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Subclinical left ventricular dysfunction in Behcet's disease assessed by two-dimensional speckle tracking echocardiography

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Aims The aim of this study was to evaluate the left ventricular (LV) systolic strain by speckle tracking echocardiography (STE) in order to provide the early detection of myocardial dysfunction in patients with Behcet's disease (BD). We also aimed to examine the relationship between LV systolic strain and N-terminal pro-B type natriuretic peptide (NT-proBNP), which is a cardiac biomarker of ventricular dysfunction.

Methods and results Longitudinal and circumferential systolic strain assessed by STE was obtained in 32 BD patients and 27 age-matched controls. NT-proBNP levels were also measured in all subjects. Regional and mean longitudinal strain (-17.8 ± 2.7 vs. $-20.5 \pm 1.8\%$; $P < 0.0001$) was significantly lower in BD patients when compared with the healthy controls. Whereas regional and mean circumferential strain values (-22.0 ± 1.6 vs. $-22.2 \pm 2.3\%$; $P = 0.62$) did not reveal a significant difference between the patients and the controls. NT-proBNP was significantly higher in the patients than in the controls (65.18 ± 84.51 vs. 30.84 ± 14.75 pg/mL; $P = 0.003$). Linear regression analyses revealed only NT-proBNP as the independent correlate of mean LV longitudinal strain ($R = 0.603$, $P = 0.001$).

Conclusion Longitudinal myocardial systolic function assessed by STE, which is a sensitive marker of subclinical ventricular dysfunction is impaired in BD. Increased NT-proBNP levels may be a sign of subclinical ventricular dysfunction in these patients.

Keywords Behcet's disease • Speckle tracking echocardiography • N-terminal pro-B type natriuretic peptide

Introduction

Behcet's disease (BD) is an inflammatory disorder of unknown aetiology, characterized by recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions.[1,2] It is now well known that BD is a multisystem disorder that may affect any organ in different combinations. Involvement of the heart is called Cardio-BD[3,4] and includes pericarditis, myocarditis, endocarditis, endomyocardial fibrosis, conduction system disturbances, coronary arteritis, acute myocardial infarction, and dilated cardiomyopathy.[5–8]

Recently, left ventricular (LV) diastolic dysfunction has been shown to be present by conventional and tissue Doppler echocardiography measurements in patients with BD.[9–11] However, these measurements have major disadvantages such as angle dependence, limited spatial resolution, and deformation analysis in one dimension.[12,13] The recent development of two-dimensional (2D) speckle tracking echocardiography (STE) overcomes some of these limitations and is used for the quantitative assessment of global and local LV function from 2D images.[14] Previous studies have indicated that 2DSTE is more sensitive than conventional echocardiography for detecting subclinical ventricular dysfunction in various clinical disorders.[15,16]

Since cardiac involvement in BD patients has not been previously evaluated by using STE, the aim of this study was to

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evaluate the LV systolic strain by STE in order to provide the early detection of myocardial dysfunction in patients with BD. We also aimed to examine the relationship between LV systolic strain and NT-proBNP, which is a cardiac biomarker of ventricular dysfunction.

Methods

A total of 47 consecutive patients with BD who were diagnosed according to the International Study Group's criteria for BD[17] were referred from the Dermatology Department for consideration of inclusion in this study and of these 32 patients were included. Exclusion criteria were as follows: Coronary artery disease, diabetes mellitus ($n = 1$), hypertension ($n = 1$), decreased LV function ($n = 1$), valvular heart disease, pulmonary artery hypertension ($n = 1$), arrhythmia ($n = 1$), renal and haematological disorders, being on medications known to affect the echocardiographic parameters ($n = 4$) and inadequate image quality ($n = 6$). Twenty-seven healthy subjects were selected and matched to the patients for sex, age, and body surface area as the control group. Twenty-two patients (68.7%) were receiving colchicine therapy. All participants signed their informed consent form before attending the study, and the local Ethics Committee approved the study protocol. All participants underwent a complete physical examination and routine laboratory analysis, including the chest radiograph and electrocardiography before the study. hs-C-reactive protein was calculated by the nephelometric method (Behring Nephelometer Analyzer, Germany) and expressed as milligram per litre. Serum levels of NT-proBNP were measured using the chemiluminescent immunometric assay (IMMULITE 2000 NT-proBNP, Siemens) and expressed as pigogram per millilitre.

