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ORIGINAL RESEARCH
Pediatric Cardiology

Evaluation of cardiac functions with atrial and ventricular myocardial strain analysis in children with cystic fibrosis

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ABSTRACT

Objective: Cystic fibrosis (CF) is a multisystem disease that primarily involves the respiratory and gastrointestinal systems. The cardiovascular system is a significant determinant of mortality and morbidity, with cardiovascular effects detectable from childhood. Our aim was to evaluate cardiac functions using myocardial strain analysis in children with cystic fibrosis.

Material and Methods: We evaluated 19 patients with CF and age- and sex-matched healthy controls, aged 5–18 years. Cardiac evaluations were conducted while patients were clinically stable, using M-mode, pulse wave, and speckle-tracking echocardiography.

Results: There was no significant difference in the conventional echocardiographic parameters, including interventricular septum diastolic diameter (IVSd), left ventricular end-diastolic diameter (LVEDD), left ventricular posterior wall diameter (LVPWd), left ventricular end-systolic diameter (LVESd), ejection fraction (EF), fractional shortening (FS), mitral annular plane systolic excursion (MAPSE), and mitral and tricuspid E and A velocities. However, right and left ventricular longitudinal strain and tricuspid annular plane systolic excursion (TAPSE) were significantly lower in the CF group compared to controls. Left ventricular end-systolic volume (LVESV) was higher in CF patients. No difference was detected in right atrial strain analysis.

Conclusion: Although conventional echocardiographic examinations showed similar results in children with cystic fibrosis and healthy controls, advanced echocardiographic examinations such as strain analysis revealed significant differences in both ventricles. These findings suggest that subclinical cardiac effects may be present in children with cystic fibrosis, underscoring the need for ongoing monitoring and further investigation.

Keywords: Cystic fibrosis; right atrium; strain echocardiography.

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Kistik fibrozisli çocuklarda atriyal ve ventriküler miyokardiyal strain analizi ile kardiyak fonksiyonların değerlendirilmesi

ÖZET

Amaç: Kistik fibrozis (KF), öncelikli olarak solunum ve gastrointestinal sistemleri etkileyen multisistemik bir hastalıktır. Kardiyovasküler sistem, çocukluk çağından itibaren tespit edilebilen etkileriyle mortalite ve morbiditenin önemli bir belirleyicisidir. Amacımız, kistik fibrozisli çocuklarda miyokardiyal strain analizi kullanarak kardiyak fonksiyonları değerlendirmekti.

Gereç ve Yöntemler: Yaşları 5–18 arasında değişen, KF'li 19 hasta ve yaş-cinsiyet uyumlu sağlıklı kontrol grubu değerlendirildi. Kardiyak değerlendirmeler, hastalar klinik olarak stabil durumdayken, M-modu, pulse wave ve speckle tracking ekokardiyografi kullanılarak yapıldı.

Bulgular: İnterventriküler septum diyastol çapı (IVSd), sol ventrikül diyastol çapı (LVEDD), sol ventrikül posterior duvar çapı (LVPWd), sol ventrikül sistol çapı (LVESd), ejeksiyon fraksiyonu (EF), fraksiyonel kısalma (FS), mitral annüler düzlem sistolik ekskürsiyonu (MAPSE) ve mitral ile triküspit E ve A dalga hızları gibi geleneksel ekokardiyografik parametrelerde anlamlı bir fark bulunmadı. Ancak, KF grubunda sağ ve sol ventrikül longitudinal strain değerleri ve triküspit annüler düzlem sistolik ekskürsiyonu (TAPSE) kontrol grubuna kıyasla anlamlı derecede düşüktü. KF hastalarında sol ventrikül sistol sonu hacmi (LVESV) daha yüksekti. Sağ atriyum strain analizinde bir fark tespit edilmedi.

