Cardiology in the Young

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Diastolic dysfunction in patients with brucellosis despite the absence of infective endocarditis

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Abstract

Background: Brucellosis is an important systemic infectious disease, especially in developing countries. Every organ and system of the human body can be affected; however, cardiovascular complications of brucellosis are rare. *Aim:* To assess cardiac functions in patients with acute brucellosis without overt cardiac involvement and to answer the following question: Is there any cardiac dysfunction despite the absence of endocarditis in these patients? *Methods:* This cross-sectional study included 67 children with brucellosis and 40 healthy children. We performed a detailed echocardiographic examination in individuals at the beginning of the treatment. Patients with infective endocarditis were excluded from the study. *Results:* Echocardiography revealed no difference of ejection fraction, mitral and tricuspid annular plane systolic excursion, pulsed-wave Doppler-derived early diastolic peak velocity (E)/late diastolic peak velocity (A) ratios in mitral and tricuspid valves between the two groups. The deceleration time of early mitral inflow was longer in patients with brucellosis. Early diastolic peak velocity of the mitral and tricuspid annuluses obtained by tissue Doppler imaging (Ea) was significantly lower in children with brucellosis. The peak velocity obtained by tissue Doppler imaging during late diastole (Aa), Ea and Ea/Aa ratios in the interventricular septum, left ventricle posterior wall and right ventricle free wall was lower in patients with brucellosis than in the control group. The E/Ea ratio, isovolumic relaxation time, right ventricle and left ventricle myocardial performance indices were higher in patients with brucellosis. *Conclusion:* Patients with acute brucellosis may have diastolic dysfunction without overt cardiac involvement and infective endocarditis.

Introduction

Brucellosis is an important systemic infectious disease, especially in developing countries, and is still highly endemic and causes high morbidity in Turkey.[1] It may involve any organ system and can lead to several complications. Numerous publications indicated that cardiovascular complications, e.g., endocarditis, myocarditis and pericarditis occur in less than 2% of brucellosis patients, so the cardiovascular complications are rare in children.[2,3] To date, no studies have investigated detailed cardiac functions in children with brucellosis. Therefore, the study aimed to assess the cardiac functions in patients with acute brucellosis without overt cardiac involvement using conventional and tissue Doppler echocardiography.

Materials and methods

Patient population

The study was performed in the Paediatric cardiology unit, Yuzuncu Yil University, Faculty of Medicine, Van, Turkey. The study group included children diagnosed with brucellosis in the Paediatric infectious unit. Sixty-seven children with brucellosis and 40 age- and sex-matched healthy patients with an innocent murmur were included as a control group. A full history was recorded, and a complete physical examination was performed by the same physician. Bodyweight, heart rate, blood pressure and electrocardiogram of all children were recorded.

Children with the structural and functional cardiac abnormality, pulmonary and systemic hypertension, anaemia, moderate or severe malnutrition, any other systemic disorders, and comorbid diseases, such as upper or lower respiratory infection, were excluded. The diagnosis was established by a positive Brucella Wright and Coombs tube agglutination tests, and/or isolation Brucella species from the blood. Echocardiographic examinations were performed before given the antibiotic therapy. This study was approved by the local ethics committee. All parents gave informed consent for participation in the study.

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Echocardiography

Transthoracic echocardiography was performed by a single experienced Paediatric cardiologist. An electrocardiogram was simultaneously recorded for all patients. 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, a 6-MHz probe (GE Vingmed Ultrasound AS, Horten, Norway). A complete echocardiographic study was performed using standard views and techniques. All measurements followed the recommendations of the American Society of Echocardiography.[4] Imaging windows obtained from the parasternal long axis and the apical four-chamber were used. The measurements of at least three cardiac consecutive cycles were averaged in sinus rhythm. All echocardiographic assessments were digitally recorded 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 and anterior wall thickness were measured by M-mode at the parasternal long axis. Fractional shortening (%) and ejection fraction (%) measurements were obtained on the echocardiography. Mitral annular plane systolic excursion and tricuspid annular plane systolic excursion were measured in millimetres as previously described.[5,6] Peak systolic velocities were evaluated by pulsed-wave Doppler. Peak systolic velocity waveforms from the ascending aorta were obtained from the five-chamber view. Peak systolic velocity waveforms from the pulmonary artery were obtained from the short axis view. Pulmonary artery pressures were obtained by the systolic transtricuspid gradient.[7] All pulmonary artery pressures were within normal limits.

