department of Pediatric Allergy and Immunology, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

Abstract

As the life expectancy improves in cystic fibrosis, cardiac dysfunction is becoming an important risk factor for morbidity and mortality. Here, the association of cardiac dysfunction with proinflammatory markers and neurohormones between cystic fibrosis patients and healthy children was investigated. Echocardiographic measurements of right and left ventricular morphology and functions together with levels of proinflammatory markers and neurohormones (renin, angiotensin-II, and aldosterone) were obtained and analysed in a study group of 21 cystic fibrosis children aged 5–18 years and compared with age- and gender-matched healthy children. It was shown that patients had significantly higher interleukin-6, C-reactive protein, renin and aldosterone levels ($p < 0.05$), dilated right ventricles, decreased left ventricle sizes, as well as both right and left ventricular dysfunction. These echocardiographic changes correlated with hypoxia, interleukin-1 α , interleukin-6, C-reactive protein, and aldosterone ($p < 0.05$) levels. The current study revealed that hypoxia, proinflammatory markers, and neurohormones are major determinants of subclinical changes in ventricular morphology and function. While the right ventricle anatomy was affected by cardiac remodeling, the left ventricle changes were induced by right ventricle dilation and hypoxia. A significant but subclinical systolic and diastolic right ventricle dysfunction in our patients was associated with hypoxia and inflammatory markers. Systolic left ventricle function was affected by hypoxia and neurohormones. Echocardiography is a reliable and non-invasive method that is used safely in cystic fibrosis children for screening and detection of cardiac anatomical and functional changes. Extensive studies are needed to determine the time and frequency of screening and treatment suggestions for such changes.

Cystic fibrosis is a genetic disorder that causes progressive organ dysfunction, mainly affecting the sinopulmonary system. As life expectancy increases, extrapulmonary comorbidities of cystic fibrosis have become recognised. A major contraindication to lung transplantation, cardiac involvement in cystic fibrosis emerges as an important complication that requires early screening and follow up.^{1–3} Although most of the studies in the literature involve adult patients and concentrate mostly on right ventricular functions, several studies have shown that subclinical deterioration of both right and left ventricular function or structure starts in childhood in cystic fibrosis patients.^{4–8} It has been postulated that myocardial involvement is multifactorial. Chronic hypoxia, recurrent inflammation and myocardial fibrosis induced by renin, angiotensinogen, and aldosterone system activation are among the most popular possible theories studied to explore the cardiac involvement in cystic fibrosis.⁹

The aim of this study was to assess both left and right ventricular function and anatomy in children with cystic fibrosis using M-mode, 2D, and Doppler echocardiography, in addition to evaluate the association of structural and functional changes of ventricles with proinflammatory markers; interleukin-1, interleukin-6, C-reactive protein, high sensitive c-reactive protein, tumour necrosis factor- α , and neurohormones (renin, angiotensin-II, aldosterone).

Materials and methods

We performed a prospective study and included 21 children aged 5–18 years (10 females, 11 males) with a confirmed diagnosis of cystic fibrosis. These patients were recruited from our paediatric pulmonology and cardiology outpatient clinic between February 2020 and 2021. All were clinically stable, had no cardiac insufficiency symptoms, no history of congenital or acquired cardiac diseases, no history of respiratory exacerbation or positive throat or sputum

culture in previous 3 months. Clinically unstable patients or patients with pulmonary exacerbation, positive throat or sputum culture were excluded from the study. During the same period, age-, and sex-matched healthy children without any acute or chronic respiratory or cardiac diseases were recruited from our social paediatrics clinic. Weight and height of all children were measured, and body mass index was calculated. Heart rate, systolic and diastolic blood pressure, and oxygen saturation were noted before an echocardiographic study was performed. Written informed consent was obtained from the parents. The study was approved by the local Clinical Research Ethics Committee of Eskisehir Osmangazi University on July 23, 2020 (E-80558721-050.99-72001).

The transthoracic echocardiographic evaluations were all performed by the same expert paediatric cardiologist using a Philips Epiq7 (Philips Ultrasound; Bothel, WA, USA). Anatomy of the heart was evaluated by two-dimensional and M-mode echocardiography whereas pulsed-wave Doppler and tissue Doppler imaging were used to measure blood flow velocities as recommended by the American Society of Echocardiography.¹⁰ All measurements were performed on three consecutive cardiac cycles and the means were calculated.