Table 1 Baseline characteristics of patients and controls

	BD, $n = 32$	Controls, $n = 27$	*P*-values
Age (year)	35.47 ± 8.96	36.44 ± 8.29	NS
Women/men	13/19	8/19	NS
BMI (kg/m^2)	24.26 ± 4.08	25.31 ± 3.65	NS
Plasma glucose (mg/dL)	95.06 ± 22.31	100.92 ± 22.56	NS
Total cholesterol (mg/dL)	171.00 ± 32.66	193.23 ± 50.15	NS
NT-pro BNP (pg/mL)	65.18 ± 84.51 (20–477)	30.84 ± 14.75 (20–76.7)	0.003
hs-C-reactive protein (mg/L)	18.74 ± 28.33	3.14 ± 3.57	<0.0001
Disease duration (years)	5.37 ± 5.57	—	—
LV ejection fraction (%)	64.91 ± 4.95	65.22 ± 4.32	NS
Left atrial diameter (mm)	33.09 ± 3.74	31.66 ± 2.40	NS
Aortic diameter diastolic (mm)	30.28 ± 3.77	29.51 ± 3.14	NS
LVEDD (mm)	45.38 ± 3.30	45.67 ± 3.25	NS
E/A	1.31 ± 0.26	1.40 ± 0.16	NS
DT (ms)	207.50 ± 34.33	174.62 ± 9.79	<0.0001
IVRT (ms)	87.96 ± 11.20	83.33 ± 9.50	NS
Sm (cm/s)	11.05 ± 1.89	10.77 ± 1.45	NS
E/Em	7.20 ± 1.55	7.01 ± 1.09	NS
Em/Am	1.23 ± 0.16	1.46 ± 0.29	0.001

Values are given as mean ± SD or min–max. BD, Behcet's disease; ns, not significant; LV, left ventricular; LVEDD, LV end-diastolic dimension; E, mitral early diastolic velocity; A, mitral late diastolic velocity; DT, mitral E-wave deceleration time; IVRT, isovolumetric relaxation time; Sm, LV systolic myocardial velocity; Em, LV myocardial early diastolic velocity; Am, LV myocardial late diastolic velocity.

Echocardiography

Echocardiographic images were obtained after 10 min rest, in the left lateral decubitus position with a Philips IE-33 machine (Philips, Bothell, USA) equipped with broadband S5-1 transducer. Three consecutive cycles were averaged for every parameter. Left atrial, aortic diastolic, LV end-systolic, and end-diastolic diameters were measured. LVEF was estimated by Simpson's rule. Transmitral pulsed-wave Doppler velocities were recorded from the apical four-chamber view with Doppler sample placed between the tips of the mitral leaflets. Early (E) and late (A) wave velocities, E/A ratio, E deceleration time (DT), and isovolumetric relaxation time (IVRT) were measured from the mitral inflow profile. The myocardial systolic (Sm), early diastolic (Em), and late diastolic (Am) velocities were obtained at the septal mitral annulus by placing a tissue Doppler sample volume. The E/Em and Em/Am ratios were subsequently calculated.

Two-dimensional speckle tracking analyses were performed on grayscale images of the left ventricle obtained in the apical four-chamber views and short-axis mid-ventricular views. Three consecutive end-expiratory cardiac cycles using the high frame rate (50 Hz or more) harmonic imaging in each echocardiographic view were acquired.