Mitral and tricuspid filling velocities were recorded from the apical four-chamber view with the pulsed-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 of the early diastolic velocity were used as both ventricular diastolic function parameters. The E/A ratios were calculated for mitral and tricuspid valves.[8]

Right and left ventricle functions were also evaluated using tissue Doppler imagination. For optimal records, Nyquist limits were adjusted to 15–20 cm/s, sample volume to 2– 5 mm and monitor velocity to 100 mm/s. Tissue Doppler imagination of mitral and tricuspid valves were performed at the level of the valve annuli in apical four-chamber planes. Isovolumic relaxation time from the end of the peak systolic velocity (S-wave) to the beginning of Ea-wave and isovolumic contraction time from the end of the Aa-wave to the beginning of the S-wave were measured. The ejection time was measured from the beginning to the end of the S-wave. Left and right ventricular myocardial performance index combining systolic and diastolic time intervals were calculated as the sum of isovolumic contraction time and isovolumic relaxation time divided by ejection time.[9,10] The resulting velocities were recorded for three cardiac cycles. The mean values of the measurements were used for statistical analysis.

Statistical analysis

The Statistical Package for the Social Sciences, Version 21 (SPSS Inc., Chicago, IL, United States of America) was used for data analysis. Descriptive statistics are presented as mean ± standard deviation. Pearson's and chi-square analyses were used to compare frequencies of findings. Independent samples Student's t-test was used to compare continuous variables in the patient group and the control group. A p-value <0.05 was considered statistically significant.

Table 1. Basic demographic, clinical and laboratory features of patient and control group

	Patient group (n = 67)	Control group (n = 40)	p-value
Age (years)	10.5 ± 3.7	11.2 ± 4.6	0.91
Gender, male/female	35/32	22/18	0.68
Body weight, kg	28.7 ± 8.7	29.1 ± 6.8	0.72
Heart rate, beat/minute	95.7 ± 8.5	88.3 ± 6.4	0.03
Systolic blood pressure, mmHg	103.6 ± 6.9	101.8 ± 8.9	0.65
Diastolic blood pressure, mmHg	62.3 ± 5.6	61.6 ± 5.8	0.69
White blood cell count (x10^9 µL)	7.3 ± 2.2		
Haemoglobin (g/dL)	12.4 ± 1.4		
Platelet count (10^3 µL)	284.6 ± 94.6		
Sedimentation rate (mm/hr)	19.7 ± 13.5		
C-reactive protein (mg/dL)	18.4 ± 23.5		

Data were expressed as mean ± standard deviation.

Results

The present study included 67 children with brucellosis (35 boys and 32 girls) and 40 healthy controls. No difference was found for age, gender, body weight, systemic systolic and diastolic blood pressure, ventricular dimensions and wall thickness between patients with brucellosis and the controls. No significant differences were found in the indices of ventricular systolic function between the two groups ($p > 0.05$). Heart rate was higher in the patient group. Electrocardiogram was normal for all patients. Demographic and basic echocardiographic characteristics of the patients and healthy controls are listed in Tables 1 and 2.

Conventional pulsed Doppler indices of both ventricles did not show significant differences between patients with brucellosis and healthy controls ($p > 0.05$). There was no significant difference in terms of isovolumic contraction time in both groups. Right and left ventricular myocardial performance indices were higher in patients with brucellosis than in the control group due to the prolongation of isovolumic relaxation time. Left ventricle E/Ea ratio and deceleration time were higher in patients with brucellosis. Left ventricle posterior wall Ea/Aa ratio was lower in the study group. Conventional pulsed Doppler and tissue Doppler echocardiographic parameters are listed in Tables 3 and 4.