The M-mode echocardiography was performed at parasternal short-axis view to measure interventricular septum diameter, left ventricular posterior wall diameter, left ventricular mass, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left ventricular fractional shortening, and ejection fraction. Biventricular longitudinal systolic function was estimated at apical 4-chamber view by mitral annular plane systolic excursion for the left ventricle and by tricuspid annular plane systolic excursion for the right ventricle. Two-dimensional echocardiography was performed to estimate left ventricular end-diastolic volume and end-systolic volume. Using the apical 4-chamber view, right ventricular end-diastolic basal diameter, mid cavity diameter, and length were measured with two-dimensional echocardiography. We estimated end-diastolic and systolic areas of the right ventricle by using apical 4-chamber echocardiography. The percentage of the right ventricle fractional area change was calculated as the difference between end-diastolic area and end-systolic area divided by end-diastolic area.

To evaluate the right and left ventricular diastolic function, the highest peak velocity of blood inflow through the mitral and tricuspid valves during early diastole (E) and the peak velocity during late diastole (A) were measured with pulse-wave Doppler.

With biventricular tissue Doppler imaging, diastolic and systolic peak velocities were measured at lateral annulus of mitral and tricuspid valves. Systolic function was evaluated by peak systolic velocity (s') and isovolumetric contraction time. Peak early (e') and late (a') diastolic myocardial velocities, and isovolumetric relaxation time were measured for diastolic function. The velocity ratios E/e' , E/A , and e'/a' were obtained to estimate diastolic function.

Circulating levels of C-reactive protein, high-sensitive C-reactive protein, interleukin-1, interleukin-6, tumour necrosis factor- α , renin, angiotensin-II, and aldosterone were measured in venous blood by ELISA at the time of echocardiographic study in all subjects.

The data were analysed with the Statistical Package for Social Sciences, Version 21 (SPSS, Chicago, USA). The type of distribution was obtained by Kolmogorov–Smirnov test. Normally distributed data were shown as mean \pm standard deviation and two groups are compared using t-test whereas

Table 1. Comparison of baseline characteristics, circulating levels of proinflammatory markers and neurohormones between CF patients and healthy children

	Cystic fibrosis	Healthy Children	<i>p</i>
**Weight (kg)	29 (22.3–45.5)	43 (26–53.5)	0.186
z-score	−1.18 \pm 1.69	0.27 \pm 1.69	0.008
*Height (cm)	144.28 \pm 18.69	145.57 \pm 19.9	0.830
z-score	−0.31 \pm 1.50	0.72 \pm 2.69	0.129
*BMI	16.09 \pm 4.06	18.50 \pm 3.46	0.046
z-score	−1.96 \pm 3.65	0.13 \pm 0.18	0.020
*Heart rate(beat/min)	97 \pm 17	87 \pm 19	0.598
**Systolic BP (mmHg)	104 (92–109)	108 (99–112)	0.190
**Diastolic BP (mmHg)	57 (53–66)	57 (55–63)	1.000
*SPO ₂ (%)	93.5 \pm 2.7	98.8 \pm 3.3	0.001
**CRP (mg/L)	4.3 (1.4–10.4)	0.6 (0.5–0.7)	0.001
*hs-CRP (pg/ml)	292.5 \pm 153.2	237.1 \pm 154.7	0.250
**Renin (ng/ml)	5.2 (3.4–9.8)	2.85 (2.21–3.86)	0.001
*Ang-II (pg/ml)	2400 \pm 832	1998 \pm 488	0.063
**Aldosterone (pg/ml)	156 (88.9–237.9)	80 (65.2–104.5)	0.001

*mean \pm standard deviation.

**median (25–75%).

Ang-II = angiotensin II; BMI = body mass index; BP = blood pressure; CRP = C-reactive protein; hsCRP = high sensitive CRP; IL = interleukin; SPO₂ = oxygen saturation; TNF- α = tumor necrosis factor-alpha.

parameters without normal distribution were expressed as median (25–75%) and comparison between two groups were made using Mann–Whitney U test for independent samples and Wilcoxon-signed rank test for dependent samples. Pearson's chi-square test was used for analysing the cross tables. Direction and strength of the relationship between the variables were determined by Pearson correlation test. The statistical significance level was set at $p < 0.05$.

Results

Comparison of baseline characteristics, circulating levels of proinflammatory markers, and neurohormones between cystic fibrosis patients and healthy children is given in Table 1. There was no significant difference between the groups in terms of weight and height ($p > 0.05$). The mean body mass index and mean z-scores of weight and body mass index were significantly lower in cystic fibrosis patients ($p = 0.046$, $p = 0.008$, $p = 0.020$ respectively). No significant difference was observed in blood pressure and heart rate between the two groups. Cystic fibrosis children had lower oxygen saturation compared to healthy children (respectively $93.5 \pm 2.7\%$ versus $98.8 \pm 3.3\%$, $p = 0.001$). Proinflammatory mediator levels were higher in cystic fibrosis patients compared to healthy children; however; significant difference was only present in levels of interleukin-6 and C-reactive protein ($p = 0.029$ and $p = 0.001$, respectively). Among neurohormonal levels, renin, and aldosterone were significantly higher in cystic fibrosis patients ($p = 0.001$ for both). There was no significant difference in angiotensin-II level between the two groups.

