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Value of Certain Echocardiographic Findings in the Initial Suspicion of Behçet's Disease

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Purpose: To describe the echocardiographic findings detected as first manifestations of Behçet's disease (BD) and compare these findings with those detected in established cases of BD receiving regular medical treatment. Methods: Two groups of patients were studied. Group 1 comprised 41 patients with BD on regular medical treatment. Group 2 comprised 5 previously healthy patients who presented to the cardiology department because of cardiac symptoms and were diagnosed in retrospect during hospitalization as BD. Thirty-two age- and sex-matched individuals served as control subjects (control group). All patients and controls underwent complete M-mode, two-dimensional, and Doppler transthoracic echocardiographic examinations. Results: Of the 41 treated patients with BD (mean age: 32 $\pm$ 8 years, 90% males, mean duration since diagnosis: 14.5 years), only 1 patient was found to have severe aortic regurgitation secondary to aortic root dilation. On the other hand, the 5 previously healthy patients who presented with cardiac symptoms (mean age: 24 $\pm$ 6 years, all males) had significant cardiac involvement and evident echocardiographic findings ($P < 0.001$). Four cases had intracardiac masses: 3 in the right atrium (RA), 1 in the right ventricle (RV), while the last patient had pericardial effusion (PE). All these patients were diagnosed in retrospect as BD. The RA masses disappeared on medical therapy, while the RV mass was surgically excised and proved to be multiple thrombi histopathologically. The patient with PE had recurrent attacks of massive effusion so a pericardial window was performed surgically. Conclusion: Diagnosis of BD might be initially suspected by the cardiologists based on certain echocardiographic findings, namely the presence of right-sided masses. Diagnosis of BD in such patients has important therapeutic implications and accordingly prognostic value. (Echocardiography 2014;31:924–930)

Key words: Behçet's disease, intracardiac masses, echocardiography, dilated aortic root, aortic regurgitation

Behçet's disease (BD) is a generalized chronic inflammatory disease characterized by recurrent oral and genital ulcerations and ocular manifestations.[1] The main clinical manifestations include the involvement of the mucocutaneous, urogenital, locomotor, ocular, neurological, gastrointestinal, respiratory, and vascular systems with vasculitis affecting arteries and veins of all sizes being the main histological feature.[2,3] The incidence and natural history of cardiac involvement in this disorder are not yet clearly documented.[4] Cardiovascular manifestations have been reported in 7–46% of patients and mortality occurs in up to 20% of those patients with marked vascular involvement. Sporadic cases of endocarditis, myocarditis, pericarditis, acute myocardial infarction, aortic aneurysm, ventricular thrombosis, congestive cardiomyopathy, and valvular dysfunction have been reported.[5–8]

As the underlying pathophysiological mechanism for cardiac involvement in BD is related to inflammation and thrombosis, and both can be suppressed by proper treatment, we hypothesized that the severity of cardiac involvement among diagnosed patients with BD on regular medical treatment is much less than among those undiagnosed untreated cases. We also investigated the role of cardiologists in the initial suspicion of BD among previously healthy individuals presenting with certain echocardiographic findings.

Methods:

Patients were divided in two groups; group 1 (n = 41) consisted of adult patients with BD on regular medical treatment (age: 32 $\pm$ 8 years,

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35 males), and group 2 (n = 5) comprised previously healthy adult males who presented to the cardiology department for evaluation of severe disabling cardiac symptoms of recent onset (dyspnea, cough, haemoptysis, and fatigue). These patients were admitted to the cardiology ward and diagnosed as cases of BD during their index hospitalization upon full rheumatological consultation. Diagnosis of BD was made based on the International Study Group for Behçet's disease criteria.[9] Thirty-two, age- and sex-matched, healthy individuals were also studied as control subjects (control group). Exclusion criteria were (1) rheumatic valvular heart disease; (2) atrial fibrillation; (3) hypertension; (4) diabetes; (5) terminal renal or hepatic failure; (6) hypothyroidism; (7) any systemic disease that can cause cardiac abnormalities (ankylosing spondylitis, rheumatoid arthritis, and systemic lupus erythematosus); and (8) Marfan syndrome.

Clinical Data:
Clinical information, including demographic data, comorbidities, presence of cardiac symptoms, history of previous deep venous thrombosis (DVT), history of prolonged bed rest or previous hospitalizations, history of thrombosis in a first-degree relative <50-year-old, and history of drug intake were collected. Laboratory evaluations including complete blood count (CBC), erythrocyte sedimentation rate (ESR), liver and renal function tests, and others were performed for patients with BD and the controls. Lower limbs and pelvic venous Doppler examinations were performed for those patients with echocardiographically detected right atrial thrombi to rule out DVT.

