

## Diastolic dysfunction in Behçet's disease and its relationship with clinical manifestations of the disease: A case-control study

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### ABSTRACT

**Objectives:** The study aimed to evaluate the frequency of diastolic dysfunction (DD) in patients with Behçet's disease (BD) and its relationship with clinical manifestations.

**Patients and methods:** Seventy patients (35 females, 35 males; mean age: 39.3±11.0 years; range, 21 to 61 years) with BD and 50 healthy controls (27 females, 23 males; mean age: 38.8±10.0 years; range, 23 to 62 years) were included in the case-control study between October 2023 and December 2023. Age, sex, smoking status, disease duration, mucocutaneous involvement, other organ involvement, treatment received of the patients were recorded. The E/A ratio (the ratio of early diastolic wave to the atrial wave) and the E/E' ratio (the ratio of early transmitral filling velocity to early diastolic mitral annular velocity), which are markers of DD, were measured by transthoracic echocardiography.

**Results:** Diastolic dysfunction was observed in 27.1% (n=19) of BD patients and 8% (n=4) of healthy controls (p=0.017). Male dominance was observed in patients with major organ involvement (MOI) compared to patients with isolated mucocutaneous involvement (p=0.001). While MOI was observed at a rate of 65.7%, ocular involvement, among the MOIs, constituted 52.9% of all BD patients. The percentage of patients with a mitral E/A ratio <1 was similar between the MOI and isolated mucocutaneous involvement groups. However, vascular involvement was observed in 47.4% of BD patients with a mitral E/A ratio <1 (p=0.034). In addition, it was observed that the group with a mitral E/A ratio <1 was older, had a longer disease duration, and had a higher erythrocyte sedimentation rate.

**Conclusion:** Diastolic dysfunction is an early sign of cardiac involvement, and prolonged vascular involvement in BD increases the risk of DD.

**Keywords:** Behçet's disease, diastolic dysfunction, vasculitis.

Behçet's disease (BD) is a chronic inflammatory disease characterized by recurrent oral ulcers and involves many organs.<sup>1</sup> In addition to mucocutaneous involvement, ocular, neurological, intestinal, and vascular involvement can be encountered in the diagnosis or follow-up of BD.<sup>2</sup>

The incidence of cardiovascular disorders increases in inflammatory rheumatic diseases such as BD.<sup>3,4</sup> However, cardiac involvement is less common in BD patients than ocular, vascular, and neurological involvement. In two large study series, cardiac involvement in BD patients was found to be between 2.4 and 6.4%.<sup>5,6</sup> Heart disease in BD involves both vascular and myocardial structures. The most common cardiac manifestations are pericarditis

and valve involvement.<sup>7</sup> Additionally, the frequency of diastolic dysfunction (DD) increases in BD patients.<sup>8</sup>

Diastolic dysfunction is an echocardiographic diagnosis and not a clinical diagnosis. Echocardiography plays an essential role in the evaluation of DD.<sup>9</sup> The ratio of early diastolic wave to the atrial wave (E/A) and the ratio of early transmitral filling velocity to early diastolic mitral annular velocity (E/E') are echocardiographic measurements used to determine DD.<sup>10</sup> Left ventricular DD plays a fundamental, overarching role in the pathophysiology of heart failure with preserved ejection fraction (EF).<sup>11</sup> Myocardial inflammation and oxidative stress are the main mechanisms of heart failure with preserved EF.<sup>12</sup>

The frequency of DD in BD has been investigated. Nevertheless, there are a limited number of studies investigating the relationship between the clinical manifestations and DD, particularly in patients with an increased risk of DD. Hence, this study aimed to evaluate the frequency of DD in BD patients and its relationship with clinical manifestations.

## PATIENTS AND METHODS

The single-center, case-control study was conducted with 70 patients (35 females, 35 males; mean age:  $39.3 \pm 11.0$  years;

range, 21 to 61 years) diagnosed with BD according to the International Study Group for BD criteria.<sup>13</sup> Patients who applied to the rheumatology clinic of Çukurova University Faculty of Medicine between October 2023 and December 2023 were included in the study. A control group of 50 individuals (27 females, 23 males; mean age:  $38.8 \pm 10.0$  years; range, 23 to 62 years) with similar age and sex and no known disease was included in the study. Patients with low EF heart failure, obesity, cancer, pregnancy, diabetes mellitus, hypertension, coronary artery disease, and severe renal or liver failure were excluded. The study protocol was approved by the Çukurova University Faculty of