Tartışma: Geleneksel ekokardiyografik incelemeler KF'li çocuklar ile sağlıklı kontroller arasında benzer sonuçlar gösterse de, strain analizi gibi ileri ekokardiyografik incelemeler her iki ventrikülde de önemli farklılıklar ortaya koymuştur. Bu bulgular, KF'li çocuklarda subklinik kardiyak etkilerin mevcut olabileceğini göstermekte ve düzenli takip ile daha ileri araştırmaların gerekliliğini vurgulamaktadır.

Anahtar Kelimeler: Kistik fibrozis; sağ atriyum; strain ekokardiyografi.

INTRODUCTION

Cystic fibrosis (CF) is a chronic disease primarily affecting the respiratory and gastrointestinal systems and leading to progressive organ dysfunction (1). Recent studies focus on the cardiovascular comorbidities of cystic fibrosis and show that fibrosis, particularly biventricular myocardial dysfunction, can occur (2). The cardiovascular system is one of the systems that determine mortality and morbidity in cystic fibrosis (3). Recent studies have shown that both systolic and diastolic functions of the heart are affected in childhood (4).

Autopsy studies and animal experiments have demonstrated cardiac effects related to CFTR mutations, including impacts on calcium metabolism in myocytes, inflammatory processes, chronic hypoxia, and neurohormonal effects (2, 5, 6). Cystic fibrosis has also been associated with an increased incidence of autoimmune diseases such as celiac disease, Crohn's disease, vasculitis, and arthritis, which could further affect myocardial function (7, 8). Echocardiographic studies have revealed myocardial dysfunction in CF patients, leading to the recognition of CF-related cardiomyopathy (6). In CF patients, the interventricular septum, posterior wall, and aorta were found to be thickened, the left ventricular ejection fraction was found to be low, and left ventricular dysfunction was associated with myocardial fibrosis (9).

Hypoxemia; in cases where there is significant right ventricular enlargement and interventricular septal motion abnormalities, is thought to indirectly influence diastolic dysfunction of the left ventricle (2). Studies evaluating cardiac functions in childhood have reported effects on both systolic and diastolic functions (2, 3, 5, 10–12). Most studies focus on the right ventricle, and there are fewer studies evaluating the left ventricle and atrium (5–10).

In this study, we aimed to evaluate both ventricular and right atrial strain using advanced echocardiographic examinations, in addition to conventional echocardiographic evaluations, and to compare these findings with those from healthy children.

MATERIAL AND METHODS

Study Subjects

This prospective study included nineteen children aged 5–18 years (9 females, 10 males) with a confirmed diagnosis of CF. These patients were recruited from our pediatric pulmonology and cardiology outpatient clinic between 2023 and 2024. Approval was obtained from the Eskişehir Osmangazi University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee with the decision number 2024-90. This study was conducted in accordance with the principles of the Declaration of Helsinki. All participants were clinically stable, with no history of respiratory exacerbation or positive throat or sputum culture. Clinically unstable patients or patients with pulmonary exacerbation or positive throat or sputum culture were excluded from the study. Age- and sex-matched 37 healthy children without any acute, chronic, or cardiac diseases were recruited from our pediatrics clinic. Weight, height, heart rate, systolic and diastolic blood pressure, and oxygen saturation were noted before the echocardiographic study was performed. Written informed consent was obtained from the parents. The study was approved by the local Clinical Research Ethics Committee (no: 2024-90).

Echocardiographic Study

All transthoracic echocardiographic evaluations were performed by the same expert pediatric cardiologist using a Philips Epiq7 (Philips Ultrasound; Bothell, WA, USA) device with