All patients had their genetic mutations analysed. Twelve patients had the major mutation of cystic fibrosis, F508del; five homozygous and eight was combined with another cystic

Table 2. Anatomical and functional echocardiographic measurements of left and right ventricles

	Cystic fibrosis	Healthy children	<i>p</i>
LV anatomical measurements			
IVSD (mm)	6.56 ± 1.15	6.87 ± 1.04	0.363
EDD (mm)	38.5 ± 4.77	42.8 ± 5.65	0.011
PWD (mm)	6.30 ± 1.01	6.87 ± 0.97	0.072
ESD (mm)	23.68 ± 3.68	26.33 ± 3.9	0.038
LVM (g/m ²)	61.75 ± 12.79	79.01 ± 29.16	0.452
EDV (ml/m ²)	89.49 ± 36.08	108.93 ± 44.08	0.176
ESV (ml/m ²)	34.77 ± 15.59	39.12 ± 18.41	0.471
LV functional measurements			
EF (%)	68.42 ± 5.49	69.09 ± 5.46	0.704
FS (%)	37.60 ± 4.49	38.64 ± 4.59	0.475
MAPSE (cm)	1.43 ± 0.33	1.78 ± 0.64	0.003
E (m/s)	0.87 ± 0.11	0.86 ± 0.24	0.787
A (m/s)	0.53 ± 0.15	0.51 ± 0.11	0.653
*E/A	1.55 (1.39–1.79)	1.71 (1.53–2.03)	0.426
MVDT (ms)	145 ± 38	171.57 ± 57	0.100
e' (cm/s)	17.21 ± 2.95	16.62 ± 3.41	0.578
a' (cm/s)	8.10 ± 2.13	6.98 ± 1.25	0.072
e'/a'	2.22 ± 0.56	2.47 ± 0.73	0.260
s' (cm/s)	9.10 ± 1.99	10.67 ± 2.07	0.027
E/e'	5.26 ± 1.15	5.24 ± 1.74	0.963
IVCT (ms)	58.57 ± 17.97	51.71 ± 10.74	0.141
IVRT (ms)	53.7 ± 13.0	52.1 ± 12.0	0.931
RV anatomical measurements			
Length (mm)	47.26 ± 13	50.85 ± 10	0.326
EDBD (mm)	31.3 ± 4.35	28.9 ± 4.31	0.079
EDMCD (mm)	26.85 ± 2.9	26.3 ± 4.03	0.610
EDA (cm ²)	21.64 ± 10.36	16.33 ± 4.68	0.039
ESA (cm ²)	14.40 ± 12.67	7.79 ± 2.95	0.025
RV functional measurements			
TAPSE (cm)	1.56 ± 0.33	1.94 ± 0.32	0.001
EF (%)	51.56 ± 9.52	59.25 ± 10.93	0.050
FAC (%)	74 ± 67	45 ± 30	0.149
E (m/s)	0.75 ± 0.15	0.70 ± 0.12	0.305
A (m/s)	0.49 ± 0.10	0.45 ± 0.09	0.139
*E/A	1.46 (1.37–1.65)	1.52 (1.36–1.83)	0.522
TR velocity (m/s)	1.31 ± 0.52	1.24 ± 0.42	0.700
e' (cm/s)	13.90 ± 3.73	15.07 ± 3.19	0.302
a' (cm/s)	8.62 ± 2.68	9.97 ± 3.25	0.150
s' (cm/s)	10.36 ± 1.67	11.99 ± 1.77	0.004
E/e'	5.61 ± 1.42	4.75 ± 0.60	0.015
e'/a'	1.69 ± 0.45	1.62 ± 0.52	0.652

(Continued)

Table 2. (Continued)

	Cystic fibrosis	Healthy children	<i>p</i>
IVCT (ms)	56.09 ± 14.62	52.71 ± 13.43	0.440
IVRT (ms)	49.7 ± 20.3	55.1 ± 19.9	0.388

*median (25–75%). Others are expressed as mean ± standard deviation.

