Left atrial volume and function in patients with Behcet’s disease assessed by real-time three-dimensional echocardiography

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Received 25 October 2011; accepted after revision 6 December 2011; online publish-ahead-of-print 6 January 2012

Aims
Behçet’s disease (BD), a multisystemic inflammatory disorder, has been associated with a number of cardiovascular dysfunctions, including endomyocardial fibrosis of the right heart, atrial fibrillation, ventricular arrhythmias and sudden cardiac death. The incidence and nature of cardiac involvement in BD are not yet clearly documented. Our aim was to evaluate left atrial (LA) volume and functions using real-time three-dimensional echocardiography (RT3DE) in Behcet’s patients without any cardiac symptom.

Methods and results
The study included 40 BD (16 females, 24 males and mean age of 33 ± 7 years) and 30 healthy (11 females, 19 males and mean age of 35 ± 6 years) subjects. All the patients’ demographic parameters such as age, gender, and duration of BD were recorded. All the individuals underwent comprehensive 2D echocardiography examination, and RT3DE was performed to assess LA volumes and mechanical functions. LA maximum volume (Vmax) and before atrial contraction volume (Vpre A), LA active stroke volume and total stroke volumes (TSV), total emptying and active emptying fractions and expansion index were significantly higher in Behcet’s disease patients when compared with the controls (P < 0.001 for all). LA passive emptying fraction was significantly lower in the patients with BD than in the controls (41 ± 7 vs. 44 ± 5, P = 0.039). There were positive correlations between TSV and high-sensitive C-reactive protein level (r = 0.413, P = 0.008), TSV, and disease duration (r = 0.417, P < 0.007).

Conclusion
Our study has shown that LA mechanical functions and volumes are impaired in BD. These results may be an early form of subclinical cardiac involvement in patients with BD who have no clinical evidence for cardiovascular disease.

Keywords
Behcet’s disease • left atrial volume • left atrial function • real-time three-dimensional echocardiography

Introduction
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.² Heart involvement is called ‘cardio-Behçet’s disease’ and rarely seen.²–⁶ Cardiovascular involvement of BD includes endocarditis, myocarditis, pericarditis, endomyocardial fibrosis of the right heart, dilated cardiomyopathy, coronary artherosclerosis, intracardiac thrombus, aortic stenosis, mitral valve prolapse, conduction system disturbances, atrial fibrillation, life-threatening ventricular arrhythmias, and sudden cardiac death.³–¹¹ Left atrial (LA) volume, as an LA functional index, has recently been identified as a potential indicator of cardiac disease and atrial arrhythmia. LA functions are important determinants of ventricular filling. Parameters of LA function may provide additional

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information about resistance before the filling of the ventricle. Additionally, the atrial emptying pattern is strongly affected by the left ventricular (LV) diastolic properties.

Many studies have shown that real-time three-dimensional echocardiography (RT3DE) provides an accurate measurement of the left atrial volume and function and could be considered a feasible and reproducible method for its clinical application.10,11 Our aim was to evaluate the left atrial volume and functions using RT3DE in Behçet’s patients without any cardiac symptom.

Methods

The study included 40 patients with Behçet’s disease and 30 healthy subjects. Behçet’s disease was diagnosed according to the criteria reported by the International Study Group for Behçet’s disease.12

A careful history was taken and a complete physical examination was performed in all the subjects. A resting 12-lead electrocardiography was obtained. All the patients’ demographic parameters such as age, gender, and duration of BD were recorded. To avoid confounding by other conditions which affect the LA volume, individuals were excluded from both groups on the basis of the following characteristics: age >45 years, body mass index (BMI) >31 kg/m², systemic hypertension (blood pressure >140/90 mmHg or ongoing antihypertensive medication), diabetes mellitus (fasting serum glucose level >126 mg/dl or ongoing diabetes medication), history of coronary artery disease (>30% luminal diameter narrowing of ≥1 coronary artery shown by angiography, history of coronary revascularization, an abnormal myocardial perfusion scan or dobutamine stress echocardiogram, regional LV akinesia and/or dyskinesia on echocardiogram, or pathologic Q waves on 12-lead electrocardiogram), antithrombotic drug use, valvular heart diseases, obstructive sleep apnea, chronic inflammatory diseases, atrial fibrillation, cardiomyopathies, renal failure, liver disease and poor-quality imaging on two-dimensional echocardiography (2DE) and/or RT3DE.