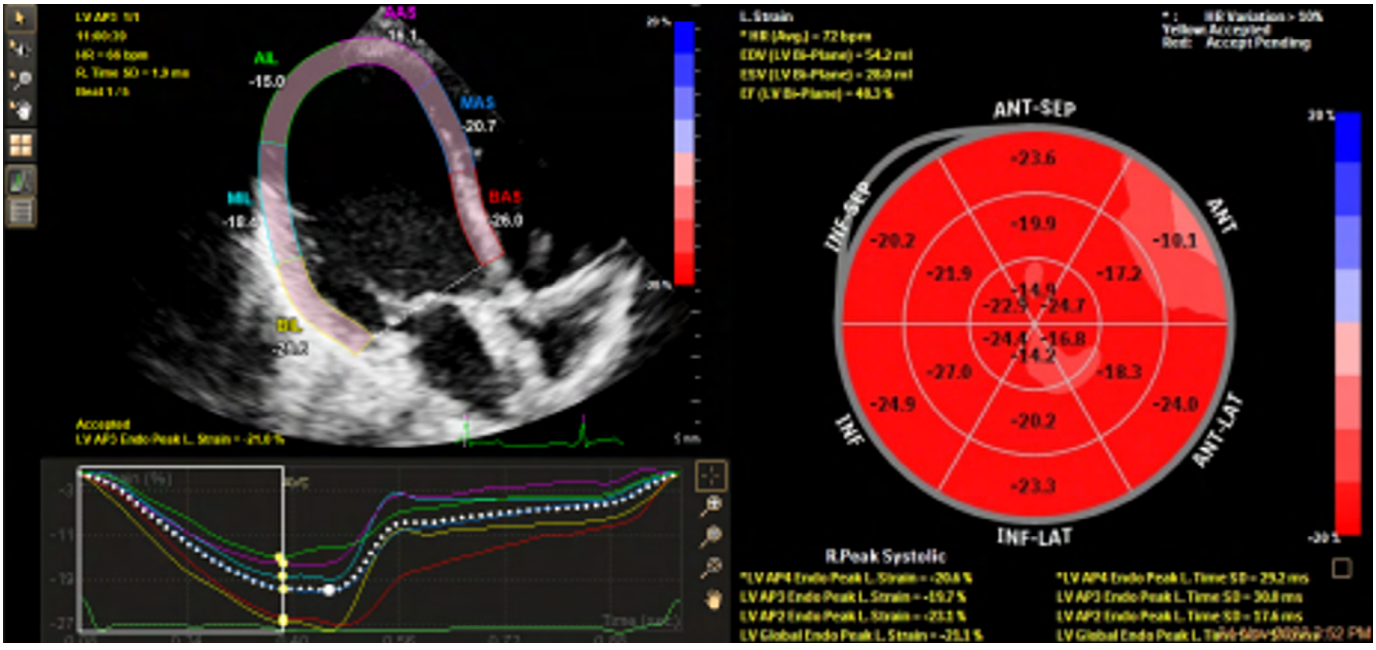

Figure 1. Left ventricul longitudinal strain analysis and bull's eye plot.

an X5 transducer and under continuous electrocardiographic monitoring. All measurements were performed at rest. The anatomy of the heart was evaluated by two-dimensional and M-mode echocardiography, whereas pulsed-wave Doppler was used to measure blood flow velocities as recommended by the American Society of Echocardiography (13). All measurements were performed over 3 consecutive cardiac cycles, and the means were calculated.

The M-mode echocardiography was performed in the parasternal short-axis view to measure interventricular septum diameter (IVSD), LV posterior wall diameter (LVPWD), LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), and ejection fraction (EF). Biventricular longitudinal systolic function was estimated in the apical 4-chamber view by mitral annular plane systolic excursion (MAPSE) for the LV and by tricuspid annular plane systolic excursion (TAPSE) for the RV. Two-dimensional echocardiography was performed to estimate LV end-diastolic volume/index (LVEDV/LVEDVi) and end-systolic volume/index (LVESV/LVESVi). We estimated the end-diastolic and systolic areas of the RV using apical 4-chamber echocardiography. The percentage of right ventricle fractional area change (FAC) was calculated as the difference between the end-diastolic area (EDA) and the end-systolic area (ESA) divided by EDA. To evaluate left and right 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 (13).

