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ORIGINAL ARTICLE

Cardiovascular Involvement in Behçet's Disease

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ABSTRACT

Objectives: This study aims to evaluate left and right ventricular functions at rest by pulsed-wave Doppler and tissue Doppler echocardiography methods in patients with Behçet's disease (BD) without overt cardiovascular disease, and compare with age and sex matched subjects.

Patients and methods: Fifty-four patients with BD (12 males, 42 females; mean age 35±8 years; range 18 to 51 years) without cardiovascular symptoms, and 36 age-matched controls (12 males, 24 females; mean age 33±5 years; range 18 to 47 years) were included. Cardiac functions were evaluated by conventional and tissue Doppler echocardiography.

Results: Although conventional indices of left ventricular systolic function were similar in both groups, mitral annular systolic velocity was lower ($p<0.001$) and myocardial performance index was higher ($p<0.001$) in patients with BD compared to the controls. As an early diagnostic marker of contractile dysfunction, intra- and interventricular dyssynchrony were more common in patients with BD. In addition, mitral E/A ratio of <1 was more common ($p<0.001$), isovolumic relaxation time ($p=0.032$) and mitral deceleration time ($p=0.037$) were longer in patients with BD compared to the control group. All Doppler parameters of right ventricular function were impaired in patients with BD. Atrial septal aneurysm was more frequent in patients with BD than controls ($p=0.007$).

Conclusion: Right ventricular and left ventricular function is impaired in patients with BD. Clinically silent cardiovascular involvement can be detected early by tissue Doppler echocardiography even in asymptomatic patients with BD.

Keywords: Behçet's disease; cardiac involvement; dyssynchrony; tissue Doppler echocardiography.

Behçet's disease (BD) is a chronic, relapsing inflammatory disorder, characterized by recurrent oral and genital ulcerations and ocular manifestations.[1] Eye inflammation, skin lesions, joint, central nervous system, large vessel and gastrointestinal system involvement emphasizes the systemic nature of the disease.[2]

The incidence and nature of cardiovascular involvement in BD have not been clearly documented yet.[3] In the literature, endocarditis, myocarditis, pericarditis, intracardiac thrombus, endomyocardial fibrosis, coronary arteritis, myocardial infarction and valvular disease have been reported as manifestations of cardiac involvement in BD.[4-8]

To date, there have been several studies investigating the cardiac functions in BD.[9-14] In those studies, conventional echocardiography has been used for the assessment of cardiac function. However, several controversial results were obtained particularly regarding diastolic functions.[9-14] Hence, novel methods for more objective estimation of the cardiac functions such as tissue Doppler echocardiography (TDE) or Doppler-derived myocardial performance index (MPI) might be helpful in BD. Such as, MPI, which combines both systolic and diastolic function,[15] ventricular dyssynchrony, which indicates heterogeneity of contraction time between different myocardial segments, may give

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a better reflection of the global left ventricular (LV) function than conventional echocardiography, though, to our knowledge, these have not been investigated so far.[16]

In this study, we aimed to evaluate LV and right ventricular (RV) functions at rest by pulsed-wave Doppler and TDE methods in patients with BD without overt cardiovascular disease, and compare to age and sex matched subjects.

PATIENTS AND METHODS

In this study, 54 consecutive patients with early BD (12 males, 42 females; mean age 35±8 years; range 15 to 51 years), all fulfilling the criteria of the International Study Group for BD[17] between June 2006 and September 2008, and 36 age-matched healthy controls (12 males, 24 females; mean age 33±5 years; range 18 to 47 years) were enrolled. All patients had less than 10 years of diagnosis. Patients with overt cardiovascular disease including coronary artery disease, renal failure, moderate or severe valvular heart disease, atrial fibrillation, and any other chronic or inflammatory disease were excluded. The drugs which were still being taken by the patients during the study were: prednisolone (n=25), colchicine (n=14), salicylate (n=10), cyclosporine (n=4), and azathiopirine (n=2). None of the patients had current or previous cardiovascular symptoms. All patients had stable normal sinus rhythm.