In all the patients, blood samples were obtained under fasting conditions from the left median antecubital vein before echocardiographic examination and placed in ethylenediaminetetraacetic acid (1.0 mg/mL) containing vials. Plasma samples were collected by centrifugation within 2 h of collection and were studied daily. Serum levels of glucose, total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol were measured using standard laboratory methods and expressed as miligrams per deciliter. High-sensitive C-reactive protein (hs-CRP) levels were calculated according to previous studies:14,15 (i) LA total stroke volume (TSV): $V_{\text{max}} - V_{\text{min}}$; (ii) LA total emptying fraction (TEF): $V_{\text{max}}/V_{\text{max}} \times 100$; (iii) LA active stroke volume (ASV): $V_{\text{max}} - V_{\text{max}}$, (iv) LA active emptying fraction (AEF): $ASV/V_{\text{pre A}} \times 100$; (v) LA expansion index (Ei): $TSV/V_{\text{max}} \times 100$; and (vi) LA passive emptying fraction (PEF): $(V_{\text{max}} - V_{\text{pre A}})/V_{\text{max}} \times 100$.

The LV ejection fraction (LVEF) was also assessed by RT3DE via evaluation of apical four-chamber and two-chamber views using the pyramidal 3D data set.16

Inter-observer variability was assessed by analysis of the RT-3DE data from 20 randomly selected subjects from each group by two independent observers, each blinded to the results obtained by the other. Inter-observer variability was 5.2% for LA $V_{\text{max}}$, 7.1% for LA $V_{\text{min}}$, and 5.6% for LA $V_{\text{pre A}}$ respectively.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 17.0 software (SPSS, Chicago, IL). All continuous variables were expressed as mean ± SD, and categorical variables were defined as

Echocardiographic evaluation

All the individuals underwent comprehensive 2DE examination according to the recommendations by the American Society of Echocardiography,13 followed by RT3DE, which was performed by two experienced investigators blinded to both BD and control groups.

A commercially available machine (IE-33; Philips Medical Systems, Bothell, USA) equipped with broadband SS-1 transducer—with digital storage software for offline analysis was used.

The following 2DE parameters were measured: LV end-diastolic diameter (LVEDD, mm), LV end-systolic diameter (LVESD, mm), aortic root (Ao, mm), LA diameter (mm), LA volume as calculated by Simpson’s methods, LA volume index (LAVI, ml/m²) as calculated by dividing LA volume by body surface area, interventricular septum thickness in diastole (IVST, mm) and posterior wall thickness in diastole (PWT, mm). Transmural pulsed-wave Doppler velocities were recorded from the apical four-chamber view with the Doppler sample placed between the tips of the mitral leaflets. The following variables were measured: peak transmural flow velocity in early diastole (E), peak transmural flow velocity in late diastole (A), E/A ratio, E deceleration time (DT) defined as the slope from the peak to the zero velocity of the E wave, and isovolumetric relaxation time (IVRT) defined as the time interval between aortic valve closure to the onset of E wave. The myocardial systolic ($S_{\text{m}}$), peak early diastolic ($E_{\text{m}}$), and peak late diastolic ($A_{\text{m}}$) velocities were obtained by placing a tissue Doppler sample volume at the septal mitral annulus. The $E/E_{\text{m}}$ and $E/A_{\text{m}}$ ratios were subsequently calculated.

RT3DE was performed with an X3 matrix-array transducer (1–3 MHz) for acquisition of ‘full-volume’ real-time pyramidal volumetric data sets along four consecutive cardiac cycles. Individuals were instructed to hold their breath, and images were coupled with electrocardiographic recordings. Apical two-chamber and four-chamber views were extracted from the pyramidal data set during expiration. Both LV and LA cavities were included in the pyramidal scan volume. Anatomic landmarks used to calculate LA volumes were manually identified by marking five points on the atrial surfaces of the mitral annulus; at the anterior, inferior, lateral and septal annuli and the fifth point at the apex of LA. Points determined to represent the pulmonary vein ostia or LA appendage were excluded from the measurement. The LA internal endocardial border of each frame was defined by automated processing and manually adjusted for pulmonary vein ostia and LA appendage exclusion. From these data, a 3D model of the LA volume was generated (Figure 1A and B). The RT3DE data sets were digitally stored and analyzed using analysis software (QLab-Philips version 7.1; Philips Medical Systems). All the stored digital data were analyzed by two independent observers who were blinded to the clinical data. (i) LA maximum volume ($V_{\text{max}}$): at end systole, the time at which the atrial volume was the largest just before the mitral valve opening, (ii) LA minimum volume ($V_{\text{min}}$): at end diastole, the time at which the atrial volume at its nadir before mitral valve closure, and (iii) before atrial contraction volume ($V_{\text{pre A}}$): the last frame before mitral valve reopening or at time of P wave on electrocardiogram (Figure 2). From the three volumes, the following measurements were selected as indices of LA function and calculated according to previous studies:14,15 (i) LA total stroke volume (TSV): $V_{\text{max}} - V_{\text{min}}$; (ii) LA total emptying fraction (TEF): $V_{\text{max}}/V_{\text{max}} \times 100$; (iii) LA active stroke volume (ASV): $V_{\text{max}} - V_{\text{max}}$, (iv) LA active emptying fraction (AEF): $ASV/V_{\text{pre A}} \times 100$; (v) LA expansion index (Ei): $TSV/V_{\text{max}} \times 100$; and (vi) LA passive emptying fraction (PEF): $(V_{\text{max}} - V_{\text{pre A}})/V_{\text{max}} \times 100$.
percentages. Differences among the groups were assessed with the \( \chi^2 \) test for categorical variables. Continuous variables were compared between the groups using the Student’s \( t \)-test or Mann–Whitney \( U \) test, depending on whether they distributed normally or did not, as tested by the Shapiro–Wilk’s test. Pearson’s correlation analysis was used to estimate the relationship between the test parameters. A \( P \) value of \( <0.05 \) was considered to be statistically significant.