Strain evaluation was performed using a Philips Epiq7 device with simultaneous ECG at frame rates of 60–90 frames/s. Images were recorded in apical four-chamber (A4C), apical three-chamber (A3C), apical two-chamber (A2C), and parasternal short-axis views (apical, medial, basal). At least three consecutive cardiac cycles were recorded for each parameter. The recorded images were transferred and analyzed on the QLAB software (Philips Medical Systems).

The mitral annulus lateral and septal and the LV apical endocardial planes were marked for each of the three apical chambers, allowing the program to generate the LV wall automatically. The LV endocardial-myocardial border was adjusted manually on the systolic and diastolic frames. Peak systolic strain and global strain values were calculated automatically by the software for six segments based on septum and LV lateral wall motion (Fig. 1). In all three parasternal short-axis views, the endocardial-myocardial border was adjusted manually after the program had automatically generated the ventricular wall. Patients whose results were abnormal due to poor image quality were excluded from the study.

For right ventricular strain, the modified apical four-chamber view was analyzed automatically, but the images were edited manually during the study. For RA strain, auto LA strain was used and analyzed in the apical four-chamber view (QLAB version 15) (Fig. 2).

For strain analysis, intraobserver and interobserver reliability were assessed using a randomly selected sample of 15 patients. Intraobserver reliability was evaluated by comparing repeated measurements by the same observer, while interobserver reliability was determined by comparing measurements between two observers (AS, PK). High concordance was demonstrated, with intraclass correlation coefficients (ICC) of 0.92 and 0.90, respectively. Statistical significance was confirmed with a p-value of <0.05, affirming the reliability and consistency of the assessments.