Medical histories, physical examinations, laboratory findings, and standard 12 lead electrocardiograms of the two groups were obtained. None of the patients had any of the active disease manifestations during echocardiographic evaluation (no symptoms for at least 1 month). All patients gave informed consent and the study protocol was approved by the local ethics committee.

The echocardiographic examinations were obtained by using 2.5-3.5 MHz transducer (GE-Vingmed Vivid 7 system). LV systolic and diastolic diameters, wall thickness, ejection fraction, aortic root, and left atrium were measured according to recommendations.[18] Parasternal long axis view was used as the gold standard for mitral valve leaflets prolapse (MVP). MVP was present when any portion of the anterior, posterior or both mitral valve leaflets prolapse ≥3 mm beyond an imaginary line drawn from the origin of the posterior aortic root to the atrioventricular groove.[18] Interatrialseptum was evaluated for atrial septal aneurysm (ASA), and patent foramen ovale (PFO) using contrast echocardiography. ASA was accepted as an abnormal bulging (>1.5 cm in length and excursion) from the midline of the interatrial septum. Valvular regurgitation was detected and semiquantitatively evaluated by means of color flow Doppler.[18]

Mitral E velocity (ME), mitral A velocity (MA), mitral E wave deceleration time (MEDT), and LV isovolumic relaxation time (IVRT), defined as time period between the termination of aortic systolic wave and beginning of ME, were measured by locating the sampling volume cursor of pulsed Doppler in the apical four chamber position at 5 mm above the mitral leaflets tips.[19]

To assess RV diastolic functions, tricuspid E velocity (TE), tricuspid A velocity (TA), and tricuspid E wave deceleration time were measured by locating the sampling volume cursor along the level of tricuspid annulus.[20] Then, adjusting the equipment of echocardiography to tissue Doppler measurements, the sampling volume cursor was located at the cross-sectional point of mitral annulus and lateral wall. Using the traces obtained from this location, ME´ and MA´ diastolic tissue Doppler velocities were measured.[21]

Right ventricular diastolic functions were measured with TDE by locating the sampling volume cursor at the cross-section point of lateral annulus and RV free wall. TE´ and TA´ diastolic tissue Doppler velocities were measured by the traces obtained from this point.[21]

Mitral S´ velocity was measured by locating the sampling volume cursor along the level of mitral annulus.[20] MPI, also known as "Tei index" was calculated from IVRT, isovolumic contraction time and ejection time[15] (MPI=IVRT+isovolumic contraction time/ejection time). Ventricular dyssynchrony was defined as intraventricular dyssynchrony and interventricular dyssynchrony.[22] LV septal-posterior wall motion delay, the time difference between peak inward motion of the ventricular septum, and the posterior wall which shows intraventricular dyssynchrony were obtained from parasternal

short axis M mode images. The time difference between from the onset of QRS to the onset of aortic flow and from the onset of QRS to the onset of pulmonary flow defined as preejection time was measured by standard pulsed Doppler and determined interventricular dyssynchrony. By tissue Doppler imaging, the peak systolic myocardial velocity (LV lateral annulus vs septal annulus for intraventricular dyssynchrony and LV lateral annulus vs. RV lateral annulus for interventricular dyssynchrony) and the timing of this peak velocity in relation to electrical activity (QRS on electrocardiogram) were calculated.

The intraobserver variability of echocardiographic measurements ranged between 4-7%, and all examinations were performed by an experienced echocardiographer, who had no knowledge of the patient's clinical information.

Statistical analysis

Parametric data were expressed as mean ± standard deviation and categorical data as percentages. Continuous parameters between independent groups were compared with Student's t-test. Comparison of categorical data between two groups was performed with the Chi-square test as appropriate. In all correlation analyses, the Pearson correlation test was used. A *p* value less than 0.05 was considered statistically significant. Statistical analyses were performed on a computer using the SPSS program, version 10.0 (SPSS Inc., Chicago, IL, USA) for Windows.