Discussion

Brucellosis is a zoonotic infection with a high prevalence in Turkey. It has a wide range of clinical complications. Cardiovascular complications, such as endocarditis, myocarditis and pericarditis, are rarely seen.[1–3,11] Ours is the first study to investigate both ventricular systolic and diastolic function in children with brucellosis without endocarditis by tissue Doppler imaging.

We found that conventional echocardiographic parameters of patients with brucellosis were similar to those of control patients. However, we detected diastolic dysfunction in children with

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Table 2. M-mode and spectral Doppler echocardiographic findings of the groups

	Patient group (n = 7)	Control group (n = 40)	p-value
LVEDD, mm	37.2 ± 4.6	38.4 ± 3.8	0.51
IVSTD, mm	6.1 ± 1.4	5.9 ± 1.5	0.48
PWTD, mm	5.1 ± 1.3	5.2 ± 1.3	0.45
Left ventricle ejection fraction, %	72.2 ± 8.5	70.6 ± 9.2	0.36
Left ventricular fractional shortening, %	41.6 ± 3.5	40.2 ± 4.3	0.42
Aortic velocity, cm/s	102.3 ± 9.3	101.7 ± 10.4	0.52
MAPSE, mm	18.1 ± 3.2	17.9 ± 3.0	0.43
Pulmonary artery velocity, cm/s	101.2 ± 10.6	102.6 ± 9.3	0.51
RV wall thickness, mm	5.3 ± 1.2	5.2 ± 1.6	0.66
RVEDD, mm	19.8 ± 2.6	20.6 ± 2.8	0.52
TAPSE, mm	16.8 ± 4.2	17.1 ± 3.7	0.72

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.

Table 3. Comparison of left ventricle pulsed-wave and tissue Doppler echocardiographic findings of the groups

	Patient group (n = 67)	Control group (n = 40)	p-value
Mitral valve peak E velocity, cm/s	86.7 ± 3.9	86.3 ± 9.4	0.84
Mitral valve peak A velocity, cm/s	53.4 ± 4.9	52.9 ± 8.7	0.72
Mitral valve E/A	1.62 ± 0.1	1.63 ± 0.2	0.48
Posterior wall peak Ea velocity, cm/s	12.1 ± 1.1	13.3 ± 3.0	0.006
Posterior wall peak Aa velocity, cm/s	8.4 ± 1.2	8.7 ± 1.4	0.38
Posterior wall peak Sa velocity, cm/s	9.4 ± 1.3	9.5 ± 1.2	0.88
Posterior wall Ea/Aa	1.44 ± 0.1	1.52 ± 0.21	0.03
Septal peak Ea velocity, cm/s	12.5 ± 2.5	13.1 ± 2.9	0.01
Septal peak Aa velocity, cm/s	8.4 ± 1.7	8.4 ± 1.5	0.77
Septal peak Sa velocity, cm/s	8.2 ± 1.6	8.3 ± 1.4	0.42
Septal Ea/Aa	1.48 ± 0.21	1.55 ± 0.41	0.03
Left ventricle E/Ea (average of septal, lateral)	7.04 ± 0.52	6.52 ± 0.48	0.006
Isovolumic contraction time of mitral annulus, ms	38.5 ± 1.5	38.6 ± 6.1	0.54
Isovolumic relaxation time of mitral annulus, ms	63.1 ± 4.4	53.6 ± 6.4	<0.001
Ejection time of mitral annulus, ms	220.9 ± 20.7	223.3 ± 34.5	0.36
Deceleration time, ms	126.5 ± 15.4	118.8 ± 25.6	0.04
MPI	0.46 ± 0.06	0.41 ± 0.02	0.002

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

Table 4. Comparison of right ventricle pulsed-wave and tissue Doppler echocardiographic findings of the groups

