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Assessment of Cardiac Functions in Infants with Cow's Milk Allergy

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Study Design A
Data Collection B
Statistical Analysis C
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Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 **İbrahim Ece**
ABCD 2 **Kaan Demirören**
CDE 3 **Nihat Demir**
EFG 1 **Abdurrahman Uner**
EFG 4 **Sevket Balli**

1 Department of Pediatric Cardiology, Yuzuncu Yil University, Faculty of Medicine, Van, Turkey
2 Department of Pediatric Gastroenterology, Yuzuncu Yil University, Faculty of Medicine, Van, Turkey
3 Department of Pediatrics, Yuzuncu Yil University, Faculty of Medicine, Van, Turkey
4 Department of Pediatric Cardiology, Balikesir Atatürk Hospital, Balikesir, Turkey

Corresponding Author: İbrahim Ece, e-mail: dribrahimECE@gmail.com

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Background: Cow's milk allergy is the most common food allergy in children, with rates estimated at 1.9% to 4.9%. Clinical phenotypes of cow's milk allergy are varied and involve 1 or more target organs, with the main targets being the skin, respiratory system, and gastrointestinal tract. To date, no studies have investigated detailed cardiac function in children with cow's milk allergy. The current study aimed to investigate cardiac function in infants with cow's milk allergy.





Material/Methods: We studied 42 infants with cow's milk allergy and 30 age- and sex-matched healthy subjects. Cardiac functions were evaluated by M-mode, pulsed-wave, and tissue Doppler echocardiography.

Results: There were no significant differences in ejection fraction or mitral and tricuspid annular plane systolic excursion between the 2 groups. Pulsed-wave Doppler-derived E/A ratios in mitral and tricuspid valves were similar in both groups. Ea/Aa ratios in the left ventricle posterior wall and right ventricle free wall were lower in patients with cow's milk allergy than in the control group. The E/Ea ratio in the left ventricle, isovolumic relaxation time, deceleration time, and right and left ventricular myocardial performance indices were higher in patients in the study group.

Conclusions: Our study identified reduced early diastolic tissue Doppler velocities in infants with cow's milk allergy.

MeSH Keywords: **Allergy and Immunology • Echocardiography • Heart Function Tests**

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Background

Cow's milk allergy (CMA) is the most common food allergy in early childhood [1]. The World Allergy Organization [2] estimated that 1.9% to 4.9% of children have CMA. CMA may be immunoglobulin E-(IgE) or non-IgE-mediated. Non-IgE-mediated disorders usually involve T cells. CMA can manifest as a number of different clinical presentations, mainly affecting the skin, gastro-intestinal tract, and respiratory systems [3]. Certain symptoms, such as angioedema or wheezing (immediate reactions), may suggest an IgE-mediated process, whereas gastro-intestinal symptoms (delayed reactions) most likely indicate a non-IgE-mediated process [4]. There are no validated tests for the diagnosis of non-IgE CMA, apart from the planned avoidance of cow's milk and cow's milk-containing foods, followed by reintroduction as a home challenge to confirm the diagnosis [5]. Tissue Doppler echocardiography (TDE) has not been investigated sufficiently to date with respect to evaluation of ventricular function in patients with CMA. Therefore, the aim of the study was to assess cardiac functions in patients with CMA without clinically evident cardiovascular disease, by using conventional and tissue Doppler echocardiography.

Material and Methods

Patient population

The study was performed in the pediatric cardiology unit, Yuzuncu Yil University, Faculty of Medicine, Van, Turkey. The study group was infants followed in the pediatric gastroenterology unit with a diagnosis of CMA and showing gastrointestinal symptoms. Our study included 42 infants with CMA (the study group) and 30 age- and sex-matched healthy subjects with innocent murmur (the control group). The infants included to the study were subjected to full history-taking, and complete physical examination was performed by the same physician. Body height and weight, heart rate, and blood pressure of all infants were recorded.

Infants with structural and functional cardiac abnormality, pulmonary and systemic hypertension, anemia, moderate or severe persistent asthma according to GINA report [6], or with any other systemic disorders and comorbid diseases (e.g., upper or lower respiratory infection) were excluded. All infants with CMA had chronic diarrhea. According to the results of laboratory tests, including complete blood count, routine biochemical tests, stool examination, tissue transglutaminase immunoglobulin A, lactose intolerance, bacterial or viral intestinal infection, or celiac disease were excluded. The diagnosis of CMA was confirmed with elimination-challenge testing method, as previously described, by a single experienced pediatric gastroenterologist [2]. Echocardiographic examinations were

performed before initiation of the cow's milk-free diet. Cases without proven diagnosis of CMA by the challenge test or unresponsiveness to cow's milk diet were excluded from the study. This study was approved by the local ethics committee. All parents gave informed consent for participation in the study.