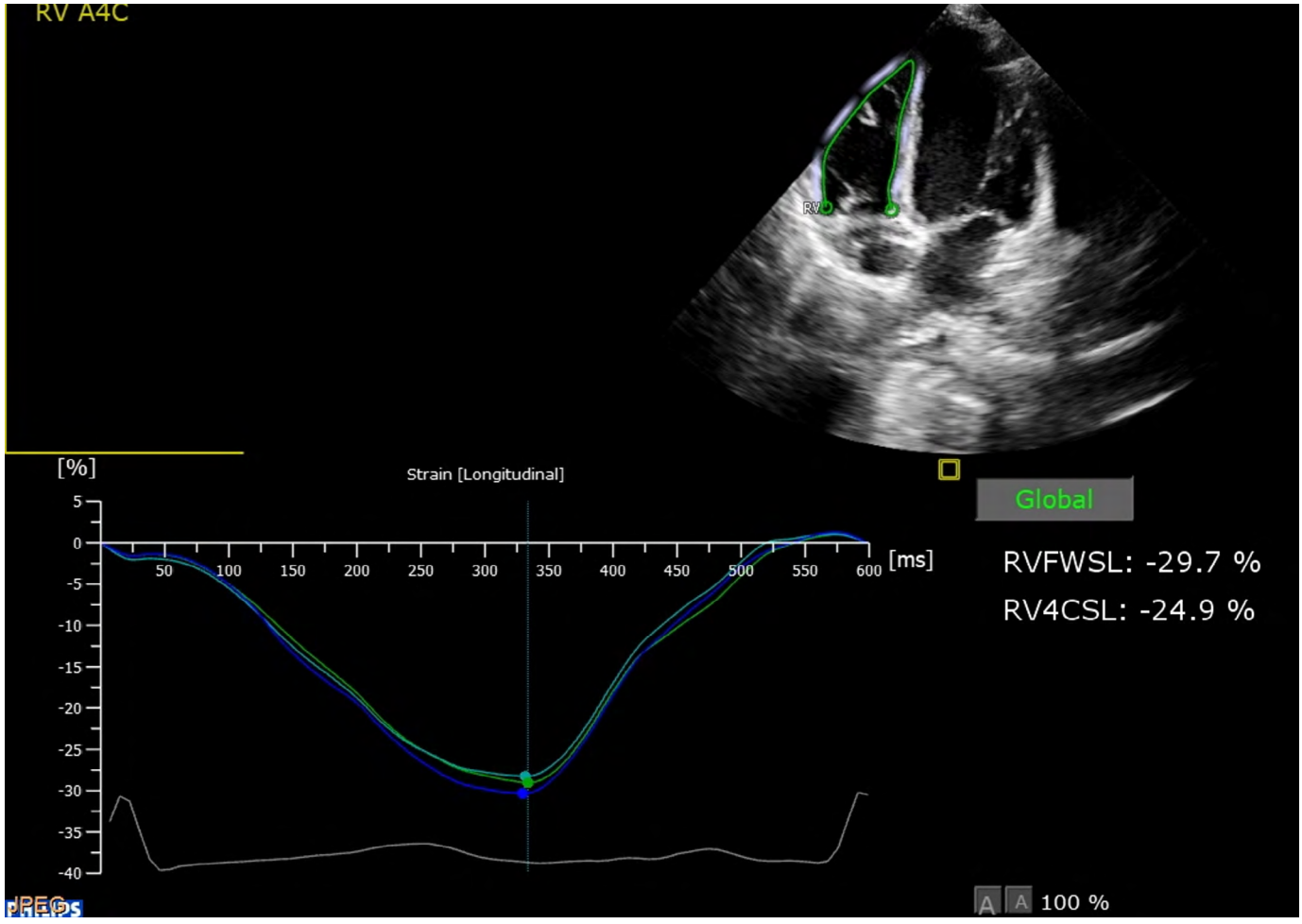

Figure 2. Right ventricul strain analysis.

The data were analyzed using the Statistical Package for Social Sciences, Version 21 (SPSS, Chicago, USA). The type of distribution was determined using the Kolmogorov-Smirnov test. Normally distributed data are presented as mean±standard deviation, and two groups were compared using the t-test, whereas parameters without normal distribution were expressed as median (25–75%) and comparisons between two groups were made using the Mann-Whitney U test for independent samples. Pearson's chi-square test was used for analyzing cross tables. The statistical significance level was set at $p<0.05$.

RESULTS

A total of 56 children were included in the study, comprising 19 with cystic fibrosis and 37 age- and sex-matched healthy controls. The cystic fibrosis group included 9 girls and 10 boys, with an average age of 136±42 months. Demographic data of the patient and control groups are presented in Table 1. Systolic blood pressure was significantly lower in the cystic fibrosis group compared to controls.

There were no significant differences in mitral and tricuspid E and A velocities or M-mode LV measurements (IVSd, LVEDd, LVPWd, LVESd, FS, MAPSE), which are conventional echocardiography

Table 1. Demographic data of patients and control group

	Cystic fibrosis	Control	p
Age (month)	136±42	118±32	0.077
Height (cm)*	138 (132–160)	137,5 (129–152,5)	0.339
Weight (kg)*	34 (22-45)	30 (22–44)	0.842
Gender			
Femail	9	21	0.514
Male	10	16	
Systolic blood pressure (mmHg)*	108 (101–109)	116 (110–120)	0.039
Diastolic blood pressure (mmHg)*	65 (60–74)	65 (60–70)	0.989
Heart rate (beat/min)	92±16	87±12	0.173

*: Median (interquartile range between 25th and 75th). Other results are given as mean (±standard deviation).

Table 2. Comparison of conventional echocardiography data in cystic fibrosis and healthy groups