**Table 1.** Characteristics of patients with Behçet's disease

	n	%	Mean $\pm$ SD	Median	Min-Max
Age (year)			39.3 $\pm$ 11.0		
Sex					
Female	35	50			
Duration of disease (year)				9.5	1-26
Oral aphthosis	70	100			
Genital aphthosis	46	65.7			
Papulopustular lesion	42	60			
Erythema nodosum	34	48.6			
Pathergy test positivity	19	27.1			
Mucocutaneous involvement only	24	34.3			
Additional major organ involvement	46	65.7			
Ocular involvement	37	52.9			
Vascular involvement					
Deep vein thrombosis	12	10			
Pulmonary embolism	2	1.7			
Thrombophlebitis	3	2.5			
Pulmonary aneurysm	2	1.7			
Neuro-Behçet	4	5.7			
Gastrointestinal system involvement	2	2.9			
Treatment					
Colchicine	56	80			
Anti TNF treatment	19	27.1			
Azathioprine	20	28.6			
Methotrexate	3	4.3			
BDCAF scor					
<4	57	81.4			
$\geq$ 4	13	18.5			
ESR (mm/h)			14.5 $\pm$ 9.3		
CRP (mg/L)			4.95 $\pm$ 4.75		

SD: Standard deviation; TNF: Tumor necrosis factor; BDCAF: Behçet's disease current activity form; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

Medicine Non-Interventional Clinical Research Ethics Committee (date: 13.10.2023; reference number: 137/57). Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Age, sex, smoking status, disease duration, mucocutaneous involvement, other organ involvement, and treatments were recorded. The echocardiographic findings, disease activity scores, and acute phase reactants were examined. The Behçet's Disease Current Activity Form was used as the disease activity score.<sup>13</sup> C-reactive protein, erythrocyte sedimentation rate, and lipid profile were extracted from the patients' files.

Transthoracic echocardiography was performed according to current guidelines (the American Society of Echocardiography and European Association of Echocardiography

guidelines)<sup>14</sup> by a blinded cardiologist using a 3 MHz sector probe with a VIVID-T8 model echocardiography device (General Electric, Boston, MA, USA) in all participants. In the parasternal long axis, aorta, left atrium, interventricular septum, left ventricular diastolic and end-systolic diameters were measured using the M-mode, and EF was calculated by the Teichholz method. Diastolic E and A waves were measured via mitral valve with pulsed-wave Doppler, and tissue Doppler and pulsed-wave Doppler were used together to calculate the E' wave from lateral mitral annulus in apical four-chamber views. Patients with an E/A ratio <1 or E/E' ratio >15 were considered to have DD.

### Statistical analysis

Data were analyzed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA).

**Table 2.** Comparison of demographic data and echocardiographic findings of patients with isolated mucocutaneous involvement and patients with MOI in Behçet's disease

	Mucocutaneous involvement only			With major organ involvement			p
	n	%	Mean±SD	n	%	Mean±SD	
Patient	24	34.3		46	65.7		
Sex							
Female	19	79.2		16	34.8		<b>0.001</b>
Age (year)			41.3±10.5			38.3±11.1	0.268
Smoker	5	20.8		23	50		<b>0.035</b>
Aorta (mm)							
<37	24			46			1.000
>37							
Left atrial (mm)							
<40	24			46			1.000
>40							
End-systolic diameter (mm)							
<40							
Mitral E/A							0.099
<1	6	25		13	28.2		
>1	18	75		33	71.7		
Mitral E/E'							0.684
<8	21			42			
8-15	3			4			
>15	0			0			

MOI: Major organ involvement; E/A: Ratio of early diastolic wave to atrial wave; E/E': Ratio of early transmitral filling velocity to early diastolic mitral annular velocity; SD: Standard deviation.

Data were presented as numbers, percentages, mean  $\pm$  standard deviation (SD), or median (interquartile range). The Kolmogorov-Smirnov test was used to assess normality. Parametric tests were applied to data that conformed to normal distribution, and nonparametric tests were applied to data that did not. The t test was used for the comparison of two independent groups with normal distribution, the Mann-Whitney U test was used for the comparison of two independent groups without normal distribution, and the chi-square test was used for the comparison of categorical data. Logistic regression analysis was applied to determine the effect of vascular involvement on DD. Analysis of covariance was used to evaluate the effect of age and disease duration on DD. A p-value  $<0.05$  was considered statistically significant.