A = mitral valve peak late diastolic velocity; a' = peak mitral valve annular late diastolic velocity; e' = peak mitral valve annular early diastolic velocity; E = mitral valve peak early diastolic velocity; EDD = end-diastolic diameter; EF = ejection fraction; ESD = end-systolic diameter; EDV = end-diastolic volume; ESV = end-systolic diameter; FS = fractional shortening; IVSD = interventricular septum diameter; IVCT = isovolumic contraction time; IVRT = isovolumic relaxation time; LVM = left ventricle mass; MAPSE = mitral annular plane systolic excursion; MPI = myocardial performance index; MVDT = mitral valve deceleration time; PWD = posterior wall diameter; s' = peak mitral valve annular systolic velocity.

fibrosis-causing variant. One patient had a mutation related with congenital bilateral absence of vas deferens and two had mutations classified as cystic fibrosis transmembrane conductance regulator-related disease. All were using pancreatic enzyme supplement and 95% were using Dornase-alfa. The mean number of hospitalisations due to pulmonary exacerbations from birth to date of the study was 4 and 6 in patients with F508del homozygous and heterozygous mutations, respectively.

Table 2 shows the comparison of anatomical and functional echocardiographic measurements of both the left and right ventricles between cystic fibrosis and healthy children. The patients group had significantly lower left ventricular end-diastolic diameter and left ventricular end-systolic diameter than the controls ($p = 0.011$, $p = 0.038$, respectively). Mitral annular plane systolic excursion was significantly different between the two groups: 1.43 ± 0.33 cm in children with cystic fibrosis and 1.78 ± 0.64 cm in healthy children ($p = 0.003$). Peak systolic myocardial velocity (s') was significantly lower in children with cystic fibrosis (9.10 ± 1.99 cm/s in children with cystic fibrosis and 10.67 ± 2.07 cm/s in healthy children, $p = 0.027$). There was no significant difference in other measurements obtained for left ventricular anatomy and function. End-diastolic and systolic areas of the right ventricle were significantly larger in cystic fibrosis patients than in the controls ($p = 0.039$, $p = 0.025$ respectively) and right ventricular ejection fraction was significantly lower in children with cystic fibrosis ($p = 0.050$). Peak systolic myocardial velocity (s') was significantly lower in the patients group ($p = 0.004$). The ratio of tricuspid valve peak early diastolic velocity to peak early diastolic myocardial velocity (E/e'), which is a parameter to estimate diastolic function, was significantly higher in children with cystic fibrosis than in healthy children ($p = 0.015$). Compared to the healthy group, tricuspid annular plane systolic excursion was found to be significantly lower in cystic fibrosis patients ($p = 0.001$). In the patient group, mean tricuspid annular plane systolic excursion was 1.51 ± 0.27 cm in 5–9 years of age, 1.44 ± 0.32 cm in 10–13 years of age, and 1.70 ± 0.37 cm in 14–18 years of age. Tricuspid regurgitation velocity used to estimate the pulmonary artery pressure was measured in all cystic fibrosis patients ($n = 21$), however, failed to be obtained in all of the control patients ($n = 12$). Although higher in cystic fibrosis patients than that of healthy subjects, there was not a significant statistical difference (1.31 ± 0.52 m/s in cystic fibrosis patients, 1.24 ± 0.42 m/s in healthy children, $p = 0.700$). The other measurements obtained for right ventricular anatomy and function were similar between the two groups ($p = >0.05$).

A correlation analysis of echocardiographic measurements of the right and left ventricles with oxygen saturation,

proinflammatory markers, and neurohormones was performed. Oxygen saturation correlated negatively with diastolic basal diameter and E/e' of the right ventricle whereas it had positive correlation with the left ventricular end-diastolic diameter, end-systolic diameter, and mitral annular plane systolic excursion. Interleukin-1 had no significant correlation with right ventricular measurements; however, it correlated negatively with the mitral annular plane systolic excursion. Interleukin-6 correlated negatively with right ventricular length and left ventricular posterior wall diameter. The tumour necrosis factor- α correlated negatively with the left ventricular end-systolic diameter and positively with E/e' while C-reactive protein correlated positively with right ventricle diastolic basal diameter and negatively with tricuspid annular plane systolic excursion and tricuspid annular peak systolic velocity (s'). Angiotensin II had a negative correlation with mitral annular peak systolic velocity and aldosterone showed negative correlation with left ventricular e'/a' . Finally, high-sensitive C-reactive protein and renin showed no correlation with any of the measurements.

Discussion

In this study, we have found significant abnormalities in both anatomy and function of the left and right ventricles. In addition, there were important correlations between several echocardiographic findings and hypoxia, proinflammatory markers, or neurohormones.