Echocardiographic Studies:
All patients and controls were examined with Philips iE33 echocardiographic machine (Philips Medical Systems, Andover, MA, USA). A broad band 2.5–3.5 MHz phased array transducer equipped with tissue Doppler imaging (TDI) mode was used. Two-dimensional imaging (2D) was performed, followed by Doppler. A single investigator, who had performed transthoracic echocardiography for >5 years and had achieved level 3 training in echocardiography, performed all the Echo/Doppler recordings.

Echocardiographic Analysis:
Two-dimensionally guided M-mode tracings were obtained from the parasternal short-axis view to measure the left ventricular (LV) dimensions and wall thickness. The LV ejection fraction (EF) was measured using the disk summation method. According to the guidelines from the American Society of Echocardiography (ASE), an EF < 55% was considered abnormal.[10] To assess the LV diastolic function, the following Doppler parameters were measured: peak E velocity, peak A wave velocity, E/A ratio, and deceleration time of E velocity. Using the TDI, the lateral mitral annular E′-wave velocity was obtained and the E/E′ ratio was then calculated.[11] For assessment of the right ventricular (RV) systolic functions, the fractional area change (FAC), the tricuspid annular plane systolic excursion (TAPSE) and S wave velocity of the lateral tricuspid annulus were measured and analyzed according to the guidelines published by the ASE in 2010.[12] The cardiac valves were assessed by 2D, color and Doppler imaging. The severity of the aortic regurgitation was assessed by measurement of the vena contracta width as well as the proximal jet width obtained from the parasternal long-axis view and its ratio to the LV outflow tract diameter (LVOT). A ratio of proximal jet width to the LVOT diameter >65% with a VC > 0.6 cm defined severe aortic regurgitation. Detected pericardial effusion (PE) was described according to its amount, site, associated fibrinous shreds, and evidence of increased intrapericardial pressure. Severe PE was defined as an echo-free space of ≥1 cm seen surrounding the heart. Detected intracardiac masses were fully analyzed regarding their location, number, size, texture, and mobility.

Statistical Methods:
Data management and analysis were performed using the SPSS statistics for Windows; version 20.0 (IBM Corp, Armonk, NY, USA). The numerical data were statistically presented in terms of mean ± standard deviation. Categorical data were summarized as count and percentage. Comparing categorical variables was done by chi-square test or Fisher's exact test, as appropriate. One-way ANOVA with post hoc Bonferroni analysis was performed to compare the normally distributed variables, while nonnormally distributed variables were compared using Kruskal–Wallis H test. A two-sided P-value <0.05 was considered statistically significant.

Results:
Of the 41 treated patients with BD (mean age: 32 ± 8 years, 87% males, mean duration since diagnosis was 14.5 years), only one patient (2%) was found to have abnormal echocardiographic findings. He had dilated aortic root by 2D imaging (Fig. 1) and severe aortic regurgitation as detected by color Doppler assessment with holodiastolic flow reversal in the proximal descending aorta. The aortic valve leaflets were almost of normal thickness and excursion with failure of proper diastolic coaptation secondary

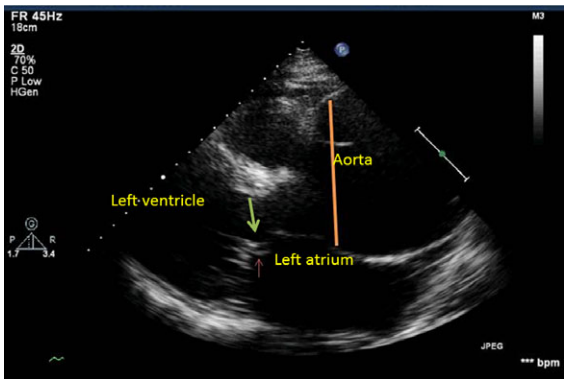

Figure 1. Parasternal long-axis view showing dilated aortic root (line). Notice also the reversed doming of the anterior mitral valve secondary to severe aortic regurge (arrow).

to aortic root dilation. His LV dimensions were large (LV end-diastolic and end-systolic dimensions were 6 and 4.1 cm, respectively). Although aortic regurgitation was severe, yet the patient did not complain of any cardiac symptoms, he had additionally old left-sided stroke with marked restriction of his physical activity. Compared to the control group, all the other examined patients (group 1) had normal resting echo/Doppler study. Eleven patients (~27%), however, had vascular affection either in the venous side (documented previous DVT and superficial thrombophlebitis in 9 patients) or in the arterial side (1 patient had femoral artery aneurysm necessitating surgical intervention and one patient had previous stroke with involvement of the middle cerebral artery). Clinical and echocardiographic characteristics of the study population are shown in Table I.