Table 1. Clinical findings of patients with Behçet's disease

Clinical finding	Number	%
Oral ulceration	54	100
Genital ulceration	51	94
Eye lesion	24	44
(+) Pathergy skin test	15	28
Arthritis	21	39
Skin lesion	30	56

RESULTS

All patients and control subjects were in functional class I of the New York Heart Association classification. All patients had a history of recurrent oral ulcerations. The general characteristics of the patients are shown in Table 1.

Oral aphthous ulcerations were seen all patients. Ocular involvement manifesting itself notably in the form of mild recurrent anterior and posterior uveitis (88%) and serious uveitis or retinal vasculitis were noted in 12%. Papulopustular lesions were seen in 30 patients (56%), and erythema nodosum in 26 patients (48%). Superficial thrombophlebitis mostly localized to the lower extremities was observed in six patients (11%).

Although baseline clinical characteristics, hemoglobin and blood cell counts were similar between patients and controls, systolic and diastolic blood pressure were significantly higher in patients with BD (Table 2). Laboratory parameters

Table 2. Clinical and laboratory characteristics of the study population

	Behçet group			Control group			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Number	54			36			–
Age (years)			35±8			33±5	0.172
Sex							0.177
Female	42	78		24	67		
Male	12	22		12	33		
Disease duration (years)			5±4			–	–
Smoking	12	22		6	17		0.357
Body mass index (kg/m^2)			25±4			24±6	0.157
Heart rate (/min)			79±16			77±5	0.400
Systolic blood pressure (mmHg)			114±16			98±7	<0.001
Diastolic blood pressure (mmHg)			77±8			67±9	<0.001
Hemoglobin (g/dL)			12.8±1.4			13.3±1.0	0.362
White blood cell			7470±2452			6325±1010	0.201
Blood glucose			78±15			78±16	0.954
Erythrocyte sedimentation rate (mm/hr)			21±13			6±2	<0.001
C reactive protein (mg/L)			1.8±1.5			0.7±0.4	<0.001
QRS duration (ms)			105±15			86±8	0.005

SD: Standard deviation.

for erythrocyte sedimentation rate and C-reactive protein were significantly higher in patients with BD.

Atrial septal aneurysm was observed in 44% of patients with BD, and in 4% of controls (p=0.007). PFO was observed in four patients (11%) and not observed in any of the controls (p=0.1). MVP was not detected in the patient or control group. Mild mitral regurgitation and mild tricuspid regurgitation were significantly higher in patients than controls (61% patients and 17% controls, p=0.001; and 56% patients %21 controls, p=0.01, respectively). Mild aortic regurgitation was seen in six patients (17%) and was not seen in any of the controls (p>0.05). Other valve functions were similar in both groups. We also detected intracardiac thrombus formation in the right atrium in two patients. On the sixth month of the anticoagulant therapy, complete lysis of intracardiac thrombosis was observed.

The dimensions and volumes of LV were significantly higher in control group, whereas wall thickness, left atrial diameters and conventional indices of LV contraction were similar in both two groups (Table 3). The diameters of RV and pulmonary artery were higher in patients.

Mitral E velocity was similar between the groups. Although diastolic parameters were within normal limits; MA, MEDT, IVRT and ME/ME´ were significantly higher in patient group (Table 4). Consistently, ME´ and ME/MA were significantly lower in patients. Furthermore, although ME/MA was <1 in 41% of patients, it was not detected in any controls.

Although conventional indices of LV contraction were similar between groups, newer indices of systolic function were affected in Behçet group. Furthermore, all parameters of LV dyssynchrony were higher in Behçet group (Table 3).

The diameter of pulmonary artery and RV were greater in patients than in controls (Table 4). Similar to LV Doppler findings; TA, tricuspid E wave deceleration time and TE/TE´ were significantly higher in Behçet group. Consistently, TE´ and TE/TA were significantly lower in patients. Also, TE/TA was <1 in 50% of patients whereas it was not detected in any controls.