Our cystic fibrosis patients had significantly lower body mass index and z-scores of body mass index and weight compared to healthy children. Anthropometric measurements in pediatric cystic fibrosis patients in previous studies were variable.^{4,5,11–14} Our results were similar to the study of Boguszewski et al.¹⁵ In correlation analysis, tumour necrosis factor- α was found to be negatively correlating with weight and body mass index whereas C-reactive protein behaved similarly with body mass index. Several studies have demonstrated that these molecules have catabolic effects both directly and indirectly on muscle and fat tissues and they are associated with cachexia.¹⁶ Elborn et al.¹⁷ also reported a similar relationship between tumour necrosis factor- α and cachexia in cystic fibrosis patients. We found that patients that had body mass index z-scores below -2 had higher interleukin-1, interleukin-6, tumour necrosis factor- α , and C-reactive protein levels. It is thought that the lower weight and body mass index z-scores in our patients group are due to cachexia caused by the continuous inflammation without any apparent exacerbation. Our results were similar to previous reports in which there was no significant difference in terms of blood pressure and heart rate between the groups.^{4,18}

Regarding the anatomy of ventricles, their function in cystic fibrosis patients was relatively less studied. Most studies focussed on either the left or the right ventricle function and showed ventricular dysfunction to a certain degree using conventional or tissue doppler echocardiography. Eising et al.⁴ and Özçelik et al.⁵ showed both diastolic and systolic right ventricular dysfunction in paediatric cystic fibrosis patients, however, failed to show any difference in terms of left ventricular function.^{4,5} Ghaderian et al.⁶ and Kızılca et al.⁸ showed systolic and diastolic dysfunction of the right and left ventricles respectively, however, did not study the counterpart ventricle.^{6,8} Few studies involving adult patients, on the other hand, managed to show both systolic and diastolic left and right ventricular dysfunction.^{14,19}

Among the parameters used to assess right ventricular diastolic function, only E/e' was significantly higher in our patient group. Although not significant, the difference in other parameters regarding right ventricular function between the groups implies that right ventricular functions were slightly affected. Given the young age of our patients, even though there was significant difference only in one but not yet all parameters, suggests that right ventricular diastolic dysfunction started in early ages, but the damage has not developed to the extent seen in adult patients.

Among the parameters to assess the systolic function of right ventricle peak tricuspid valve annular systolic velocity (s'), tricuspid annular plane systolic excursion and ejection fraction in our patient group were significantly lower than that of the healthy group. Our results of tricuspid annular plane systolic excursion and peak tricuspid valve annular systolic velocity (s') were similar to the findings of other reports in which tricuspid annular plane systolic excursion and s' were significantly lower in cystic fibrosis children and adolescents.^{4–7} In addition, our results of tricuspid annular plane systolic excursion were found to be lower than that of previous reports and published normal values.^{4,7,20} Peak tricuspid valve annular systolic velocity (s') in our study was similar to that of the study of Eising et al.⁴ but lower than normal published values.^{4,21} Mean right ventricular ejection fraction of cystic fibrosis patients in the current study was significantly lower compared to healthy children. Considering that ejection fraction between 41–55% indicates mild dysfunction, together with lower tricuspid annular plane systolic excursion and s' values, we can conclude that systolic functions of right ventricle were also impaired. There are studies in the literature suggesting that right ventricular systolic dysfunction could develop as a result of pulmonary hypertension, chronic hypoxia, chronic inflammation, or neurohormonal changes.^{14,22–25} Diagnosis of pulmonary hypertension depends on the severity of the disease as well as methods used for diagnosis.^{26,27} Right heart catheterisation is the gold-standard method for the accurate measurement of pulmonary hypertension however echocardiographic measurements of tricuspid regurgitation velocity, pulmonary regurgitation velocity, and interventricular septum positioning is also a practicable way to have an estimation of it. Instead of an invasive procedure, we preferred to measure tricuspid regurgitation velocity with echocardiography for proper estimation of pulmonary artery pressure where its elevation would indicate pulmonary hypertension.²⁸ Although tricuspid regurgitation velocity was higher in cystic fibrosis patients, the difference was not significant. We failed to detect an evident pulmonary hypertension in any of our patients. An explanation may be that all our patients were young with mild cystic fibrosis and were clinically stable during the measurements without any exacerbations. It was argued in previous studies that patients without pulmonary hypertension might have increased pulmonary artery pressure which could lead to right ventricular dysfunction.²⁹ Higher E/e' values in our patients suggest that they had higher right ventricular filling pressure. Although insignificant, higher tricuspid regurgitation velocity combined with significantly higher E/e' values in patient's group might suggest subtle changes in right atrial pressure and pulmonary artery pressure. These changes have not yet affected measurements of tricuspid regurgitation velocity but might have caused right ventricular dysfunction.