## RESULTS

Healthy controls and BD patients were similar in terms of age, sex, and smoking status. The characteristics of the patients with BD are shown in Table 1. Ocular involvement was the most common after mucocutaneous involvement, followed by vascular involvement (Table 1).

When the echocardiographic findings of BD patients and the healthy control group were examined, it was shown that the frequency of patients with a mitral E/A ratio  $<1$  was higher in BD patients ( $p=0.017$ ). However, no statistically significant difference was observed between the groups in the E/E' ratio ( $p=0.519$ ). The EF of all patients was within normal limits.

The comparison of demographic data and echocardiographic findings of patients with

**Table 3.** Characteristics of Behçet's patients with diastolic dysfunction

	E/A $>1$ (n=51)					E/A $<1$ (n=19)					p
	n	%	Mean $\pm$ SD	Median	IQR	n	%	Mean $\pm$ SD	Median	IQR	
Age (year)			36.3 $\pm$ 9.3					47.4 $\pm$ 11.1			<b>&lt;0.001</b>
Sex											0.591
Female	24					11					
Male	27					8					
Smoking status	24					4					0.089
Treatment											
Colchicine	41	80.4				15	78.9				0.893
Anti TNF treatment	12	23.5				7	36.8				0.417
Azathioprine											
Methotrexate	2	3.9				1	5.3				1.000
ESR (mm/h)			12.33 $\pm$ 7.23					20.42 $\pm$ 11.72			<b>0.013</b>
CRP level (mg/L)			4.27 $\pm$ 2.95					6.75 $\pm$ 7.53			0.377
LDL (mg/dL)			103.61 $\pm$ 31.01					119.21 $\pm$ 43.08			0.124
HDL (mg/dL)			50.41 $\pm$ 13.43					48.17 $\pm$ 11.61			0.717
Triglyceride (mg/dL)			134.40 $\pm$ 68.31					178 $\pm$ 146.38			0.287
Duration of disease			9.57 $\pm$ 6.66					13.84 $\pm$ 6.41			<b>0.017</b>
BDCAF score											0.984
$<4$	41	80.4				16	84.2				
$\geq 4$	10	19.6				3	15.8				
BDCAF score				1	3				2	3	
Mucocutaneous involvement only	18	35.3				6	31.6				0.533
With major organ involvement	33	64.7				13	68.4				0.994
Ocular involvement	26	51.0				11	57.9				0.806
Vascular involvement	11	21.6				9	47.4				<b>0.034</b>

E/A: Ratio of early diastolic wave to atrial wave; SD: Standard deviation; IQR: Interquartile range; TNF: Anti tumor necrosis factor ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; BDCAF: Behçet's disease current activity form.

isolated mucocutaneous involvement and patients with major organ involvement (MOI) is summarized in Table 2. While 79.2% of patients with mucocutaneous involvement were female, only 34.8% of patients with MOI were female ( $p=0.001$ ). It was observed that the smoking rate was higher in patients with MOI ( $p=0.035$ ).

The characteristics of BD patients with a mitral E/A ratio  $<1$  are shown in detail in Table 3. BD patients with a mitral E/A ratio  $<1$  were older and had longer disease duration. Age was directly related to disease duration. After accounting for age, there was no observed impact of illness duration on the mitral E/A ratio ( $p=0.719$ ).

When the mitral E/A ratio was compared between individuals with and without vascular involvement, the risk of DD was increased in patients with vascular involvement (odds ratio= 3.27, 95% confidence interval 1.06-10.03).

## DISCUSSION

This study demonstrated the importance of echocardiography in the noninvasive evaluation of DD in BD patients and the relationship between organ involvement and DD. In our study, similar to the literature, it was observed that patients with MOI were more likely to be male. In a previous study, male patients with BD were shown to have a more aggressive course.<sup>15</sup> Our study showed that smoking is more common in BD patients with MOI, such as ocular involvement and vascular involvement, compared to patients with isolated mucocutaneous involvement. Previous studies have shown smoking to be an independent risk factor for both subclinical atherosclerosis and cardiovascular disease.<sup>16,17</sup>