Table 2 Circumferential and longitudinal strain values assessed by Speckle tracking echocardiography

	BD, $n = 32$	Controls, $n = 27$	*P*-values
Longitudinal Strain (%)			
Basal septum	−14.5 ± 2.9	−17.0 ± 2.6	0.001
Mid septum	−17.4 ± 3.9	−20.0 ± 3.4	0.009
Apical septum	−21.0 ± 3.2	−23.9 ± 3.6	0.002
Basal lateral	−15.5 ± 2.7	−17.4 ± 2.6	0.011
Mid lateral	−16.8 ± 3.0	−19.4 ± 3.3	0.003
Apical lateral	−19.8 ± 3.0	−22.4 ± 2.8	0.002
Apex	−21.1 ± 2.7	−23.5 ± 2.6	0.001
Mean longitudinal strain	−18.0 ± 2.3	−20.5 ± 1.8	<0.0001
Circumferential strain (%)			
Anteroseptal	−22.6 ± 2.9	−22.4 ± 4.0	0.82
Anterior	−21.0 ± 3.7	−22.3 ± 4.0	0.22
Anterolateral	−21.6 ± 3.8	−21.7 ± 4.0	0.87
Inferolateral	−22.3 ± 2.9	−22.8 ± 4.3	0.63
Inferior	−22.5 ± 3.5	−21.2 ± 3.8	0.18
Inferoseptal	−21.8 ± 3.0	−22.9 ± 4.1	0.24
Mean circumferential strain	−22.0 ± 1.6	−22.2 ± 2.3	0.63

Data were subsequently transferred to the computer for off-line analysis using developed 2D speckle tracking software (TMQA, Q-Lab, Philips). One cardiac cycle was analysed in each patient. The analysis was initiated through four-chamber apical view in the end-diastolic frame and three anatomic landmarks including septal and lateral points on the mitral annulus and the apical endocardium were manually set to initialize the analysis. Following initialization, the software automatically placed region of interest equidistantly on the endocardial LV cavity surface. Manual adjustment of region of interest was performed when necessary. Thereafter, the software automatically analyzed target area according to seven segments. After automated tracking analysis, visual inspection of the tracking was performed. If the tracking was not satisfactory, manual adjustments were made to the tracking points throughout the cardiac cycle and thereafter automatic tracking repeated until satisfactory tracking results were achieved. Short-axis images at the mid-ventricular level were replaced on the region of interest circle on outer contour of myocardial border. Septal region was marked by activating the tissue tracking button. The software automatically analysed target area according to six segments. From the apical view; longitudinal strain was assessed through basal septal, midseptal, apical septal, apex, apical lateral, midlateral, and basal lateral wall segments. From the short-axis view, circumferential strain was assessed from the six mid-segments of the anteroseptal, anterior, anterolateral, inferolateral, inferior, and inferoseptal walls. The mean longitudinal and circumferential strain was obtained.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 17.0 software (SPSS, Inc., Chicago, IL, USA). All continuous variables were expressed as mean ± SD, and categorical variables were defined as percentages. Categorical data were compared using the χ^2 test. Continuous variables were compared between the groups using Student's *t*-test or Mann–Whitney *U* test, depending on whether they distributed normally or did not, as tested by the Shapiro–Wilk test. Multiple linear regression analysis (stepwise method) was used to identify independent clinical determinants of LV strain. A *P*-value < 0.05 was considered to be statistically significant.

Results

Clinical characteristics and laboratory findings of 32 BD and 27 control subjects are listed in *Table 1*. The patients and the controls were similar regarding the age, gender, dislipidaemia, and BMI. The median BD diagnosis duration was 5.37 ± 5.57 years. Plasma levels of hs-C-reactive protein and NT-proBNP were significantly higher in the patients than in the controls (18.74 ± 28.33 vs. 3.15 ± 3.82 mg/L, $P < 0.0001$; 65.18 ± 84.51 vs. 30.84 ± 14.75 pg/mL, $P = 0.003$). LV end-diastolic diameter, aortic diameter, LVEF, E/A ratio, Sm, IVRT, E/Em were also similar between the groups. DT was significantly higher (207.50 ± 34.33 vs. 174.62 ± 9.79 ms, $P < 0.0001$) and Em/Am ratio was significantly lower (1.23 ± 0.16 vs. 1.46 ± 0.29, $P = 0.001$) in the patients. The LV longitudinal and circumferential systolic strain parameters of the patients and the controls are shown in *Table 2*. An example of STE analysis is shown in *Figures 1 and 2*. All segments showed a significant decrease in longitudinal strain in BD patients when compared