Similar to the previous reports in which tissue Doppler and pulsed wave Doppler imaging was used, we failed to show left ventricular diastolic dysfunction in cystic fibrosis patients. On the other hand, mitral annular plane systolic excursion and mitral

annular peak systolic velocity (s') were significantly different in the patient group from that of healthy children, indicating a left ventricular systolic dysfunction. Compared to published reference values, measurements of mitral annular plane systolic excursion in our patients were within normal range below 9 years of age but below normal as the age increases.²⁰ Mitral annular peak systolic velocity (s') correlates well with ejection fraction and has been shown to detect early deterioration of left ventricular systolic function in cases where ejection fraction was within normal range. In agreement with the present study, previous studies involving paediatric cystic fibrosis patients showed no difference in ejection fraction.^{8,30} Unlike Eising et. al⁴ and Kızılca et. al⁸, our patients had significantly lower mitral annular peak systolic velocity (s') compared to healthy children and to published normal values while their ejection fraction was normal.^{4,8,31} These findings suggest that left ventricular systolic dysfunction starts in early ages and becomes more pronounced as the disease progresses with age.

Increased right ventricular end-diastolic basal diameter, end-diastolic mid cavity diameter, and length are associated with right ventricular dilation and previous studies involving cystic fibrosis patients showed different degrees of enlargement in the right ventricle.^{7,24,32,33} In our study, both end-diastolic and end-systolic right ventricular areas were significantly larger in cystic fibrosis patients, however, although end-diastolic basal diameter, end-diastolic mid cavity diameter and length were larger, the difference was not statistically significant. Right ventricular morphology also influences left ventricular anatomy.³⁴ The studies involving left ventricular anatomy in cystic fibrosis patients showed controversial results. Eising et. Al⁴ reported that both controls and paediatric cystic fibrosis patients had similar left ventricular morphology.⁴ Although Kızılca et al⁸ had higher values for interventricular septum diameter, left ventricular posterior wall diameter, and left ventricular end-diastolic diameter in paediatric cystic fibrosis patients compared to healthy controls, the difference was not statistically significant.⁸ On the other hand, studies that involved adult patients showed significantly smaller dimensions of the left ventricle compared to controls.^{14,19} In our study, both left ventricular end-diastolic diameter and end-systolic diameter were significantly smaller in patients compared to controls. Our study showed that right ventricular diameters and areas increased whereas left ventricular diameter and volumes together with interventricular septum diameter decreased in cystic fibrosis patients.

To identify causes of both anatomical and functional abnormalities of the left and right ventricles in cystic fibrosis, we explored associations of hypoxia, proinflammatory markers, and neurohormones. In cystic fibrosis, hypoxia induces remodeling in pulmonary arterioles, leading to increased pulmonary artery pressure and pulmonary hypertension.³⁵ Significantly lower oxygen saturation of our cystic fibrosis patients showed that they have chronic hypoxia. Oxygen saturation negatively correlating with right ventricular end-diastolic basal diameter but positively correlating with left ventricular end-diastolic diameter and end-systolic diameter suggested that even without pulmonary hypertension, chronic hypoxia might have caused increased pulmonary artery pressure which leads to changes that induced right ventricular dilation and eventually smaller left ventricles. Not only hypoxia but also ongoing inflammation and activation of renin, angiotensin-II, and aldosterone system might have induced anatomical and functional changes in ventricles. A high aldosterone level causes activation of C-reactive protein and

interleukin-6, vascular inflammation, and endothelial dysfunction which eventually induces cardiac and pulmonary remodelling.^{36,37} In our study, the right ventricular end-diastolic basal diameter was found to be positively correlating with aldosterone and C-reactive protein, the right ventricular length did so negatively with interleukin-6 and the right ventricular end-diastolic area correlated negatively with aldosterone. High C-reactive protein probably leads to cardiac hypertrophy, fibrosis, oxidative stress, inflammation, and renin, angiotensin-II, and aldosterone system activation. The negative correlation of oxygen saturation with C-reactive protein, renin, and aldosterone in the current study supports the idea that these processes might activate each other and cause a vicious cycle that eventually creates cardiac and pulmonary remodelling leading to increased pulmonary artery pressure.³⁸ A positive correlation between tricuspid annular plane systolic excursion and oxygen saturation suggested that right ventricular systolic dysfunction occurred secondary to a possible increase in pulmonary artery pressure in cystic fibrosis patients. Besides, negative correlation of peak tricuspid valve annular systolic velocity and tricuspid annular plane systolic excursion with C-reactive protein suggested that even in clinically stable patients, continuous inflammation impairs right ventricular systolic functions. Left ventricular systolic dysfunction was also found to be associated with chronic hypoxia, ongoing inflammation, and cardiac remodelling since mitral annular plane systolic excursion positively correlates with oxygen saturation.

