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NONINVASIVE CARDIAC EVALUATION OF YOUNG PATIENT WITH CYSTIC FIBROSIS*

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SUMMARY: Küçükosmanoğlu O, Özbarlas N, Göçmen A, Özçelik U, Kiper N, Bilgiç A. (Chest Disease and Cardiology Units, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Noninvasive cardiac evaluation of young patients with cystic fibrosis. Turk J Pediatr 1998; 40: 571-578.

Cardiac involvement was evaluated by echocardiography in 26 young cystic fibrosis patients. The mean age was 48.4 months (range 3 months to 15 years). The findings were compared with 26 age-and sex-matched children without a history of cardiopulmonary complaints. All patients had normal values of left ventricular ejection fraction and fractional shortening. Interventricular septal and posterior left ventricular wall thicknesses were similar to control group but right ventricular free wall thickness was found greater than in the control group. Abnormal septal motion was documented in six patients. Right ventricular pre-ejection period to ventricular ejection time ratio was found over the upper limit of normal in two patients and there was a negative correlation with clinical Shwachman scores (r: –0,55). Left ventricular pre-ejection period to ventricular ejection time ratio was found over the upper limit of normal in five patients. For both mitral and tricuspid valves, the mean ratios of peak velocity during passive filling (E) phase of diastole to peak velocity during atrial contraction (A) phase were found significantly lower than in the control group ($p<0.05$). Early diastolic peak velocity was similar to that in the control group but late atrial peak velocity was higher in the patient group ($p<0.05$). Isovolumic relaxation time was found the same as in the control group. We conclude that cardiac changes in diastolic and systolic functions begin at very young ages in cystic fibrosis patients. *Key words: cardiac involvement, cystic fibrosis, echocardiography.*

Cystic fibrosis is the most common lethal inherited disease among Caucasians, with an incidence of 1:2500[1]. It is a multisystem disorder with lung involvement as the major cause of mortality and morbidity[2]. Cor pulmonale is a frequent terminal finding in patients with cystic fibrosis as a result of lung involvement.

Chronic cor pulmonale is defined by the World Health Organization[3] as "hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lung, except when these pulmonary alterations are the

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result of diseases that primarily affect the left side of the heart or of congenital heart disease*. Cor pulmonale has been demonstrated on autopsy in as many as 70 percent of children dying of cystic fibrosis[4]. Clinical recognition of cor pulmonale is often difficult because the usual signs may be a reflection of an underlying lung disease with or without cardiac failure. Neither electrocardiography nor radiography is a valuable method for diagnosis cor pulmonale in cystic fibrosis. Cardiac catheterization is an invasive procedure and cannot be done routinely. Echocardiography is a reliable, noninvasive technique that is useful in the diagnosis of cor pulmonale as well as many cardiac disorders.

The aim of the present study was to make an early determination of cor pulmonale and other cardiac dysfunction in a young group of cystic fibrosis patients and to detect a correlation between clinical status and cardiac functions.

Material and Methods

There were 29 cystic fibrosis patients (15 male, 14 female) ranging in age from three months to 15 years (mean 48.4 ± 8.6 months) in the study. Echocardiographic data were not suitable for analysis in three patients. Patients were studied during their clinically stable stage. Twenty-seven of them were outpatients; two were hospitalized, but were studied after clinical stabilization. None of the subjects were desaturated or took medications overnight. All subjects underwent count of whole blood cells, arterial pH and blood gases analysis, electrocardiography, chest x-ray radiographs and detailed echocardiographic study. All data were obtained in daytime within 24 hours. After physical examination patients were scored by Shwachman criteria[5]. Scores were determined by an investigator who was not aware of the results of the cardiac tests. In the control group, 26 age-and sex-matched children without a history of cardiopulmonary complaints underwent echocardiographic study.

Cardiac evaluation: Cardio-thoracic ratios of subjects were estimated in chest radiographs. Electrocardiographic measurements included QRS axis, amplitude of R wave and R/S ratio in V_1, and depth of S wave in V_6. Results above the upper limit of normal were accepted as evidence of right ventricular hypertrophy.