	Cystic fibrosis	Control	p
Mitral E (cm/sn)	87.26±11.52	88.65±15.09	0.727
Mitral A (cm/sn)	54.37±9.29	53.15±10.49	0.671
MAPSE (mm)	13.3 (11.8–16.6)	12.3 (11.6–13.9)	0.132
Tricuspid E (cm/sn)	73.37±14.54	68.40±12.22	0.183
Tricuspid regurgitation velocity	1.29±0.55	1.29±0.42	0.243
Tricuspit A (cm/sn)	49.00±11.1	44.21±10.13	0.111
TAPSE (mm)	15.84±3.2	18.40±3.44	**0.09**
IVSd (mm)	6.49±1.08	6.58±1.1	0.773
LVEDd (mm)	38.79±4.95	39.91±4.75	0.420
LVPWd (mm)	6.38±1.02	6.39±0.92	0.956
LVESd (mm)	24.05±3.83	24.27±3.53	0.839
EF (%)	68.57±5.6	69.81±6.17	0.471
FS (%)	37.73±4.58	38.99±5.41	0.393
LVEDV (ml)*	85.6 (58.9–113)	66.7 (58.5–88.6)	0.150
LVEDV index (ml/m^2)	79.17±26.28	67.68±19.57	0.110
LVESV (ml)*	33.7 (19.5–43)	24.8 (17.9–28.7)	**0.025**
LVESV index (ml/m^2)	30.61±11.17	23.17±7.28	**0.015**
RV FAC (%)	43.4±8.32	43.2±9.12	0.944
PAAT (ms)	56.39±15.87	57.04±1771	0.902

*: Median (interquartile range between 25th and 75th). Other results are given as mean (±standard deviation); E: mitral early diastolic peak filling velocity; A: mitral late diastolic peak filling velocity; MAPSE: Mitral valve annular plane systolic movement; TAPSE: Tricuspid annular plane systolic excursion; IVSD: Interventricular septum diameter; LVEDD: Left ventricular end diastolic diameter; PWD: Posterior wall diameter; ESD: End-systolic diameter; LVEF: Left ventricular ejection fraction; FAC: Fractional area change; LVSF: Left ventricular fractional shortening; EDV: Left ventricular end-diastolic volume; ESV: End-systolic volume; RV FAC: Right ventricular fractional area change; PAAT: Pulmonary artery acceleration time.

parameters. Left ventricular ejection fraction (EF), LVEDV, and RV FAC measured by Simpson's method were comparable between the CF and control groups. However, TAPSE was significantly lower, and LVESV was significantly higher in the CF group than in the control group. While the LVEDV index was similar between the healthy and patient groups, the LVESV index was higher in the CF group (Table 2).

Strain analysis revealed that right ventricular free wall strain and 4-chamber strain were significantly lower in the CF group compared to controls. Left ventricular longitudinal strain was also reduced compared to controls across the 3-chamber, 4-chamber, 2-chamber, and global longitudinal strain. Circumferential strain was significantly lower in the midventricular region in the CF group compared to controls. No significant differences were detected in basal, apical, or global circumferential strain measurements. Right atrial reservoir, conduit, and contraction strain measurements did not differ significantly from those of the control group (Table 3).

The relationship between strain parameters, tricuspid regurgitation velocity, and TAPSE and MAPSE is presented in Table 4. A mild positive correlation was found between tricuspid regurgitation velocity and both the left ventricular 2-chamber and global longitudinal strain. MAPSE showed a moderate positive correlation with all left ventricular strain measurements, while TAPSE was weakly correlated with RV4CS and all LV strain parameters.

DISCUSSION

In this study, although no significant difference was observed in children with cystic fibrosis compared to healthy children by conventional echocardiographic examination, lower values were observed in right ventricular and left ventricular strain analysis compared to healthy children. Right atrial strain was studied for the first time in pediatric patients with cystic fibrosis, and no difference was found compared to healthy children.

In our study, there were no statistically significant differences in age, height, and weight compared to healthy controls. The patients were evaluated when they were clinically stable. It is thought that the lack of a significant difference may be because the evaluations were not conducted during the pulmonary exacerbation period, all patients were in a clinically stable state, and their nutritional and metabolic follow-ups and treatments were carried out regularly. This may also be related to the milder gastrointestinal system involvement in our patients or its control with treatment. Similar results regarding anthropometric measurements have been reported in the literature, as well as studies in which the CF group had lower values (3, 11, 14–17).