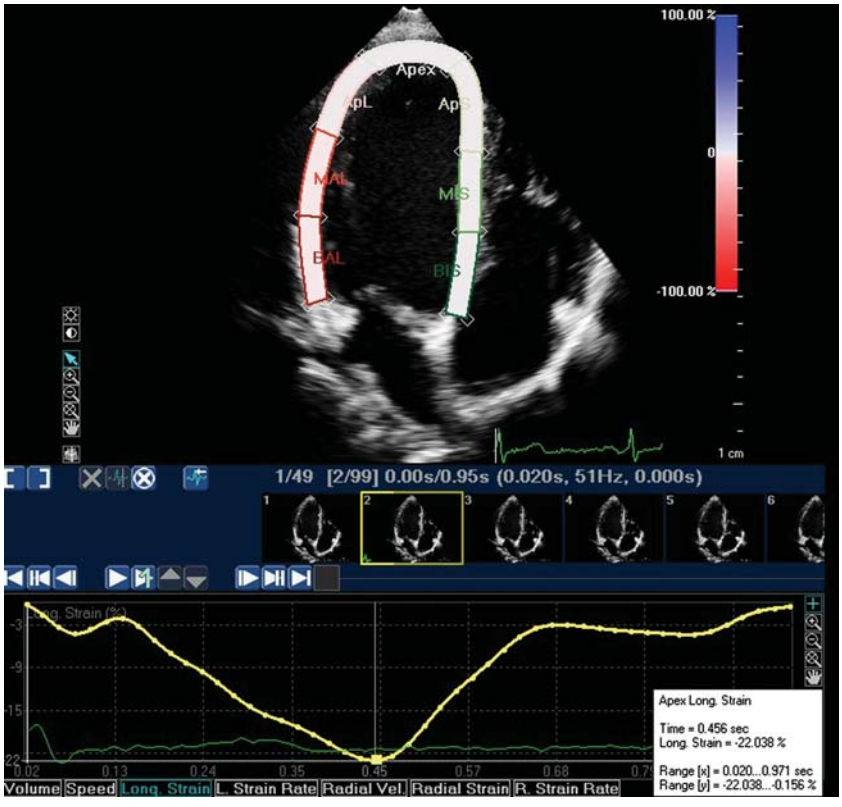

Figure 1 Apical longitudinal strain on left ventricular apical four-chamber view (through automatically analysed seven segments by STE using QLAB software).

with the healthy controls. Regional circumferential strain did not reveal a significant difference between the patients and the controls. As a result, mean longitudinal strain (-18.0 ± 2.3 vs. $-20.5 \pm 1.8\%$; $P < 0.0001$) was significantly impaired in the BD group than in the control group. Whereas mean circumferential strain was similar between the groups (-22.0 ± 1.6 vs. -22.2 ± 2.3; $P = 0.62$). In addition, we detected no difference in longitudinal strain values according to the presence of clinical findings ($P > 0.05$) (*Table 3*) and no significant difference in terms of longitudinal strain values was observed between the patients who were and were not receiving colchicine ($P > 0.05$). The multiple stepwise linear regression analyses using age, disease duration, LVEF, NT-proBNP as covariates were performed and revealed only NT-proBNP as the independent correlate of mean LV longitudinal strain ($R = 0.603$, $P = 0.001$).

Discussion

Our study revealed that; (i) longitudinal systolic strain was significantly impaired in patients with BD compared with the healthy controls and (ii) NT-proBNP levels were higher in BD patients when compared with the controls. Increased NT-proBNP was correlated with mean longitudinal strain.