Echocardiographic studies of patients and control group were done by a blinded pediatric cardiologist using a Toshiba SSH-160A echocardiograph and 5, 3.75, 2.5 mHz transducers. Left ventricular end-diastolic and end-systolic diameters, interventricular wall thickness, posterior left ventricular wall thickness, left ventricular ejection fraction, left ventricular fractional shortening, right ventricular wall thickness, motion of interventricular septum, and left and right ventricular systolic time intervals were determined by m-mode echocardiography. Diastolic

diameters of right ventricular inflow tract, outflow tract, and right ventricular body were determined by two dimensional echocardiography[6]. Right and left ventricular diastolic filling patterns were determined by pulsed Doppler echocardiography. The examinations of mitral and tricuspid inflow were performed from the apical four chamber view, with the sample volume placed at the mitral valve and tricuspid valve annulus, respectively. Measurements included: early diastolic peak velocity (E), peak velocity during atrial contraction (A), the ratio of early-to-late time velocity (E/A) and isovolumic relaxation time.

Control group data were compared with cystic fibrosis group data by Student's t test. Cystic fibrosis group data were also compared to clinical variables by standard linear regression and correlation analysis.

Results

The Shwachman scores of patients were found excellent in seven, good in 12, moderate in six, and severe in one patient. All but one patient had hemoglobin levels more than 10 g/dl (9.7 g/dl). None of the patients had blood pH less than 7.35, paCO2 more than 45 mmHg and paO2 less than 50 mmHg.

Cardiac evaluation: Innocent murmur was heard in four patients. One patient had pansystolic murmur (ventricular septal defect was noted previously). Cyanosis was not seen in any patient. Heart rate was found significantly increased in cystic fibrosis group (mean 126 ± 5.9 vs 101 ± 2/min; $p<0.05$).

Electrocardiography showed right ventricular hypertrophy in eight patients. The evidence of right atrial dilatation (p wave greater than 2.5 mm) was not noted in any patient.

Chest radiographs showed mild cardiomegaly in two patients. Cardio-thoracic ratios were 9.57 and 0.56, respectively.

In echocardiographic examination, abnormal septal motion was documented in six patients. Five of them had flattened and one had reversed septal motion. All patients had normal values of left ventricular ejection fraction and fractional shortening (mean 65.9 ± 1.2% and 34.7 ± 0.9%, respectively), but these values were significantly less than control group values (mean 71.2 ± 1% and 39.8 ± 0.98%, respectively) ($p<0.05$). Interventricular septal wall and posterior left ventricular wall thicknesses were found similar to control group. However, thickness of right ventricular free wall was found significantly greater than in the control group (mean 5.38 ± 0.14 mm vs 4.35 ± 0.10 mm) ($p<0.05$) (Table I).

Right ventricular pre-ejection period to ventricular ejection time ratio was found over the upper limit of normal (0.30) in two patients. Left ventricular pre-ejection period to ventricular ejection time ratio was found over the upper limit of normal (0.40)[7] in five patients. Although mean values of both right and left ventricular

Table I: Results of M-Mode Echocardiographic Studies in Patients and Control Subjects

Measurement	Patient	Control	p Value
LVEF (%)	65.96 ± 1.2	71.2 ± 1.04	<0.05
LVFS (%)	34.77 ± 0.9	39.8 ± 0.98	<0.05
PLVWT (mm)	5.46 ± 0.15	5.7 ± 0.16	>0.05
IVSWT (mm)	5.42 ± 0.15	5.5 ± 0.16	>0.05
RVWT (mm)	5.38 ± 0.14	4.35 ± 0.1	<0.05
RV PEP/VET	0.23 ± 0.01	0.21 ± 0.06	>0.05
LV PEP/VET	0.33 ± 0.0014	0.31 ± 0.07	>0.05

LVEF: left ventricular ejection fraction, LVFS: left ventricular fractional shortening, PLVWT: posterior left ventricular wall thickness, IVSWT: interventricular septal wall thickness, RVWT: right ventricular wall thickness, RV PEP/VET: right ventricular pre-ejection period to ventricular ejection time ratio, LV PEP/VET: left ventricular pre-ejection to ventricular ejection time ratio.

pre-ejection period to ventricular ejection time ratios were found higher than in the control group, these differences were not significant (p>0.05) (Table I).