Echocardiographic Findings in Group 2 Patients:

All patients in group 2 (mean age: 24 ± 6 years, all males) had positive echocardiographic findings. The first patient (19-year-old) presented with recurrent attacks of hemoptysis of 1 week duration. Echocardiographic examination revealed multiple large masses (Fig. 2) attached to the right ventricular walls (both the lateral and septal walls were involved) and protruding toward the RV cavity proper (Fig. 3). Smaller mass was also seen related to the RV apex. The patient underwent surgical removal of these masses which proved to be thrombi by histopathological examination and accordingly the patient was kept on heparin infusion. During his postoperative hospital stay, the patient reported a painful genital ulcer and subsequent full

TABLE I

Clinical and Echocardiographic Characteristics of the Study Population

	Control Group (n = 32)	Group 1 (n = 41)	Group 2 (n = 5)
Age (years)	28 ± 6	32 ± 8	24 ± 6*
Male, No. (%)	26 (81)	36 (88)	5 (100)
Smoking, No. (%)	12 (38)	16 (40)	1 (20)
ESR (mm/1st hour)	12 ± 8	19 ± 14	38 ± 19*†
Serum creatinine (mg/dL)	0.9 ± 0.3	0.7 ± 0.1	0.8 ± 0.1
ALT (U/L)	23 ± 10	29 ± 24	18 ± 4
AST (U/L)	21 ± 5	25 ± 12	26 ± 10
Total cholesterol (mg/dL)	169 ± 41	194 ± 45†	117 ± 24*†
Serum triglycerides (mg/dL)	105 ± 58	119 ± 73	119 ± 32
LVIDd (mm)	48 ± 4	50 ± 5	47 ± 3
LVIDs (mm)	31 ± 3	32 ± 5	28 ± 2
EF (%)	64 ± 6	65 ± 5	69 ± 3
Mitral E/E' ratio	4.5 ± 1.1	4.8 ± 1.8	4.8 ± 0.8
Mitral E/A ratio	1.6 ± 0.3	1.4 ± 0.4	1.4 ± 0.2
Left atrial dimensions (mm)	31 ± 5	31 ± 3	30 ± 2
Echocardiographic findings, No. (%)			
Intracardiac thrombi	0 (0)	0 (0)	4 (80)‡
Severe pericardial effusion	0 (0)	0 (0)	1 (20)
Aortic regurgitation	0 (0)	1 (2)	0 (0)
Aortic root dilatation	0 (0)	1 (2)	0 (0)

Data are presented as mean ± SD or number (%). ALT = alanine aminotransferase; AST = aspartate aminotransferase; LVEF = left ventricular ejection fraction; ESR = erythrocyte sedimentation rate; LVIDd = left ventricular internal dimension at end-diastole; LVIDs = left ventricular internal dimension at end-systole.
*$P < 0.05$ compared to patients with Behçet's disease on regular medical treatment.
†$P < 0.05$ compared to control group.
‡$P < 0.001$ compared to other groups.

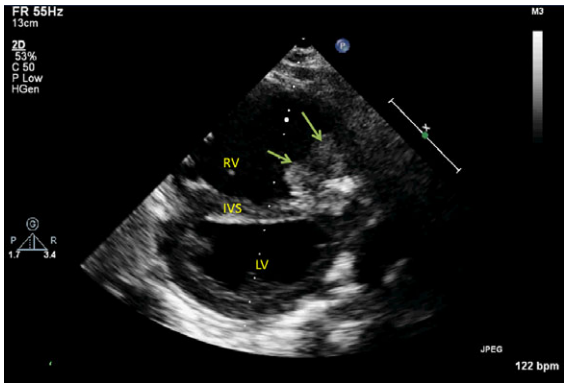

Figure 2. Parasternal short-axis view showing multiple masses related to the septal wall of the right ventricle (RV). Note also the right ventricular cavity dilation and D-shaped septum secondary to pulmonary embolization and subsequent pulmonary hypertension. Left ventricular (LV) is the left ventricle.

