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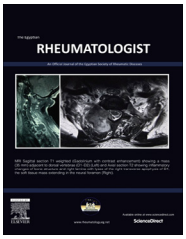

ORIGINAL ARTICLE

Assessment of left ventricular function and aortic elastic properties in patients with Behçet's disease using conventional and tissue Doppler echocardiography

Waleed A. Hassan [a,*], **Hany H. Ebaid** [b]

[a] *Rheumatology and Rehabilitation Department, Faculty of Medicine, Benha University Hospital, Egypt*
[b] *Cardiology Department, Faculty of Medicine, Benha University Hospital, Egypt*

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KEYWORDS

Behçet's disease;
Left ventricular dysfunction;
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Abstract *Background:* Behçet disease (BD) is a multisystemic, chronic inflammatory disorder of unknown etiology with diffuse clinical manifestations including the cardiovascular system.

Aim of the work: To assess left ventricular (LV) function and thoracic aorta elastic properties in BD patients using Doppler echocardiography and to correlate echocardiographic findings with disease activity.

Patients and methods: The LV functions and thoracic aorta elastic properties were assessed in 30 BD patients and 30 controls using conventional and Tissue Doppler Imaging (TDI) echocardiography. Disease activity was evaluated using Behçet's disease current activity form (BDCAF). Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), cholesterol and triglyceride levels were measured.

Results: In BD patients, ESR and CRP were significantly elevated while cholesterol and triglycerides were comparable to the levels in the control. In conventional echocardiography, BD patients had significantly higher aortic diastolic diameter ($p < 0.05$), aortic stiffness index ($p < 0.001$), isovolumic relaxation time ($p < 0.001$), flow propagation velocity (FPV) and peak E-wave velocity/FPV (E/FPV) ($p < 0.001$) than the control group while aortic strain was significantly lower

* Corresponding author. Mobile: +20 1095000886.
E-mail address: waleed22101979@yahoo.com (W.A. Hassan).
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in BD patients ($p < 0.05$). Lateral mitral TDI echocardiography showed that myocardial performance index was statically higher in BD patients ($p < 0.001$) while peak myocardial velocity and myocardial acceleration during isovolumic contraction were significantly lower ($p < 0.001$). The BDCAF showed a significant correlation with different echocardiographic parameters of systolic and diastolic dysfunction.

Conclusions: Behçet disease patients have impaired LV systolic and diastolic functions and altered aortic elastic properties that correlate with disease activity. TDI is more sensitive than conventional echocardiography for the detection of early ventricular dysfunction in patients with BD.

1. Introduction

Behçet disease (BD) is a generalized chronic inflammatory disease characterized by a triad of recurrent oral aphthous ulcers, genital ulcers and uveitis but can involve many other systems [1]. Several markers and mechanisms have been involved in the pathogenesis of BD and development of vascuitis including oxidative stress [2], apoptosis [3,4], cytokine and adipocytokine overproduction [5–7], vascular endothelial growth factors [8,9] and gene polymorphism [10]. Vasculitis and endothelial dysfunction are believed to be the pathogenic mechanism of a part but not the whole of the clinical spectrum of the disease [11]. In a study on Egyptian patients with BD, pulmonary artery aneurysm one of the most serious aspects of the disease was a leading cause of mortality [12].

Symptomatic cardiac disease is uncommon (1–6%) in BD [13], but it was found in about 16.5% of a registry of Behçet autopsy cases in Japan [14]. Cardiac involvement is more common in male patients and shows more arterial and venous lesions when compared with those without cardiac manifestations [15]. Cardiac involvement includes intracardiac thrombosis, pericardial involvement, myocardial and endocardial complications and coronary artery disease [16]. Subclinical coronary endothelial dysfunction was detected in 52% of asymptomatic Egyptian BD patients in spite of a normal coronary angiography [17]. In another study on Egyptian BD patients, a morphologic evidence of subclinical carotid artery atherosclerosis was verified and the disease activity significantly suggested cardiovascular involvement. [18].

Endocardial involvement may be limited to heart valves including mitral and aortic valve prolapse, mitral or aortic insufficiency, or involvement may include the endocardial surface of cardiac chambers [19]. Endocardial involvement may lead to endocardial fibrosis involving the right or left ventricle [20] and may predispose to intracavitary thrombus formation, which may lead to pulmonary emboli [21]. Also, the inflammatory process may involve arteries and arterioles of the coronary system leading to silent ischemia, myocardial infarction and systolic or diastolic dysfunction [22] which may be due to filling abnormalities [23].