Conventional echocardiographic measurements and mitral and tricuspid valve Doppler velocities were similar to those of the healthy group. Although our findings differ from the study conducted by Baño-Rodrigo et al. (12), which evaluated patients in a similar age group, they are consistent with several studies in the literature (3, 10, 11). Additionally, TAPSE was found to be lower than in healthy children, similar to findings in many studies (3, 5, 12, 18–20). While in our previous study, LVESV showed similar results to those of healthy children, in our current study, LVESV and LVESV index were higher than in healthy children (5). However, the age group in this study consisted of slightly older children. It is also thought that this might result from effects on systolic functions. While our findings differ from those of previous studies, they are supported by research showing effects on LV diameter and size in adults and animal models (2).

Right ventricular functions in children with cystic fibrosis have been studied relatively more frequently with conventional and tissue Doppler imaging (TDI), and effects have been demonstrated (3, 11, 12, 18). Strain evaluation has been performed less frequently, and different results have been reported. Eising et al. (3) reported no difference in LVGLS, RVGLS, and septum strain between CF patients and controls but found lower strain values in the CF group when accounting for weight, height, and FEV1. Ozçelik et al. (11) reported differences in RV strain. Gürel et al. (19) observed lower strain results in the adult cystic fibrosis

Table 3. Comparison of both ventricle and right atrial strain analysis results

	Cystic fibrosis	Control	p
RVFWS (%)	-25.54±5.82	-30.51±4.72	**0.001**
RV4CS (%)	-21.74±3.68	-26.49±3.65	**<0.001**
LV Longitudinal 3C (%)	-17.53±3.9	-21.71±2.58	**<0.001**
LV Longitudinal 4C (%)	-18.07±3.85	-22.21±2.74	**<0.001**
LV Longitudinal 2C (%)	-17.53±4.1	-22.46±3.08	**<0.001**
LV Longitudinal global (%)*	-18.4 (14.8–20.5)	-22.28 (20.7–23.7)	**<0.001**
LV Circumferential basal (%)	-21.86±5.06	-23.79±3.82	0.12
LV Circumferential medial (%)	-22.05±4.8	-24.71±3.79	**0.02**
LV Cirkumferansiyel apical (%)	-25.74±8.6	-26.47±6.11	0.718
LV Circumferential global (%)	-23.19±4.75	-24.94±3.11	0.105
RA reservoir (%)	-39.31±10.31	-38.60±6.72	0.761
RA conduit (%)	-27.06±7.94	-28.43±8.36	0.564
RA contraction (%)*	-11.65 (7–16.9)	-8.95 (5.4–15.15)	0.569

*: Median (25th and 75th interquartile range). Other results are given as mean (±standard deviation). RV FWS: Right ventricular free wall strain; RV4Cs: Right ventricular 4 chamber strain; LV: Left ventricle; RA: Right atrium.

Table 4. Correlation analysis of strain parameters with TR velocity, TAPSE, and MAPSE

	TR velocity	p	MAPSE	p	TAPSE	p
RVFWS (%)	-0.003	0.986	0.233	0.090	0.213	0.122
RV4CS (%)	-0.040	0.806	0.230	0.095	0.277*	**0.043**
LV Longitudinal 3C (%)	0.272	0.082	0.508**	**<0.0001**	0.362**	**0.007**
LV Longitudinal 4C (%)	0.196	0.214	0.423**	**0.001**	0.305*	**0.024**
LV Longitudinal 2C (%)	0.366*	**0.017**	0.496**	**<0.0001**	0.318*	**0.018**
LV Longitudinal Global (%)	0.356*	**0.019**	0.570**	**<0.0001**	0.386**	**0.003**
LV Circumferential basal (%)	0.383*	**0.013**	0.108	0.437	0.220	0.110
LV Circumferential medial (%)	0.098	0.543	0.226	0.1	0.356**	**0.008**
LV Cirkumferansiyel apical (%)	0.196	0.220	-0.065	0.638	0.020	0.885
LV Longitudinal global (%)	0.256	0.102	0.071	0.06	0.215	0.115