Our study showed that left ventricular diameter and volumes were measured significantly smaller in cystic fibrosis patients whereas their right ventricles were dilated. It is highly possible that a process starting with hypoxia, renin, angiotensin-II, aldosterone activation, and inflammation proceeds to increase pulmonary artery pressure which eventually leads to right ventricular changes in cystic fibrosis patients. Right ventricular dilation causes leftward septal bowing and compression of the left ventricle.

This research is subject to several limitations. Firstly, the sample size was small. The second limitation was that we did not use invasive tools for the measurements of pressures and evaluation of ventricular functions. No cardiac marker measurements were made to determine their association with echocardiographic measurements and inflammatory markers. However, none of our patients had any symptom or examination finding suggesting cardiac insufficiency.

In conclusion, although conventional echocardiographic imaging was not sufficient to fully reveal systolic and diastolic dysfunction in cystic fibrosis children, tissue doppler imaging, and detailed measurements in this present study managed to show significant functional changes and impairments. The probable causes of these changes are chronic hypoxia as well as high levels of inflammatory markers and neurohormones even in the clinically stable cystic fibrosis patients. Shown that cardiac damage starts early in childhood in cystic fibrosis patients and that these changes are only subclinical, imaging methods and tests for screening structural and functional impairments must be employed at the time of diagnosis and conducted at frequent intervals. We think that this study will contribute to the literature as there are very few studies in the literature evaluating anatomy and function of both the right and left ventricles and their association with inflammatory markers and neurohormones. Using new echocardiographic techniques like 3D imaging and strain might provide additional information. Further comprehensive studies are needed to decide on when and how to screen these patients and provide treatment options.

Acknowledgements. None.

Financial support. The study was funded by Eskisehir Osmangazi University Scientific Research Project Commission (Grant number [TTU-2021-1570]).

Competing interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Ethics Committee of Eskisehir Osmangazi University) Date 23.07.2020 / No. E-80558721-050.99-72001.