	Patient group (n = 67)	Control group (n = 40)	p-value
Tricuspid peak E velocity, cm/s	83.22 ± 9.72	86.85 ± 10.14	0.62
Tricuspid peak A velocity, cm/s	51.3 ± 7.81	53.9 ± 8.32	0.55
Tricuspid valve E/A	1.62 ± 0.18	1.61 ± 0.42	0.71
Tricuspid annulus peak Ea velocity, cm/s	12.2 ± 1.6	13.55 ± .1.8	0.006
Tricuspid annulus peak Aa velocity, cm/s	8.1 ± 2.4	8.1 ± 2.1	0.78
Tricuspid annulus Ea/Aa	1.51 ± 0.14	1.67 ± 0.16	0.003
Right ventricle E/Ea	6.82 ± 0.55	6.41 ± 0.61	0.005
Tricuspid annulus peak systolic velocity Sa, cm/s	10.4 ± 1.4	10.2 ± 1.7	0.48
Isovolumic contraction time of tricuspid annulus, ms	36.82 ± 6.41	36.24 ± 6.84	0.82
Isovolumic relaxation time of tricuspid annulus, ms	67.52 ± 9.5	55.26 ± 8.72	0.003
Ejection time of tricuspid annulus, ms	281.94 ± 18.3	277.27 ± 20.8	0.64
MPI	0.37 ± 0.05	0.33 ± 0.03	0.003

Data were expressed as mean ± standard deviation.
MPI = Myocardial performance index.

brucellosis using tissue Doppler imaging. No patient had pericarditis or endocarditis. Average isovolumic relaxation time and myocardial performance indices of both right and left ventricles in patients with brucellosis were significantly higher than in control patients. E/Ea is a clinically useful index for evaluating ventricular diastolic functions.[12–15] In our study, the mean of this ratio of both ventricles was significantly higher in patients with brucellosis.

The myocardial performance index is used to evaluate both systolic and diastolic ventricular functions.[16] Because of prolonged isovolumic relaxation time, increased myocardial performance index suggests ventricular diastolic dysfunction.[17,18] Therefore, in our study, subclinical diastolic dysfunction was found using diastolic myocardial velocities and tissue Doppler imaging-derived myocardial performance index in children with brucellosis. The increase of myocardial performance index was due to the prolonged isovolumic relaxation time of both ventricles.

Diastolic impairments are unclear, but the myocardial injury may be due to a direct effect of the microorganism, or by the local deposit of immune complexes.[19]

There was no consensus on the optimal type and duration of medical and interventional therapies in brucellosis. The choice of regimen and duration of antimicrobial therapy should be based on the presence of focal disease and underlying conditions. Although we did not found endocarditis in our patients, they received treatment for at least three months. We believe that brucellosis with diastolic cardiac dysfunction cannot be safely considered an uncomplicated form of the disease. There is a need for further extensive prospective studies on the treatment of cardiovascular features of this disease in the absence of concomitant endocarditis.

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Study limitations

First, the small sample size of each group poses a limitation; thus, our results should be verified by more comprehensive studies. Second, we detected diastolic dysfunction in infants with brucellosis using tissue Doppler imaging. However, we did not study the same group of patients after the resolution of the disease and evaluate treatment duration and clinical outcomes to demonstrate the normalisation of those echocardiographic parameters and have a conclusion regarding the prolongation of the treatment. Finally, the absence of performing cardiac MRI in this study is another limitation.

Conclusion

This study showed that despite apparently normal clinical and conventional echocardiographic findings, tissue Doppler imaging revealed subclinical diastolic dysfunction in children with brucellosis. We cannot exactly clarify that these changes are due to systemic infection and response to it or Brucella infection, but we are considering that these changes are probably due to Brucella infection. Tissue Doppler imaging may be useful, particularly for the identification of abnormalities of ventricular diastolic function in brucellosis. There is a need for further wider observational tissue Doppler and other imaging studies focusing on cardiac functions in children with brucellosis for more information about the disease and its cardiac effects.

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Authors' contributions. İ.E: Conception and study design, echocardiographic examination, analysis, writing the article; S.E: echocardiographic examination, data collection, statistics, language editing; G.İ.B: patient selection, clinical examination and management of patients; M.T: Literature research, data collection.

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Ethical approval. Ethical approval was obtained from the Institutional Ethical Committee. All procedures performed were in accordance with the ethical standards and with the 1964 Helsinki Declaration and its later amendments.

Informed consent. Informed written consent was obtained from parents of all individual patients included in the study.

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