In this study, no patient with abnormal mitral E/E' ratio was found. Therefore, DD was determined by the mitral E/A ratio.<sup>18-20</sup> In the current study, DD was more common in BD patients as compared to controls (27.1% vs. 8%). Studies have shown that indicators of DD are more common in BD patients than in the controls.<sup>3,18,20</sup> In the study conducted by Gemici et al.,<sup>18</sup> 30.9% of patients had a mitral E/A ratio  $<1$  in the BD group, while in the study of Yavuz et al.,<sup>20</sup> 29% of patients had a mitral

E/A ratio  $<1$  in the BD group. Baris et al.<sup>8</sup> found a rate of mitral E/A ratio  $<1$  in 37.5% of BD patients and 11.5% in the control group. In the same study, E/E' was not found to be significant.

We observed that BD patients with a mitral E/A ratio  $<1$  (indicator of DD) were older, and the erythrocyte sedimentation rate was higher. However, DD was not correlated with disease activity or duration of the disease. It was observed that 25% of patients with only mucocutaneous involvement and 28% of patients with MOI had a mitral E/A ratio  $<1$ . Although it was hypothesized that the cardiac risk profile would increase in patients with MOI, no difference was observed in our study. Therefore, echocardiographic evaluation of BD patients for DD is of great importance, even if they do not have MOI and additional risk factors. When patients with MOI were examined in detail, we observed that the rate of patients with a mitral E/A ratio  $<1$  was higher in patients with vascular involvement. Although the pathogenesis of vascular involvement in BD is not clear, the study by Yücel et al.<sup>21</sup> showed that the amino acid metabolites observed in BD with vascular involvement are related to the antioxidant pathway and are more atherogenic. All these findings suggest that DD is associated with inflammation. To our knowledge, although previous studies have investigated DD in BD patients compared to a control group, organ involvement and clinical characteristics of BD patients have not been detailed. Therefore, organ involvement and the mitral E/A ratio could not be compared with other studies.

Although we concluded that BD has a high rate of DD, the pathophysiological mechanisms remain unclear. There are microcirculation abnormalities in BD. It is well known that most of the intrinsic blood flow to the heart occurs during diastole. Coronary flow reserve is a way to assess the microcirculation of the heart and, thereby, the endothelial function.<sup>22</sup> It has been shown that coronary flow reserve is reduced in patients with scleroderma, rheumatoid arthritis, psoriasis, and BD, although they do not have coronary artery disease. The common feature of these diseases is the presence of systemic inflammation. Microvascular inflammation may be a cause of asymptomatic DD in BD. Systemic inflammation has been shown to be one cause of subclinical

atherosclerosis.<sup>23-25</sup> Additionally, it has been shown that arterial intima-media thickness increases in patients with vasculitis, even in the absence of subclinical atherosclerosis.<sup>26</sup> Considering all these data, it can be said that inflammation plays an important role in the pathogenesis of DD.

Diastolic dysfunction is an independent predictor of congestive heart failure and an early sign of cardiac involvement. In the study of Geri et al.,<sup>5</sup> in which cardiac involvement was evaluated in BD patients, it was shown that cardiac involvement was associated with poor prognosis and that disease treatment improved the prognosis. We think that evaluating patients in this respect to prevent the disease before significant cardiac involvement can reduce morbidity and mortality.

The study had some limitations. The primary limitation was the small number of patients, preventing the generalization of the results to the entire population with BD. Another limitation was the lack of isovolumetric relaxation time and e-wave deceleration time measurements on echocardiography.

In conclusion, controlling risk factors is important in preventing DD and the resulting heart failure. It should be taken into consideration that patients with BD are more likely to develop DD and heart failure. Cardiac evaluation should be included in routine follow-ups. All BD patients, particularly those with vascular involvement, high acute phase reactants, and older age, should be evaluated regarding cardiac involvement at regular intervals.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** Authorship contribution: conception and design of study: G.V., R.E.A., I.T., Z.T.; Acquisition of data: G.V., I.T., Z.T., S.Ö.; Analysis and interpretation of data: G.V., I.T., B.M., Z.T.; Drafting the article or revising it critically for important intellectual content: G.V., R.E.A., I.T., Z.T., B.M., S.Ö.; Final approval of the version to be submitted: G.V., R.E.A., I.T., Z.T., B.M., S.Ö. All co-authors take full responsibility for the integrity and accuracy of all aspects of the research. All authors approve the submitted version of the manuscript.

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