RV FWS: Right ventricular free wall strain; RV4Cs: Right ventricular 4 chamber strain; LV: Left ventricle; MAPSE: Mitral annular plane systolic excursion; TAPSE: tricuspid annular plane systolic excursion; TR: Tricuspid regurgitation.

group with bronchiectasis compared to non-CF bronchiectasis and healthy controls. Similarly, Sciatti (18) and Labombarda (21) found reduced RV strain using TDI and speckle tracking in young adults. Our study's findings of significantly lower right ventricular strain in CF patients are in agreement with the literature.

Left ventricular strain analysis has been less frequently evaluated, with effects on LV strain primarily documented in adults (3, 21). Kizilca et al. (10) found no difference in LV global longitudinal strain among children but observed significantly lower strain values in several segments compared to healthy controls. Similarly, various studies using TDI have demonstrated impacts on left ventricular systolic function (5, 10, 12).

Assessing right atrial strain in children with cystic fibrosis is crucial for the early detection of right atrial dysfunction, which may reflect increased pulmonary pressures and right ventricular overload, potentially leading to right heart failure. This evaluation provides insight into the cardiovascular complications associated with advanced pulmonary disease in cystic fibrosis. No studies were found evaluating right atrial strain in the childhood age group. Gürel et al. (19) found lower global RA strain values in adults with bronchiectasis compared to healthy controls. No other studies evaluating RA strain were found in the literature. The patient group included in the study conducted by Gürel et al. (19) is quite different from ours; it is thought that the

difference with our study can be explained by age and clinical presentation. Effects on atrial strain may develop over time.

In our study, correlation analysis revealed that tricuspid regurgitation velocity was weakly correlated with left ventricular strain parameters. However, no association was found with right ventricular strain. Moreover, our study did not include any patients being followed for pulmonary hypertension or with elevated TR velocity. Despite this, a positive correlation between TR velocity and LV strain parameters was detected. Although no similar studies were found, it can be speculated that LV strain may be affected due to LV-RV interaction.

MAPSE was positively correlated with all LV strain parameters, supporting the impact on LV strain. TAPSE was weakly correlated with both LV and RV strain parameters. TAPSE, a conventional measurement, was found to be lower than in healthy children and was correlated with strain parameters. It may serve as a valuable parameter in routine practice for children with cystic fibrosis.

Limitations

The study's limitations include the small sample size, single-center design, and the lack of left atrial strain assessment, cardiac magnetic resonance imaging, and invasive measurements such as pulmonary artery pressure. Despite these limitations, the study's strength lies in its inclusion of advanced echocardiographic techniques, such as atrial strain and right ventricular strain, which are rarely performed in pediatric CF patients.

As a result, although conventional echocardiographic measurements did not reveal significant differences in systolic and diastolic functions between children with cystic fibrosis and healthy controls, advanced echocardiographic examinations, such as strain imaging, detected effects in both ventricles compared to healthy children. TAPSE, a conventional measurement, was found to be lower than in healthy children and was correlated with strain parameters. It may serve as a valuable parameter in routine practice for children with cystic fibrosis. Subclinical effects can be demonstrated by including advanced echocardiographic methods in the follow-up of children with cystic fibrosis.

Ethics Committee Approval: The Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee granted approval for this study (date: 03.10.2024, number: 2024-90).

Authorship Contributions: Concept – AS, PK; Design – AS, PK, BU; Supervision – BU, KH; Fundings – BU, KH; Materials – ÖÖY, KH; Data collection and/or processing – AS, ÖÖY, PK; Analysis and/or interpretation – AS, PK, BU; Literature review – AS, ÖÖY, PK, BU, KH; Writing – AS, ÖÖY, PK; Critical review – BU, KH.

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Yazma Yardımı için Yapay Zeka Kullanımı: Beyan edilmedi.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastaların ailelerinden alınmıştır.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

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