References

- Spahr JE, Love RB, Francois M, Radford K, Meyer KC. Lung transplantation for cystic fibrosis: current concepts and one center's experience. *J Cyst Fibros.* 2007; 6: 334–350.
- Lynch JP, Sayah DM, Belperio JA, Weigt SS. Lung transplantation for cystic fibrosis: results, indications, complications, and controversies. *Semin Respir Crit Care Med* 2015; 36: 299–320.
- Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update—a consensus report from the pulmonary scientific council of the international society for heart and lung transplantation. *J Heart Lung Transplant* 2006; 25: 745–755.
- Eising JB, van der Ent CK, Teske AJ, Vanderschuren MM, Uiterwaal C, Meijboom FJ. Young patients with cystic fibrosis demonstrate subtle alterations of the cardiovascular system. *J Cyst Fibros* 2018; 17: 643–649.
- 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: 159–164.
- Ghaderian M, Keivanfar M, Barani Beiranvand S, Reisi M. Cardiac involvement in mild cystic fibrosis lung involvement assessed by Tissue-Doppler echocardiography. *Int J Pediatr.* 2019; 7: 10205–10214.
- 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. *J Cyst Fibros* 2012; 11: 274–280.
- Kizilca O, Demircan T, Isik S, et al. Tissue doppler and speckle tracking echocardiography assessment of left ventricular function in children with cystic fibrosis. *Echocardiography* 2020; 37: 1634–1641.
- Bright-Thomas RJ, Webb AK. The heart in cystic fibrosis. *J R Soc Med.* 2002; 41: 2–10.
- Lopez L, Colan SD, Frommelt PC, 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: 465–95; quiz 576–7.
- Tham A, Katz TE, Sutherland RE, et al. Micronutrient intake in children with cystic fibrosis in Sydney. *Australia J Cyst Fibros* 2020; 19: 146–152.
- Marín VB, Velandia S, Hunter B, et al. Energy expenditure, nutrition status, and body composition in children with cystic fibrosis. *Nutrition* 2004; 20: 181–186.
- Stapleton D, Kerr D, Gurrin L, Sherriff J, Sly P. Height and weight fail to detect early signs of malnutrition in children with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2001; 33: 319–325.
- Ionescu AA, Ionescu AA, Payne N, Obieta-Fresnedo I, Fraser AG, Shale DJ. Subclinical right ventricular dysfunction in cystic fibrosis. a study using tissue Doppler echocardiography. *Am J Respir Crit Care Med* 2001; 163: 1212–1218.
- Boguszewski MC, Kamoi TO, Radominski RB, et al. Insulin-like growth factor-1, leptin, body composition, and clinical status interactions in children with cystic fibrosis. *Horm Res Paediatr* 2007; 67: 250–256.
- Webster JM, Kempen LJ, Hardy RS, Langen RC. Inflammation and skeletal muscle wasting during cachexia. *Front Physiol* 2020; 11: 597675.
- Elborn JS, Cordon SM, Western PJ, Macdonald IA, Shale DJ. Tumour necrosis factor-alpha, resting energy expenditure and cachexia in cystic fibrosis. *Clin Sci.* 1993; 85: 563–568.
- Poore S, Berry B, Eidson D, McKie KT, Harris RA. Evidence of vascular endothelial dysfunction in young patients with cystic fibrosis. *Chest* 2013; 143: 939–945.
- Dordevic A, Genger M, Schwarz C, et al. Batrial remodeling in patients with cystic fibrosis running title: atrial function in cystic fibrosis. *J Clin Med* 2019; 8: 1141.
- Keskin M, Kaya Ö., Yoldaş T, et al. Tricuspid annular plane systolic excursion and mitral annular plane systolic excursion cardiac reference values in 1300 healthy children: single-center results. *Echocardiography.* 2020; 37: 1251–1257.
- Koestenberger M, Nagel B, Ravekes W, et al. Reference values of tricuspid annular peak systolic velocity in healthy pediatric patients, calculation of z score, and comparison to tricuspid annular plane systolic excursion. *Am J Cardiol.* 2012; 109: 116–121.
- Tissot C, Singh Y, Sekarski N. Echocardiographic evaluation of ventricular function-for the neonatologist and pediatric intensivist. *Front Pediatr* 2012; 6: 79.
- Courtney JM, Ennis M, Elborn JS. Cytokines and inflammatory mediators in cystic fibrosis. *J Cyst Fibros.* 2004; 3: 223–231.
- Labombarda F, Pellissier A, Ellafi M, et al. Myocardial strain assessment in cystic fibrosis. *J Am Soc Echocardiogr.* 2011; 24: 1037–1045.
- 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: 1764–1769.
- Rovedder PME, Andrade FP, PdTR Dalcin. Pulmonary hypertension and pulmonary disorders in cystic fibrosis. *Cardiovasc pharmacol open acc Los Angeles* 2014; 4: 4–p.
- Tonelli AR. Pulmonary hypertension survival effects and treatment options in cystic fibrosis. *Curr Opin Pulm Med* 2018; 19: 652–661.
- Ratjen F. Pulmonary artery hypertension: an underrated disease manifestation in cystic fibrosis? *Lancet Resp Med* 2016; 4: 596–598.
- Shah PH, Lee JH, Salvi DJ, Rabbani R, Gavini DR, Hamid P. Cardiovascular system involvement in cystic fibrosis. *Cureus* 2021; 13: e16723.
- Giacchi V, Rotolo N, Amato B, et al. Heart involvement in children and adults with cystic fibrosis: correlation with pulmonary indexes and inflammation markers. *Heart Lung Circ* 2015; 24: 1002–1010.
- Koestenberger M, Nagel B, Ravekes W, et al. Reference values of the mitral annular peak systolic velocity (Sm) in 690 healthy pediatric patients, calculation of Z-score values, and comparison to the mitral annular plane systolic excursion (MAPSE). *Echocardiography* 2014; 31: 1122–1130.
- Jacobstein MD, Hirschfeld SS, Winnie G, Doershuk C, Liebman J. Ventricular interdependence in severe cystic fibrosis: a two-dimensional echocardiographic study. *Chest* 1981; 80: 399–404.
- Lester LA, Egge AC, Hubbard VS, Camerini-Otero CS, Fink RJ. Echocardiography in cystic fibrosis: a proposed scoring system. *J Pediatr.* 1980; 97: 742–748.
- Bornstein AB, Rao SS, Marwaha KL. Left ventricular hypertrophy. *StatPearls publishing.* <https://www.ncbi.nlm.nih.gov/books/NBK557534/>. Accessed 23 December 2021.
- Li D, Wang B, Wang H, Liu Q. Prognostic significance of pulmonary hypertension in patients with cystic fibrosis: a systematic review and meta-analysis. *Medicine (Baltimore)* 2018; 97: e9708.
- Brilla CG, Rupp H, Funck R, Maisch B. The renin-angiotensin-aldosterone system and myocardial collagen matrix remodelling in congestive heart failure. *Eur Heart J* 1995; 16: 107–109.
- Adams KF Jr. Pathophysiologic role of the renin-angiotensin-aldosterone and sympathetic nervous systems in heart failure. *Am J Health Syst Pharm* 2014; 61: S4–13.
- Nagai T, Anzai T, Kaneko H, et al. C-reactive protein overexpression exacerbates pressure overload-induced cardiac remodeling through enhanced inflammatory response. *Hypertension* 2011; 57: 208–215.