Ventricular diastolic function can be assessed by invasive and non-invasive methods. Invasive measures for the assessment of left ventricular (LV) diastolic function include the peak instantaneous rate of LV pressure decline, the time constant of LV relaxation, and the stiffness modulus. [24] Although echocardiography does not directly measure these parameters, it is the most practical non-invasive method for evaluating LV diastolic function through measurement of LV volumes and ejection fraction (LVEF) [25]. Also, measurement of LV wall thicknesses (to identify presence and extent of LV hypertrophy), left atrial (LA) volumes and pulmonary artery (PA) pressures can help in the assessment of diastolic function as patients with diastolic heart failure frequently have LV hypertrophy, LA enlargement and increased PA pressures [26].

Tissue Doppler imaging (TDI) is the technique widely used to detect subtle minimal impairment in myocardial function and it enables measurement of high amplitude and low frequency Doppler shifts caused by myocardial motion. Segmental and global function can be measured and it is minimally affected by preload in patients with impaired LV relaxation [27,28].

This study aimed to assess LV function and thoracic aorta elastic properties in patients with BD using conventional and tissue Doppler echocardiography and to correlate echocardiographic findings with disease activity.

2. Patients and methods

2.1. Participants

Thirty patients, fulfilling the International Criteria for BD [29], were recruited from the in-patients and out-patients' clinic of the Rheumatology and Rehabilitation Department of Benha University Hospitals between April 2014 and February 2015. Thirty age and sex matched apparently healthy individuals with comparable body mass index (BMI) from the hospital personnel, undergraduates; medical and nursing staffs were also included as a *control group*. Patients older than 50, or who have pre-existing overt heart diseases (e.g. ischemic heart disease, conduction abnormalities, heart failure) or traditional cardiovascular risk factors (e.g. hypertension, diabetes mellitus, hyperlipidemia, smoking, BMI > 35) were excluded.

Patients' evaluation included full history taking with recording of the disease duration, thorough physical examination, body mass index (BMI) assessment, Behçet's disease manifestations including vascular, cutaneous, oral and genital ulceration. Fundus examination was undertaken by slit lamp for the detection of ocular manifestations such as uveitis, retinal vasculitis and optic neuritis and ongoing medications were recorded. Disease activity using the Behçet's Disease Current Activity Form (BDCAF) [30] was assessed in all patients. The local ethics committee of our institution (Benha University, Faculty of Medicine) approved the study and all participants gave a written informed consent before being enrolled in this study.

2.2. Laboratory investigations

Blood specimens were collected after an overnight fasting and analyzed for complete blood count (CBC), erythrocyte sedimentation rate (ESR) by Westergren's method in mm/hour, C-Reactive protein (CRP). Cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol.

2.3. Echocardiographic examination

Echocardiography was done using a VIVID 7 EG cardiac ultrasound scanner, which included software for the acquisition of both standard cardiac ultrasound and Doppler myocardial imaging data using 2.5-MHz transducer. Standard echocardiography analysis was done using two-dimensional, m-mode, and Doppler flow measurements performed according to the American society of echocardiography recommendations [31].

2.4. Conventional Echocardiography

- *Measurements of left ventricle (LV) and thoracic aorta*: The following parameters were measured: LV end diastolic diameter (LVEDD), LV end systolic diameter (LVESD), fractional shortening (FS%), LV outflow diameter, left atrial (LA) diameter, interventricular septal thickness, posterior wall thickness in diastole, aortic systolic diameter (Ao S), aortic diastolic diameter (Ao D), aortic strain (AS), aortic stiffness index and aortic pressure strain modulus.
- *Doppler measurements*: The following parameters were measured; mitral diastolic flow, isovolumic relaxation time (IVRT), velocity time integral (VTI) and stroke volume.
- *Color M mode measurements*: It was used to measure the flow propagation velocity (FPV) and to calculate the peak E-wave velocity/FPV (E/FPV) (E/FPV) ratio; patients were divided to those with a ratio <1.7 and those >1.7.