Echocardiography

Transthoracic echocardiography was performed by a single experienced pediatric cardiologist. An electrocardiogram was simultaneously recorded in all subjects. The patients were studied without sedation while they were lying quietly in the supine and left lateral positions. Assessments were performed using the General Electric Medical Systems ViVid 6 dimension echocardiography device with a 6-MHz probe (GE Vingmed Ultrasound AS, Horten, Norway). A complete echocardiographic study was performed using standard views and techniques. All measurements were performed using the recommendations of the American Society of Echocardiography [7]. Imaging windows obtained from the parasternal long axis and the apical 4-chamber view were used. The measurements of at least 3 cardiac consecutive cycles were averaged in sinus rhythm. All echocardiographic assessments were digitally recorded (DVD-CD) to enable later investigation. The analyses were performed using a commercially available computer software program (Echopac 2008; GE Vingmed).

End-diastolic and end-systolic dimensions of the left ventricle (LV) and anterior wall thickness were measured by M-mode at the parasternal long axis. Fractional shortening (FS) (%) and ejection fraction (EF) (%) measurements were obtained on the echocardiography. Mitral annular plane systolic excursion (MAPSE) and tricuspid annular plane systolic excursion (TAPSE) were measured in millimeters, as previously described [8,9]. Peak systolic velocities were evaluated by pulsed wave Doppler. Peak systolic velocity waveforms from the ascending aorta were obtained from the 5-chamber view. Peak systolic velocity waveforms from the pulmonary artery were obtained from the short axis view. Pulmonary artery pressures were obtained by systolic transtricuspid gradient [10]. All pulmonary artery pressures were within normal limits.

Mitral and tricuspid filling velocities were recorded from the apical 4-chamber view with the pulse-wave Doppler sample volume placed at the tip of its leaflets during diastole. The peak velocity during early diastole (E), peak velocity during late diastole (A), and deceleration time (DT) of the early diastolic velocity were used as both ventricular diastolic function parameters. The ratios of E to A were calculated for mitral and tricuspid valves [11].

Right ventricle (RV) and LV functions were also evaluated using TDE. For optimal records, Nyquist limits were adjusted to

Table 1. Some features of patient and control groups.

	Patient group (n=42)	Control group (n=30)	p value
Age at diagnosis, months	10.8±5.3	11.2±4.6	>0.05
Gender, male/female	25/17	18/12	>0.05
Body weight, kg	9.1±1.5	9.5±1.3	>0.05
Body height/cm	73.4±6.2	75.1±4.4	>0.05
Heart rate, beat/minute	128.6±7.5	124.8±6.4	>0.05
Systolic blood pressure, mmHg	88.3±5.9	90.2 ±6.3	>0.05
Diastolic blood pressure, mmHg	52.6±4.6	53.2±4.8	>0.05

Data were expressed as mean ± standard deviation.

Table 2. Basic echocardiographic findings of the groups.

	Patient group (n=42)	Control group (n=30)	p value
LVEDD, mm	22.2±4.6	23.4±3.8	>0.05
IVSTD, mm	4.2±1.4	4.3±1.5	>0.05
PWTD, mm	3.8±1.3	3.9±1.3	>0.05
Left ventricle ejection fraction, %	74.2±8.5	75.6±9.2	>0.05
Left ventricular fractional shortening, %	42.6±4.2	43.2±4.5	>0.05
Aortic velocity, cm/s	105.3±10.3	102.7±10.2	>0.05
MAPSE, mm	15.1±3.2	14.9±3.0	>0.05
Pulmonary artery velocity, cm/s	100.3±11.4	99.6±8.6	>0.05
RV wall thickness, mm	3.3±1.3	3.2±1.2	>0.05
RVEDD, mm	14.2±2.4	14.4±2.3	>0.05
TAPSE, mm	14.84±4.21	15.14±3.82	>0.05

Data were expressed as mean ± standard deviation. IVSTD – interventricular septum thickness in diastole; LVEDD – left ventricular end-diastolic diameter; MAPSE – mitral annular plane systolic excursion; PWTD – posterior wall thickness in diastole; RV – right ventricular; RVEDD – right ventricular end-diastolic diameter; TAPSE – tricuspid annular plane systolic excursion.