DISCUSSION

The incidence and natural history of cardiac involvement in BD have not been clearly documented yet. Cardiovascular manifestations have been reported in 7-46% of cases with BD

Table 3. Conventional and systolic parameters of the left ventricle

Indices	Behçet group	Control group	
	Mean±SD	Mean±SD	*p*
Left ventricular end diastolic diameter (mm)	48±3.2	50±3.7	0.012
Left ventricular end systolic diameter (mm)	30±3.2	32±3.7	0.028
Left ventricular end diastolic volume (ml)	99±19	109±17	0.008
Left ventricular end systolic volume (ml)	36±11	42±7	0.005
Left ventricular mass (g/m^2)	148±19	144±22	0.372
Interventricular septum thickness (mm)	9±1	8±1	0.117
Posterior wall thickness (mm)	9±1	8±1	0.266
Left atrium (mm)	34±4	35±1	0.084
Left ventricular ejection fraction (%)	63±6	62±3	0.834
Fractional shortening (%)	37±4	36±5	0.788
Stroke volume (mm^3)	61±15	67±12	0.074
Diameter of pulmonary artery (mm)	20±2	18±2	<0.001
Diameter of the right ventricle (mm)	27±3	23±2	<0.001
Myocardial performance index	0.52±0.11	0.40±0.11	<0.001
Mitral S' velocity (cm/s)	8.8±2.4	10.3±0.8	<0.001
Mitral isovolumic contraction time (ms)	75±19	57±14	<0.001
Ejection time (ms)	279±35	302±21	<0.001
Septal-to-posterior wall delay (ms)	44±51	3±1	<0.001
Septal-to-lateral wall delay (ms)	16±20	3±2	<0.001
Lateral-to-right ventricle wall delay (ms)	23±21	5±3	<0.001

SD: Standard deviation.

Table 4. Diastolic indices of the left ventricle

	Behçet group			Control group			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Mitral E velocity (cm/s)			73±17			73±10	0.939
Mitral A velocity (cm/s)			68±16			53±6	<0.001
Mitral E velocity/A <1 (%)		41			0		<0.001
Mitral E velocity/A			1.15±0.4			1.4±0.3	0.006
Mitral E deceleration time (ms)			177±21			163±36	0.037
Mitral isovolumic relaxation time (ms)			74.3±17			66.5±16	0.032
Mitral E´ velocity (cm/s)			13.5±5			16.5±4	0.003
Mitral A´ velocity (cm/s)			10±3			9.5±1	0.193
Mitral E velocity/E´			7±5			5±2	0.005
Tricuspid E´ velocity (cm/s)			55±11			56±3	0.263
Tricuspid A velocity (cm/s)			55±16			41±3	<0.001
Tricuspid E velocity/A			1.1±0.4			1.4±0.2	<0.001
Tricuspid E velocity/A <1 (n)	50			0			<0.001
Tricuspid E deceleration time			177±58			122±21	<0.001
Tricuspid E´ velocity (cm/s)			11±3			14±2	<0.001
Tricuspid A´ velocity (cm/s)			15±6.0			11±1	<0.001

SD: Standard deviation.

and mortality occurs in up to 20% of those patients with marked vascular involvement.[23]

Both systolic and diastolic blood pressure measurements were significantly higher in Behçet group. Our hypothesis is that the increased blood pressure in BD might be caused by changes in normal responsiveness of the vascular bed to pressure stimuli because of vasculitis or autonomic nervous dysfunction.