2.5. Tissue Doppler Imaging (TDI)

It was obtained in an apical four-chamber view; a 5 mm sample volume was placed just apical to the lateral mitral annulus. Frame rate was adjusted between 120–180 frames/s and a cine-loop of 3–5 consecutive heart beats was recorded. The following were measured:

- *Systolic indices* that include peak myocardial velocity during isovolumic contraction (IVV), myocardial acceleration during isovolumic contraction (IVA), peak velocity during systolic ejection (Sa), myocardial performance index (MPI) were calculated as the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time.
- *Diastolic indices* that include peak early (E) and late myocardial diastolic velocity (A).

Statistical analysis: The collected data were analyzed using SPSS version 16. Categorical data were presented as number and percentages while continuous variables were presented as mean and SD if parametric, and as median and range if non parametric. Chi square, Z-test, Mann Whitney U test, Kruskal–Wallis test and Spearman's correlation coefficients were used as tests of significance. Two sided p-value < 0.05 was considered significant.

3. Results

Thirty BD patients (ages ranged from 18 to 49 years) with a mean of 32.67 ± 9.55 years and thirty age and sex matched apparently healthy control (ages ranged from 19 to 49 years) with a mean of 33.2 ± 9.9 years were included in the study. There was no significant difference between both groups regarding the mean of systolic BP, diastolic BP, BMI, cholesterol and triglycerides ($p > 0.05$). Patients' clinical and laboratory features are shown in (Table 1).

Regarding conventional echocardiography (Table 2); aortic diastolic diameter, aortic stiffness index, isovolumic relaxation time, FPV and E/FPV were significantly higher ($p < 0.05$) in BD patients compared to the control group while the aortic strain was significantly lower in BD patients compared to the control group ($p < 0.05$). Other parameters (LVEDD, LVESD posterior wall thickness, Septal thickness) showed no significant difference between patients and control.

Regarding TDI parameters (Table 3); myocardial performance index (MPI) was statistically higher in BD patients compared to the control group ($p < 0.001$) while peak myocardial velocity (LV IVV) and acceleration (LVIVA) during isovolumic contraction were significantly lower ($p < 0.001$). There was also a statistically significant difference among diastolic parameters: peak early (E wave) ($p < 0.001$) and late (A wave) diastolic myocardial velocity being significantly lower in BD patients compared to the control group ($p < 0.05$). Peak velocity during systolic ejection (Sa) showed no statistically significant difference between BD patients and control ($p > 0.05$).

Table 1 Clinical and laboratory characteristics, disease activity of the Behçet's disease (BD) patients and controls.

Characteristics	BD ($n = 30$)	Control ($n = 30$)	p
Male/female	19/11	18/12	>0.5
Disease duration (years)	4.3 ± 3.4	–	
Oral ulcers	30 (100)	–	
Genital ulcers	19 (63.3)	–	
Eye involvement	12 (40)	–	
Vascular involvement	7 (23.3)	–	
Positive pathergy test	8 (26.7)	–	
Body mass index	27.9 ± 4.5	28.3 ± 5.2	>0.5
Heart rate (beat/min.)	77.2 ± 3.5	76.1 ± 5.2	>0.5
Systolic BP (mmHg)	120.7 ± 6.8	118.3 ± 5.5	>0.5
Diastolic BP (mmHg)	77.2 ± 4.5	76.7 ± 4.4	>0.5
ESR (mm/1sthr)	37.7 ± 16.8	12.7 ± 5.6	<0.5*
CRP (mg/l)	14.2 ± 11.08	4.3 ± 2.5	<0.5*
Cholesterol (mg/dl)	173.2 ± 26.7	185.3 ± 21.7	>0.5
HDL-cholesterol (mg/dl)	51.03 ± 10.5	48.2 ± 11.2	>0.5
LDL-cholesterol (mg/dl)	118.4 ± 13.9	120.4 ± 9.6	>0.5
Triglycerides (mg/dl)	139.2 ± 18.6	139.3 ± 10.4	>0.5
BDCAF	4.2 ± 3.2	–	

ESR = Erythrocyte sedimentation rate, CRP = C reactive protein, BDCAF = Behçet's Disease Current Activity Form. Results are presented as n (%) or mean ± SD.

* Significant $p < 0.05$.

Table 2 Comparison between conventional echocardiographic characteristics of the Behçet's disease (BD) patients and controls.