15–20 cm/s, sample volume to 2–5 mm, and monitor velocity to 100 mm/s. TDE of mitral and tricuspid walls were performed at the level of mitral and tricuspid valve annuli in apical 4-chamber planes. Isovolumic relaxation time (IVRT) from the end of the S-wave to the beginning of Ea-wave and isovolumic contraction time (IVCT) from the end of the Aa wave to the beginning of the S-wave were measured. The ejection time (ET) was measured from the beginning to the end of the S-wave. Left and right ventricular myocardial performance index (MPI) combining systolic and diastolic time intervals was calculated as the sum of IVCT and IVRT divided by ET [12,13]. The resulting velocities were recorded for 3 cardiac cycles.

The mean values of the measurements were used for statistical analysis.

Statistical analysis

The statistical package SPSS version 11.5 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Descriptive statistics are presented as mean ±SD. Pearson and chi-square analyses were used to compare frequencies of findings. Independent samples t test was used to compare continuous variables in the CMA group and the control group. A p value <0.05 was considered statistically significant.

Table 3. Comparison of left ventricle echocardiographic findings of the groups.

	Patient group (n=42)	Control group (n=30)	p value
Mitral valve peak E velocity, cm/s	93.1±10.7	89.3±9.4	>0.05
Mitral valve peak A velocity, cm/s	82.3±9.8	80.5±8.7	>0.05
Mitral valve E/A	1.13±0.1	1.10 ±0.2	>0.05
Posterior wall peak Ea velocity, cm/s	11.4±2.3	14.4±3.0	<0.001
Posterior wall peak Aa velocity, cm/s	9.7±1.8	10.3±1.4	>0.05
Posterior wall peak Sa velocity, cm/s	9.9±1.3	9.8±1.2	>0.05
Posterior wall Ea/Aa	1.17±0.24	1.39±0.21	<0.001
Septal peak Ea velocity, cm/s	14.1±2.2	14.2±2.8	>0.05
Septal peak Aa velocity, cm/s	8.5±1.8	8.5±1.4	>0.05
Septal peak Sa velocity, cm/s	8.4±1.7	8.3±1.3	>0.05
Septal Ea/Aa	1.65±0.21	1.67±0.43	>0.05
Left ventricle E/Ea (average of septal, lateral)	7.30±0.52	6.24±0.48	<0.001
Isovolumic contraction time of mitral annulus, ms	40.3±5.9	39.6±6.1	>0.05
Isovolumic relaxation time of mitral annulus, ms	65.6±7.8	53.6±6.4	<0.001
Ejection time of mitral annulus, ms	220.2±38.8	223.3±34.5	>0.05
Deceleration time, ms	138.2±33.8	118.8±25.6	<0.01
MPI	0.48±0.06	0.41±0.02	<0.001

Data were expressed as mean ± standard deviation. MPI – myocardial performance index.

Table 4. Comparison of right ventricle echocardiographic findings of the groups.

	Patient group (n=42)	Control group (n=30)	p value
Tricuspid peak E velocity, cm/s	80.21±9.72	81.31±10.14	>0.05
Tricuspid peak A velocity, cm/s	69.14±7.81	72.59±8.32	>0.05
Tricuspid valve E/A	1.16±0.18	1.12±0.42	>0.05
Tricuspid anulus peak Ea velocity, cm/s	14.76±1.6	11.32±1.8	<0.001
Tricuspid anulus peak Aa velocity, cm/s	13.18±2.4	8.57±2.1	<0.001
Tricuspid anulus Ea/Aa	1.11±0.12	1.32±0.18	<0.001
Tricuspid anulus peak systolic velocity Sa, cm/s	10.51±1.6	10.41±1.9	>0.05
Isovolumic contraction time of tricuspid annulus, ms	39.82±6.41	41.24±6.84	>0.05
Isovolumic relaxation time of tricuspid annulus, ms	78.42±10.5	58.36±9.72	<0.001
Ejection time of tricuspid annulus, ms	251.57±18.3	242.92±20.8	>0.05
MPI	0.47±0.01	0.41±0.02	<0.001

Data were expressed as mean ± standard deviation. MPI – myocardial performance index.

Results

The present study enrolled 42 infants with CMA (25 boys and 17 girls) and 30 healthy controls. Patients were diagnosed at a mean age of 10.8 ± 5.3 months. No difference was found for age, sex, body height and weight, systemic systolic and diastolic blood pressure, heart rate, ventricular dimensions, or wall thickness between patients with CMA and the controls. Demographic and echocardiographic characteristics of the patients and healthy controls are listed in Tables 1 and 2.