**Results**

Baseline clinical and laboratory characteristics of 40 BD (16 females, 24 males and mean age of 33 ± 7 years) and 30 healthy (11 females, 19 males and mean age of 35 ± 6 years) subjects are listed in Table 1. There were no significant differences between Behcet’s patients and the controls in terms of age, gender, BMI, systolic and diastolic blood pressures, total cholesterol, HDL cholesterol, LDL cholesterol and glucose, whereas triglyceride was significantly lower in the Behcet’s patients when compared with that of the controls (120 ± 8 mg/dL vs. 166 ± 8 mg/dL, \( P = 0.013 \)) and hs-CRP was significantly higher in the Behcet’s patients when compared with the controls (15 ± 2 mg/L vs. 2.6 ± 3 mg/L, \( P < 0.0001 \)). LVEDD, LVESD, aortic diameter, LA diameter, IVST, PW, E/A ratio, \( S_m \), \( E/E_m \), LAVI and LAVI of the two groups were similar. IVRT and DT were significantly higher in the patients with BD than in the controls (90 ± 11 vs. 80 ± 8 ms, \( P < 0.0001 \) and 201 ± 3 vs. 174 ± 9.7 ms, \( P < 0.0001 \), respectively). However, \( E_m/A_m \) ratio was significantly lower (1.25 ± 0.15 vs. 1.44 ± 0.28, \( P < 0.0001 \)) in the patients with BD than those in the controls.

**Real-time 3DE findings**

All of the following results are shown in Table 2. \( V_{\text{max}} \), \( V_{\text{pre A}} \), TSV, TEF, ASV, AEF and EI were significantly higher in the Behcet’s patients when compared with that in the controls (\( P < 0.0001 \) for all). However, PEF was significantly lower in the patients with BD than that in the controls (41 ± 7 vs. 44 ± 5, \( P = 0.039 \)). LVEF and the minimum LA volume of the two groups were similar. There were modest positive correlations between TSV and hs-CRP levels (\( r = 0.413, P = 0.008 \)), and TSV and disease duration (\( r = 0.417, P < 0.007 \)); similarly, there were modest positive correlations between expansion index and hs-CRP, and EI and disease duration (\( r = 0.423, P < 0.007 \) vs. \( r = 0.417, P < 0.007 \)).
respectively). However, there was no correlation between TSV and the ages of the patients.

**Discussion**

Previous studies have examined the prognostic value of LA size in predicting the risk of subsequent development of atrial fibrillation, cerebrovascular events, acute myocardial infarction, congestive heart failure, as well as cardiac, and all-cause mortality.\(^\text{17-21}\) LA volume can be estimated using a number of different methods, such as biplanar disc summation (Simpson’s rule), the area-length method, and the prolate-ellipsoid method on 2DE. This estimate takes geometric inferences into consideration and may have limited application in cases with severe anatomic alterations in the LA.\(^\text{22}\) On the other hand, LA volume and mechanical functions analysis using RT3DE has been a validated method.\(^\text{10,23,24}\)

The main findings of the current study were a significant increase in the LA volume and augmentation of LA active systolic functions in BD patients compared with the controls as analyzed using RT3DE and a decrease in LA PEF. Moreover, there were no differences in LA diameters and LAVI of the BD patients and controls. It is known that LAVI is a better marker than the LA diameter for measuring LA size. Although controls had higher BMI values than those with BD and it did not reach the statistical significance, LA diameters and LAVI were interestingly higher in BD patients compared with the controls.