Echocardiographic parameter Mean ± SD	BD (n = 30)	Control (n = 30)	p
LVEDD (mm/m^2)	23.7 ± 1.5	23.1 ± 1.5	>0.05
LVESD (mm/m^2)	15.02 ± 1.6	14.9 ± 0.8	>0.05
Septal thickness (mm/m^2)	4.7 ± 0.3	4.8 ± 0.2	>0.05
Posterior wall thickness (mm/m^2)	4.7 ± 0.3	4.7 ± 0.4	>0.05
Left atrial diameter (mm/m^2)	17.5 ± 1.2	17.5 ± 1.6	>0.05
Ao S (mm/m^2)	14.8 ± 0.7	14.4 ± 0.9	>0.05
Ao D (mm/m^2)	13.4 ± 0.6	12.6 ± 1.1	<0.05*
Aortic strain (%)	5.8 ± 2.98	8.2 ± 2.5	<0.05*
Aortic stiffness index	9.2 ± 4.98	4.9 ± 1.1	<0.001**
Stroke volume (ml)	57.1 ± 6.7	54.2 ± 5.5	>0.05
IVRT (ms)	89.8 ± 3.6	76.4 ± 5.4	<0.001**
VTI (cm)	17.98 ± 0.6	17.3 ± 1.4	>0.05
E/A ratio	1.1 ± 0.02	1.1 ± 0.03	>0.05
FPV (cm/s)	45.4 ± 4.6	65.3 ± 5.99	<0.001**
E/FPV	1.6 ± 0.2	1.1 ± 0.1	<0.001**

LV = left ventricular, EDD = end diastolic volume, ESD = end systolic volume, AoS = aortic systolic diameter, Ao D = aortic diastolic diameter, IVRT = isovolumic relaxation time, VTI = velocity time integral, E/A = peak early/late myocardial velocity ratio, FPV = flow propagation velocity.
* Significant $p < 0.05$.
** Highly significant $p < 0.001$.

Table 3 Comparison between Tissue Doppler Imaging characteristics of the Behçet's disease (BD) patients and controls.

TDI parameter Mean ± SD	BD (n = 30)	Control (n = 30)	p
LV Sa (m/s)	0.12 ± 0.006	0.12 ± 0.01	>0.5
LV IVV (m/s)	0.11 ± 0.016	0.13 ± 0.006	<0.001**
LV IVA (m/s^2)	2.28 ± 0.35	3.60 ± 0.11	<0.001**
LV MPI	0.42 ± 0.007	0.28 ± 0.02	<0.001**
E (cm/s)	0.12 ± 0.009	0.14 ± 0.01	<0.001**
A (cm/s)	0.11 ± 0.02	0.12 ± 0.007	<0.05*

TDI: Tissue Doppler Imaging, LV = left ventricular, Sa = peak velocity during systolic ejection, IVV = peak myocardial velocity during isovolumic contraction, IVA = myocardial acceleration during isovolumic contraction, MPI = myocardial performance index. E = peak early diastolic myocardial velocity, A = peak late diastolic myocardial velocity.
* Significant $p < 0.05$.
** Highly significant $p < 0.001$.

The BDCAF significantly correlated with IVRT (r = 0.54, $p < 0.05$), E/FPV (r = 0.53, $p < 0.05$) and the aortic stiffness index (r = 0.71, $p < 0.001$) and a significant negative correlation with LVMPI (r = −0.57, $p < 0.05$), aortic strain (r = −0.52, $p < 0.05$), FPV (r = −0.58, $p < 0.05$) LVIVA (r = −0.51, $p < 0.05$), LVIVV (r = −0.47, $p < 0.05$) and E wave (r = −0.48, $p < 0.05$) (Table 4).

Table 4 Correlations between Behçet's Disease Current Activity Form (BDCAF) and different conventional and tissue Doppler echocardiography variables in Behçet's disease (BD) patients.

Echocardiographic parameters	BDCAF	
	r	p
LVEDD (mm/m^2)	0.12	>0.5
LVESD (mm/m^2)	0.16	>0.5
Septal thickness (mm/m^2)	0.13	>0.5
Posterior wall thickness (mm/m^2)	0.21	>0.5
Aortic strain (%)	−0.52	<0.5*
Aortic stiffness index	0.71	<0.001**
IVRT (ms)	0.54	<0.5*
VTI (cm)	0.14	>0.5
E/A	0.12	>0.5
FPV (cm/s)	−0.58	<0.5*
E/EPV	0.53	<0.5*
LV TDI Sa (m/s)	0.18	>0.5
LV IVV (m/s)	−0.47	<0.5*
LV IVA (m/s^2)	−0.51	<0.5*
LV MPI	0.57	<0.5*
E wave (cm/s)	−0.48	<0.5*
A wave (cm/s)	−0.27	>0.5