Diastolic measurement of right ventricular inflow tract, outflow tract and body values, which were determined by two dimensional echocardiography, were found similar to normal control group (Table II).

Right and left ventricular diastolic filling patterns were detected by pulsed Doppler echocardiography. For both mitral and tricuspid valves, the mean ratios of peak velocity filling during the passive filling phase of diastole to peak velocity during atrial contraction phase were found significantly lower than in the controls for both ventricles (p<0.05). Early diastolic peak velocity was similar to that in control group, but late atrial peak velocity was higher in cystic fibrosis patient (p<0.05).

Table II: Right Ventricular Diastolic Diameters of Patients and Control Subjects (mean ± SD)

Measurement	Patient	Control	p Value
RVIT (mm)	23.9 ± 0.1	24.2 ± 0.13	>0.05
RVOT (mm)	20.7 ± 0.9	21.2 ± 0.7	>0.05
Long Axis (mm)	37.5 ± 1.3	36.5 ± 0.9	>0.05
Short Axis (mm)	22.2 ± 1.07	22.3 ± 0.5	>0.05

RVIT: right ventricular inflow tract, RVOT: right ventricular outflow tract.

Table III: Right and Left Ventricular Diastolic Filling Parameters by Pulsed Doppler Echocardiography in Patients and Normal Control Subjects (mean ± SD)

Measurement	Patient	Control	p Value
Mitral E(m/s)	0.56 ± 0.04	0.54 ± 0.02	>0.05
Mitral A(m/s)	0.37 ± 0.03	0.32 ± 0.03	<0.05
Tricuspid E(m/s)	0.52 ± 0.05	0.50 ± 0.04	>0.05
Tricuspid A(m/s)	0.36 ± 0.04	0.30 ± 0.02	<0.05
Mitral E/A	1.51 ± 0.04	1.66 ± 0.05	<0.05
Tricuspid E/A	1.43 ± 0.04	1.67 ± 0.05	<0.05
Mitral IVRT	45.6 ± 1.07	46.2 ± 0.55	>0.05
Tricuspid IVRT	47.46 ± 1.39	46.5 ± 0.72	>0.05

E: early diastolic peak velocity; A: peak velocity during atrial contraction; IVRT: isovolumic relaxation time.

Isovolumic relaxation time was found the same as in the control group (Table III).

The right ventricular pre-ejection period to ventricular ejection time ratio significantly increased as the Shwachman score decreased (r: –0.55). The left ventricle systolic time intervals, ejection fraction and fractional shortening did not correlate with clinical scores. Our echocardiographic studies showed that 20 patients had normal hearts; one had a structural heart disease (ventricular septal defect) and five had functional cardiac abnormalities (two of them had cor pulmonale due to cystic fibrosis). This information is summarized in Table IV.

Table IV: Patients with Abnormal Cardiac Functions

Patient	Age	Gender	Score	pH	pO2	pCO2	RV PEP/VET	LV PEP/VET
1	9.5	male	40	7.38	72.9	39.0	0.450*	0.500*
2	15	female	62	7.41	85.0	37.5	0.304*	0.409*
3.	1.5	female	80	7.40	75.0	31.3	0.290	0.400*
4	3.8	male	91	7.43	84.7	34.6	0.250	0.420*
5	4.4	male	93	7.35	60.8	37.7	0.170	0.430*

* Abnormal (over upper limit of normal).