Although these higher values observed in BD patients were not statistically significant, these measurements were consistent with RT3DE measurements. This finding suggests that RT3DE is a more sensitive technique.

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E_m/A_m \text{ ratio is an indicator of diastolic dysfunction. It has been shown in previous studies that } E_m/A_m \text{ ratio is decreased in BD patients.}^\text{25,26}
\]

In our study, \(E_m/A_m\) ratio was decreased in BD patients in comparison to controls.

LA mechanical functions consist of reservoir, conduit, and booster pump functions at different stages of cardiac cycle. The reservoir function takes effect during ventricular systole, passive conduit function in early diastole, and booster pump function during ventricular diastole in the presence of sinus rhythm.

Our results show that the decrease in LA PEF is related to elevated end-diastolic LV pressure, and the increase in LA active emptying volume is associated with a compensatory mechanism in LA contraction.\(^\text{26,27}\) Changes in the LA PEF and LA active emptying volume indicate deterioration of atrial conduit and booster functions.
pump functions. In addition, El increased in our study; this finding indicates impaired LA reservoir function, which also suggests deterioration of contraction and relaxation of the LA myocardium.27,28 Studies in which myocardia of Behcet's patients are examined have shown microvascular inflammation, focal fibrinoid deposits and fibroblast proliferation, which affect intramyocardium, small coronary arteries, arterioles and especially medial portions of small vessels.29–31 These structural changes in the myocardia of our asymptomatic patients with Behcet's disease may indirectly alter atrial myocardium by causing diastolic dysfunction without affecting systolic functions of the LV. LA volume and mechanical function disorders found in our study may be due to this affected atrial myocardium. In addition, we suggest that microvascular inflammatory changes may contribute to afore-mentioned process by directly affecting atrial myocardium and vascular structures.

It has been shown in the previous studies that many chronic inflammatory diseases involve the left atrium, which leads to an increase in cardiac events.32–34 In our study, there were modest positive correlations between TSV and hs-CRP and between TSV and the duration of the disease. There were also modest positive correlations between El and hs-CRP and between El and the duration of the disease. These findings suggest that the inflammatory process may cause the remodeling of the left atrium.

Study limitations

Our study has a cross-sectional design and the lack of follow-up of the patients. Another limitation is the relatively small sample size of the patient population. Thus, long-term follow-up and large-scale prospective studies are needed to determine the predictive value of LA mechanical functions and volumes in patients with BD. Finally, LA appendage plays an important role in the LA reservoir function, especially during increases in LA pressure or volume.35 However, we did not include LA appendage for the calculation of LA function and volume. Studies that include measurements of LA appendage functions will be more meaningful.

In conclusion, our study showed that LA mechanical function and volume are impaired in BD. These results may be indicative of subclinical cardiac involvement in BD, when there is clinical evidence for cardiovascular disease. Microvascular cardiac involvement and chronic inflammatory processes in Behcet's disease may cause functional and structural changes in the LA. Hence, we suggest that atrial arrhythmias may develop in these patients due to impaired LA functions.

Conflict of interest: none declared.

References


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Ostium secundum atrial septal defect and partial anomalous pulmonary venous connection

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Image description
Partial anomalous pulmonary venous connection is rarely documented in adults. Symptoms occur if more than one anomalous vein is present or associated defects occur, such as sinus venosus atrial septal defect (ASD) or, uncommonly, secundum ASD.

A 47-year-old woman presented with worsening shortness of breath. A small secundum ASD associated with a large, single anomalous pulmonary vein (APV) draining into the inferior vena cava (IVC) was discovered. We postulated that, as a consequence of obesity, newly diagnosed hypertension, and diastolic dysfunction, she became increasingly symptomatic due to increased left-to-right shunting, predominantly through the APV. Successful surgical correction improved her symptoms and reversed her right-sided remodelling and pulmonary hypertension.

Transthoracic echocardiography of the left heart was normal except for the presence of mild diastolic dysfunction, dilated right heart chambers with mild tricuspid regurgitation, and a systolic pulmonary pressure of 55 mmHg.

A transesophageal echocardiogram revealed a small secundum ASD of ~10 mm through which blood shunted from left to right [Panel A]. The most striking feature was a large vessel draining blood into the IVC just above the drainage site of the hepatic veins (HV) [Panel B, Supplementary data online, Video S1]. The left pulmonary veins were draining into the left atrium.

A 64-mm computed tomography angiogram of the chest confirmed normal pulmonary arteries and lung architecture. A large, single, right-sided APV draining into the IVC below the diaphragm was noted [Panels C (anterior view of thorax) and D (posterior view of thorax)]. RA, right atrium.

Conflict of interest: none declared.

Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.