Conventional pulsed Doppler indices of both ventricles, such as E, A, and ratio of E to A, did not show significant differences between patients with CMA and healthy controls ($p > 0.05$). No significant differences were found in the indices of ventricular systolic function (EF, tissue Doppler S wave velocity, MAPSE or TAPSE) between the 2 groups ($p > 0.05$). There was no significant difference in term of IVCT in either group. Right and left ventricular MPI were higher in patients with CMA than in the control group due to prolongation of IVRT. LV E/Ea ratio and DT were higher in patients with CMA. The tricuspid free wall Ea/Aa and LV posterior wall Ea/Aa ratio were lower in the study group. Conventional pulsed Doppler and tissue Doppler echocardiographic parameters are listed in Tables 3 and 4.

Discussion

Our literature review led us to conclude that this is the first study to investigate ventricular systolic and diastolic function in patients with CMA without clinically evident cardiovascular disease, by using conventional and tissue Doppler echocardiography. We found that conventional echocardiographic parameters of patients with CMA were similar to those of healthy controls. Right and left ventricular dimensions, wall thickness, and systolic functions were similar. However, we detected diastolic dysfunction in infants with CMA by using TDE. LV posterior wall Ea/Aa and tricuspid Ea/Aa ratios were significantly lower and mean ratio of E/Ea and DT of LV were significantly higher in the study group. In addition, average IVRT and MPI of the right and left ventricle in patients with CMA were significantly greater than in healthy controls.

CMA results from an immunological reaction to 1 or more milk proteins. The pathogenesis of non-IgE-mediated reactions is supported by different theories: reactions mediated by Th1 cells, interactions between T lymphocytes, and mast cells and neurons that alter the function of the smooth muscle and intestinal motility [14]. In infants with CMA, diastolic impairments are unclear, but may be explained by the hypothesis that abnormal intestinal permeability in patients with CMA is due to increased systemic absorption of various luminal antigens or infectious agents that may cause myocardial damage through immune-mediated mechanisms [15]. Consequently, myocardial injury may

be secondary to an immune response directed against an antigen present in both the myocardium and the small intestine.

In a study [16] performed in patients with celiac disease – a disorder involving intestinal absorption abnormalities – TDE showed a significant increase in LV IVRT and MPI parameters in the patients. They suggested that TDE is better to use in identifying subclinical early-stage cardiac changes in patients with celiac disease. In another study [17], subclinical systolic dysfunction of the LV was determined in children with celiac disease using TDE. Some theories have been proposed to explain the development of cardiomyopathy – specifically, that intestinal malabsorption leads to increased intestinal absorption of antigens and infectious agents, and activate immune mechanisms causing damage to the small intestine and myocardium [16–18].

This study is the first to assess the MPI of both ventricles using TDE in children with CMA. MPI is a useful clinical index of global ventricular function for evaluating both systolic and diastolic function [19]. Because of prolonged IVRT, increased MPI suggests ventricular diastolic dysfunction [20,21]. Therefore, in our study, subclinical diastolic dysfunction was found using diastolic myocardial velocities and TDE-derived MPI in infants with CMA. The increase of MPI was due to the prolonged IVRT of both ventricles.

Left ventricular diastolic dysfunction has been recognized as an important primary cause of heart failure [22,23]. The early diastolic velocity of the mitral valve annulus (Ea) reflects the rate of myocardial relaxation. When combined with measurement of the early transmitral flow velocity (E), the resultant ratio (E/Ea) correlates well with mean left ventricular diastolic pressure. E/Ea was introduced by Nagueh et al. [24] for noninvasive assessment of filling pressure. The E/A ratio is affected by preload alteration, but the E/Ea ratio is not affected. E/Ea has been shown to be a clinically useful index in various studies [24–28]. In our study, the mean ratio of E/Ea of LV was significantly higher in the study group.

Conclusions

To our best knowledge, this is the first study conducted to evaluate cardiac functions using TDE in infants with CMA. This study showed that although the clinical and conventional echocardiographic findings of infants with CMA were apparently normal, TDE examination showed subclinical left and right ventricle dysfunction. Diastolic impairments are unclear, but myocardial injury may be secondary to an immune response directed against an antigen present in both the myocardium and the small intestine. Although CMA in children is a benign and self-limited condition, cardiac involvement in CMA suggests that early diagnosis and treatment is important. There

is a need for further observational TDE studies demonstrating ventricular function in infants with CMA.

Study limitations

Firstly, the small sample size of each group poses a limitation; thus, our results should be verified by more comprehensive

studies. Secondly, we detected diastolic dysfunction in infants with CMA using by TDE, but we did not study the same group of patients in a second echocardiographic study after the resolution of CMA to demonstrate the normalization of those echocardiographic parameters.

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