LV = left ventricular, EDD = end diastolic volume, ESD = end systolic volume, Ao S = aortic systolic diameter, Ao D = aortic diastolic diameter, IVRT = isovolumic relaxation time, VTI = velocity time integral, E/A = peak early/late myocardial velocity ratio, FPV = flow propagation velocity, Sa = peak velocity during systolic ejection, IVV = peak myocardial velocity during isovolumic contraction, IVA = myocardial acceleration during isovolumic contraction, MPI = myocardial performance index. E = peak early diastolic myocardial velocity, A = peak late diastolic myocardial velocity.
* Significant $p < 0.05$.
** Highly significant $p < 0.001$.

4. Discussion

Behçet disease (BD) may affect many systems and the underlying pathological mechanism is believed to be due to involvement of the arteries and arterioles with narrowing of their lumen by focal fibrinoid deposition and fibroelastic proliferation. [32]. Cardiac involvement in BD can be seen frequently without symptoms [33] and silent myocardial ischemia that is defined as objective documentation of myocardial ischemia in the absence of angina or ischemic equivalents has also been reported in patients with BD [34].

In the present study, it was shown that left ventricle diastolic functions were impaired in BD patients as measured by conventional echocardiography and TDI in the form of prolonged isovolumic relaxation time (IVRT) ($p < 0.001$), low flow propagation velocity(FPV) ($p < 0.001$), prolonged [E ($p < 0.001$) and A waves ($p < 0.05$)]. Our results confirmed the results of others who found impairment of LV diastolic functions in BD patients compared to the controls [35–37]. This can be explained as vasculitis affecting the intramural and small coronary arteries which may cause weakening of endocardial and myocardial tissue and replacement by fibrosis due to myocardial ischemia [38].

Güllü et al. [39] reported a high prevalence of silent myocardial ischemia (25%) and Türkölmez et al. [40] recommended myocardial perfusion scintigraphy in patients with long lasting BD for screening of silent myocardial ischemia. Also, we found altered aortic elastic properties in the form of decreased aortic strain and increased aortic stiffness index

which provides another explanation to significant diastolic dysfunction in BD patients. Our results confirmed the results of others which found increased aortic stiffness in BD patients [38,41,42]. This increase in arterial stiffness in BD patients may be related to endothelial dysfunction and the inflammatory process associated with BD [43] leading to smooth muscle cell proliferation and increased synthesis of structural proteins including collagen [45]. In contrast to our results, in the study of Kürüm et al. [44] they found no difference in arterial stiffness between BD and control and they attribute this to the small sample size and short disease duration.

Tissue Doppler imaging (TDI) allows quantitative measurements of myocardial contraction and relaxation velocities of a selected myocardial segment and early detection of subclinical global and regional myocardial dysfunctions [28]. In our study TDI detected early left ventricular systolic dysfunction that was not evident by conventional echocardiography in the form of decreased peak myocardial velocity (IVV) and acceleration (IVA) during isovolumic contraction and increased myocardial performance index (MPI) ($p < 0.001$). Yagmur et al. [37] suggested that impaired systolic function before the development of overt cardiac failure may be due to early affection of subendocardial longitudinal fibers with no distortion in circumferential function in BD due to the deterioration in coronary microvascular function, which is attributed to small vessel vasculitis.

We found a significant correlation between BDCAF and aortic stiffness parameters; aortic strain ($r = -0.52$, $p < 0.05$), aortic stiffness index ($r = 0.68$, $p < 0.05$) and also with the systolic and diastolic dysfunction parameters. Caldas et al. [42] found increased arterial stiffness in BD with systemic disease more than in mucocutaneous BD patients. This can be related to the inflammatory process that causes atherosclerosis through altered lipid peroxidation [45] and increased levels of intracellular adhesion molecules. Also, Ikonomidis et al. [38] found BD with vascular complication to have more myocardial and aortic wall dysfunction and attributed this to a common pathophysiologic pathway that may elevate inflammatory cytokines as interleukin-2 (IL-2) and IL-6.

In conclusion, BD patients have impaired left ventricular systolic and diastolic functions and altered aortic elastic properties that correlate with disease activity. Tissue Doppler Imaging is more sensitive than conventional echocardiography for the detection of early ventricular dysfunction in patients with BD.

Conflict of interest

None.

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