Discussion

Patients with cystic fibrosis survive longer than before because of earlier diagnosis, better nutritional management and aggressive medical intervention. However, intractability of pulmonary disease and related cor pulmonale remains the major cause of morbidity and mortality. The diagnosis of cor pulmonale in cystic fibrosis patients by physical examination is often difficult. Noninvasive evaluation of cardiac function in cystic fibrosis patients using electrocardiography, vectorcardiography, radionuclide angiocardiography and echocardiography have been reported earlier[8,9]. In the present study, we evaluated the cardiac status of a young group of cystic fibrosis patients (mean age 48.4 ± 8.6 months) by noninvasive methods. Most of the patients (73%) had good or excellent clinical scores.

Electrocardiographic findings of patients that showed right ventricular hypertrophy had no correlation with echocardiographic study and clinical scores. Siassi et al[10]. Studied 34 cystic fibrosis patients by cardiac catheterization and did not find any correlation between electrocardiographic findings and cor pulmonale.

Chronic alveolar hypoxia and recurrent pulmonary infections are responsible for the pulmonary hypertension and resultant cor pulmonale seen in cystic fibrosis. Ryland and Reid[11], in their study of the heart and lungs in patients with cystic fibrosis, observed that those with severe lung disease did not always develop right ventricular hypertrophy. When right ventricular hypertrophy was present, however, it generally reflected the degree of abnormal structural remodeling of the pulmonary vascular bed. An increase in the muscularity of small veins was also observed. As an evidence of cor pulmonale, right ventricular pre-ejection period to ventricular ejection time ratio was found abnormally elevated in two patients, and one of them also had reversed septal motion. The only parameter that was found to correlate with clinical scores was the ratio of right ventricular pre-ejection period to ventricular ejection time. Because the left ventricular pre-ejection period to ventricular ejection time ratio was found abnormally elevated in five patients, we suggested that the left ventricle was affected at the same time as the right ventricle. Left ventricular involvement may be related to right ventricular dysfunction, chronic hypoxia, hypercapnia, reduced coronary blood flow due to increased right atrial pressure and viral or bacterial infections.

Doppler echocardiographic measurements of left and right ventricular diastolic filling patterns demonstrated a significantly lower E to A peak velocity ratio and a greater atrial filling fraction than in control subjects. Johnson et al.[12] studied left ventricular diastolic filling in 25 cystic fibrosis patients with a mean age of sixteen and noted a lower E/A ratio and greater A velocity. In the present study, we showed that changes in diastolic functions begin at very young ages in cystic

fibrosis patients. We cannot say that all our patients had abnormal diastolic functions because there is no reported accurate data about diastolic functions of normal subjects. We compared the results of the cystic fibrosis group to the normal group and found that diastolic functions of the patient group were different from those of the normal group. In cystic fibrosis, pulmonary blood flow and left atrial pressure are decreased because of impaired right ventricular performance and increased pulmonary resistance. As a result, left ventricular preload also diminishes. At the same time, afterload augmentation has also been seen as a result of hypoxemia-induced vasoconstriction. These changes in preload and afterload may lead to an increase in A velocity. Right ventricular pressure and volume overload can cause flattening or reversion of interventricular septal movement and also influence diastolic filling of left ventricle. On the other hand, shortening of diastole due to increased heart rate can also be related to increased A velocity and decreased E/A ratio.

Early detection of cor pulmonale and analysis of all these parameters in young patients with cystic fibrosis may provide some useful information for management of the disease. Among the echocardiographic abnormalities detected in our cystic fibrosis patients, elevation in the right ventricular pre-ejection period to ventricular ejection time ratio seems to be the most important one clinically as it shows the presence of cor pulmonale. As these patients do not benefit from any mode of medical treatment, they are candidates for heart-lung or lung transplantation[13]. Other abnormalities detected in echocardiography (elevations in left ventricular pre-ejection period to ventricular ejection time ratio, abnormal septal motion, changes in diastolic filling patterns) show that cardiac involvement has already commenced. Further follow-up studies will be required to show whether the results of the present study have any prognostic significance.

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