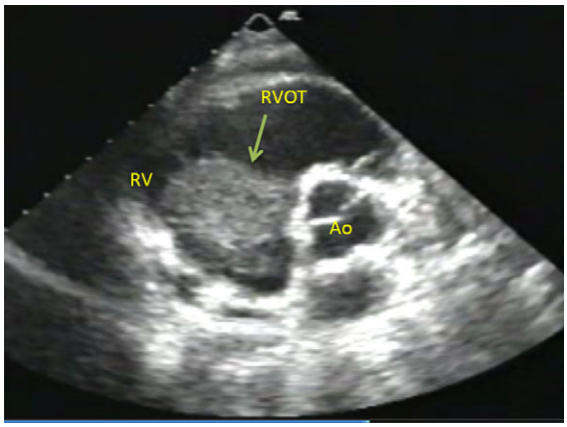

Figure 3. Parasternal short-axis view showing the aorta (Ao), the right ventricular outflow tract (RVOT), and the right ventricle (RV). There is a large irregular mass (arrow) is seen filling the right ventricular cavity.

rheumatological consultation proved diagnosis of BD. Unfortunately, the patient developed severe attack of hemoptysis and arrested before starting treatment of BD. The second patient presented with dyspnea, fatigue, and bilateral lower limb edema. Echocardiography revealed severe PE with no evidence of increased pericardial pressure. Diagnostic pericardiocentesis revealed exudate with no malignant or pus cells detected. Following pericardiocentesis, the patient complained of a painful oral ulcer and again full rheumatological assessment proved diagnosis of BD. The remaining 3 patients had multiple small-to-moderate-sized freely mobile masses within the right atrial cavity (Fig. 4). These masses were diagnosed initially by the echocardiographer as

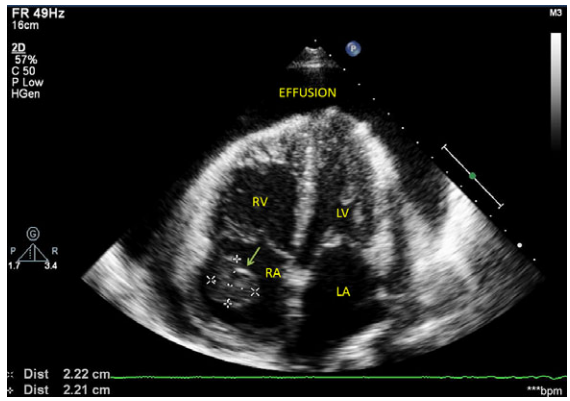

Figure 4. Apical four-chamber view showing the right ventricle (RV), left ventricle (LV), left atrium (LA), and right atrium (RA). There is a well-defined rounded mass (thrombus) in the RA (arrow).

TABLE II

Clinical Characteristics of the Untreated Patients with Behçet's Disease (Group 2)

Characteristics	(n = 5)
Age (years)	24 ± 6
Male	5 (100)
Smoking	1 (20)
Dyspnea	3 (60)
Chest pain	1 (20)
Hemoptysis	1 (20)
History of oral ulceration	5 (100)
History of genital ulceration	5 (100)
Ocular lesions	2 (40)
Skin lesions	1 (20)
Positive pathergy test	2 (40)
Lower limb deep vein thrombosis	0 (0)
Previous history of a thrombotic event	0 (0)
Intracardiac masses	4 (80)
Pericardial effusion	2 (40)
Death	1 (20)
Surgical intervention	2 (40)
In-hospital mortality	1 (20)

Data are expressed as mean ± SD for continuous variables or as number (percentage) for categorical data.

thrombi and anticoagulation therapy was initiated. Venous duplex examinations of the lower limbs and pelvic veins were normal. Tests to rule out inherited causes of hypercoagulable state were not performed because the diagnosis of BD was established before hospital discharge while the patients were on oral anticoagulation therapy. These patients received intravenous followed by oral steroids and warfarin with disappearance of the masses within 8 weeks from starting treatment. Clinical characteristics of group 2 patients are shown in Table II.

Discussion:

Incidence of Cardiac versus Vascular Involvement in BD:

Several published data suggested that the incidence of cardiovascular involvement in BD is highly variable.[5,13–19] While being extremely rare in some reports, others suggested that it can reach up to 46% of patients with lethal outcomes in about 20% of severe cases.[20] One possible explanation of this variability may be due to the difference in the incidence of cardiac versus vascular complications in BD. According to the present study, the cardiac involvement seems to be uncommon among patients with BD on regular medical treatment so that routine echocardiographic assessment of all BD patients cannot be recommended in the absence of clinical signs and symptoms as assessed by the primary physician. On the contrary, approximately one-third of patients with BD develop vascular complications, which include aneurysm formation, arterial or venous occlusive disease, and stroke due to vasculitis of all size vessels.[21] The present study showed that about 27% of patients with BD on regular treatment had some form of vascular complications. Venous complications in the form of DVT and superficial thrombophlebitis were documented in 9 patients, while arterial complications in the form of femoral artery aneurysm and middle cerebral artery involvement were reported in 2 patients. Also, we noticed that the occurrence of vascular complications (venous or arterial), unlike cardiac affection, seems to be not prevented by treatment of BD. Careful examination of the vascular system in every follow-up visit of those patients with recommendation of further imaging test(s) might be accordingly beneficial in those patients. It is important here to mention that involvement of the aorta also can be categorized as vascular rather than pure cardiac complication. Patients with BD can develop aortic regurgitation (cardiac complication) secondary to dilation of the aortic root (Behçet aortitis), while the valve leaflets remain of normal thickness and structure as in our case, however, due to the associated LV enlargement; we classified the abnormality as cardiac rather than pure vascular complication in the analysis of data. While being uncommon in treated patients with BD, significant echocardiographic abnormalities were evident in all previously undiagnosed patients with BD who presented to the cardiology department with severe cardiac symptoms. Eighty percent of those patients had right-sided intracardiac masses. Knowing that the characteristic pathophysiological findings in BD are thrombosis and vasculitis, it seems that the initiation of proper medical therapy for BD treats effectively the thrombotic events with resolution of the intracardiac thrombi (ICT), while the risk of vasculitis (aortitis and vascular complications) remains always there. Further well-designed studies are needed for better understanding of such an entity.

Types of Cardiac Affection in BD:

Many studies had previously evaluated the types of cardiac affection in BD patients. Some examined the LV systolic and diastolic functions using various imaging modalities with inconsistent results.[22–25] Higher incidence of mitral valve prolapse, atrial septal aneurysm,[26] pericarditis,[5] aortic aneurysm,[5,8] endocarditis, intracardiac thrombosis, endomyocardial fibrosis, and myocardial aneurysms were also documented among patients with BD compared to controls. First-degree atrioventricular block, right bundle branch block, ventricular premature beats, and ventricular tachycardia can occur secondary to involvement of the conduction system and ventricular dilation in BD.[27] These studies examined only patients with established diagnosis of BD on regular medical treatment. On the other hand, life-threatening cardiac complications were not examined adequately in previous well-designed studies. Only few case reports of acute cardiac emergencies as acute ST-segment elevation myocardial infarction, severe acute mitral regurgitation, and acute left-sided heart failure were reported in treated patients with BD.[28]

Cardiac Involvement as First Manifestation of BD and Role of Echocardiographers in Initial Suspicion of the Disease:

Based on previously published data, ICT are extremely rare in BD patients.[19] They are more commonly seen in young adults, and sometimes are the first manifestations of the disease.[29] ICT can be misdiagnosed as an intracardiac tumor and can lead to pulmonary embolism or to cerebrovascular disease via a patent foramen ovale (PFO).[29–31] While BD complicated by ICT seems to be confined predominantly to patients from the Mediterranean basin and Middle East,[19,32] published data among these countries are somehow few, most of these published data are case reports from Turkey,[7,33–37] Morocco,[38–40] Tunisia,[29,41] France,[42] Jordan,[43] Italy,[44] and Spain.[45] We do not know exactly what about the other countries, how severe the cardiac involvement is, and how it was managed. Mogulkoc et al.[19] reviewed all published articles about BD with ICT in the English literature from 1966 to 1999 and found only 25 patients. This figure seems to underestimate the real incidence of ICT in patients with BD especially in certain areas of the

world. Rarity of studies in this issue actually represents a challenge for physicians caring about BD because BD has various presentations and complications that differ geographically and genetically. We expect that getting more studies from the Mediterranean and Middle East countries can help much in better understanding of the disease with subsequent better management and prognosis worldwide.

Finally, we think that routine inquiry about the occurrence of oral/genital ulcers can be of great value in the early diagnosis and treatment of BD with subsequent prevention of the development of ICT among these patients. Adding routinely the question about orogenital ulcers to the medical records of adolescents and young males seems simple, easy, and of great cost-benefit value. Importantly, BD must be included in the differential diagnosis of patients presenting by ICT especially among young previously healthy males.

Conclusion:

Thrombi in the right-sided cardiac chambers as detected by echocardiography could be the first manifestation of previously undiagnosed BD. These thrombi respond favorably to proper medical therapy. Vascular rather than cardiac complications are common among patients with BD on medical therapy.

Study Limitations:

The major limitation of the study is the small number of patients. A multicenter international registry for collecting all cases of BD worldwide can help in better understanding of the disease with subsequent better management and outcome.

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