The prevalence of MVP was reported to be 6-50% in previous studies.[24,25] In our study, MVP was not detected in the patient or control group. These discrepancies may be related to strictly applied echocardiographic diagnostic criteria for MVP in our study. In autopsy studies, PFO was detected in approximately 25-35% of cases.[26] In our study, there was no difference between the BD patients and control subjects with respect to the incidence of PFO (11% vs. 4%, p=0.12). Also, our findings were not different from previous reports.[27] However, we detected an increased incidence of ASA in patients with BD (44% vs. 4%, p=0.007). The etiology of ASA in this disorder can be attributed to systemic vasculitis and tissue derangement. Although mild mitral and tricuspid regurgitation were more frequent in patients with BD, there was no structural valve anomaly in any patient and the incidences of mild AR or other valvular abnormalities were similar between the groups.

The previous studies using conventional echocardiography reported that LV diastolic dysfunction was more frequent in patients with BD.[9-12] Komsuoglu et al.[10] reported that MEDT and IVRT were significantly prolonged and the ME/MA ratio was lower in patients with BD compared with the control group. Gemici et al.[12] showed that ME, MA and ME/MA ratio were similar, but IVRT and MEDT were significantly prolonged in patients. Nevertheless, it is well known that conventional techniques may be dependent on loading conditions and are influenced strongly by aortic or left atrial pressures.[28,29] With the assistance of TDE, diastolic function can be evaluated independently from loading conditions.[30] So, we used both conventional echocardiography and TDE in our study.

By using conventional Doppler techniques, we detected that all parameters of LV diastolic function except for ME were impaired in Behçet group, but still in the normal range. In TDE, although ME´ was within normal reference limits, it was significantly lower in Behçet group compared to the control group. Consistently, ME/ME´ was greater in patient group compared to the control group. Although ME/ME´ is a marker of increased LV end-diastolic pressure, whether this finding shows LV diastolic dysfunction in this case is not clear. At the end of exercise, diastolic parameters changed similarly in two groups, but the statistical significance of ME/MA ratio was lost.

All Doppler parameters of RV function, except for TE, were impaired in Behçet group similar to LV. Tricuspid annular motion can be

assessed easily with TDE.[31,32] However, like other parameters of RV function, the tricuspid annular velocities are load dependent. This method has been accepted as a convenient means of quantitatively evaluating RV systolic function and has been used as a diagnostic tool by a number of groups.[33,34] The sensitivity of tricuspid annular motion for the detection of early RV dysfunction may be superior to more conventional imaging techniques.[33] Therefore, lower TE/TA and TE´, and higher TE/TE in BD may be clinically relevant findings.

Most studies that evaluate LV systolic function in BD have reported no difference between patients and control groups,[10-12] but Calguneri et al.[9] reported that mean ejection fraction, which was evaluated by radionuclide ventriculography, despite being in the normal range, was significantly lower in patients when compared with controls. In our study, the dimensions of LV were higher in control group, but conventional indices of LV systolic function were similar between groups like previous studies.[10-12]

Myocardial performance index is an easy, reproducible, quantitative method to evaluate both LV systolic and diastolic function, independent from heart rate and blood pressure. We detected that MPI was significantly higher in Behçet group, and greater MPI was consistent with impaired LV function[15] as in a previous study of Tavil et al.[35] Consistently, MS´ was significantly lower in Behçet group in our study.

Asynchronous LV electromechanical activation was shown to be associated with deteriorated LV remodeling and dilation.[36] Also, a small study has shown a positive relationship between reduced systolic dyssynchrony and increased LVEF.[37] In our study, despite being in normal range, LV septal to posterior wall delay time, LV septal to lateral wall delay time, LV lateral to RV wall delay time, and preejection time difference were all higher in Behçet group compared to the control group.

Thus, we conclude that LV systolic function may be affected in BD, and despite conventional LV systolic function indices, increased MPI, decreased MS´ and impaired ventricular synchrony might aid in early identification. As a single-center study, the major limitation of this study is its small sample size and female dominance (major clinical involvement is seen more in male patients with BD). Thus further studies are required for more definitive validation.

In conclusion, we detected through conventional and newer echocardiographic methods that the RV and LV diastolic function were impaired in patients with BD compared to healthy controls. LV systolic dysfunction could be detected only if newer echocardiographic methods were used.

Declaration of conflicting interests

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