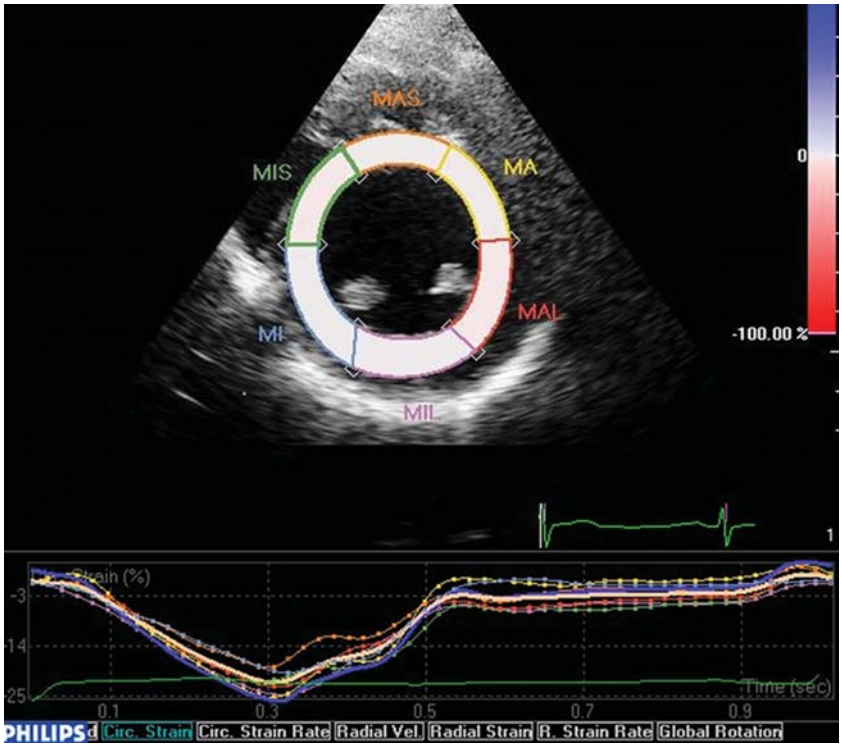

Figure 2 Regional circumferential strain on left ventricular short-axis view (through automatically analysed six segments by STE using QLAB software).

Table 3 Mean longitudinal strain values in the patients with Behcet's disease according to the clinical findings

Clinical findings	Patients (*n*, %)	Mean LS with clinical findings (%)	Mean LS without clinical findings (%)	*P*-values
Oral aphthous ulcers	32 (100)	-18.0 ± 2.3	—	—
Genital ulcers	21 (65.6)	-18.4 ± 2.1	-17.3 ± 2.6	0.25
Vascular involvement	6 (18.8)	-17.0 ± 1.1	-18.2 ± 2.5	0.16
Skin lesions	19 (59.4)	-18.2 ± 2.1	-17.8 ± 2.6	0.64
Ocular involvement	12 (37.5)	-18.3 ± 2.8	-17.8 ± 2.0	0.63
Arthritis/arthropathy	8 (25)	-17.7 ± 2.8	-18.1 ± 2.2	0.68
Positive pathergy test	15 (46.8)	-17.5 ± 2.6	-18.5 ± 2.0	0.24

Although cardiac involvement is not a common manifestation of BD, its presence may be a sign for poor prognosis. Microvascular inflammation probably causes the cardiac involvement in BD.[18] Inflammation of the small vessels arises as a common finding and the medial layer of the arteries is usually involved.[19] Focal fibrinoid deposition and fibroblast proliferation affecting the intramyocardial or small coronary arteries and arterioles observed in patients with BD may be responsible for microcirculation abnormalities and cause myocardial ischaemia and endomyocardial fibrosis.[5,20] However, the vasculitis in coronary vascular bed results in coronary thrombosis and aneurysm.[18] LV dysfunction may result from the disease process.[21]

There have been several studies evaluating the systolic and the diastolic functions in BD. LV functions have been detected to be impaired in the studies using radionucleid methods.[21–23] Kaya *et al.*[22] have detected hypokinesia due to distorted coronary microvascular circulation in 30.4% of BD patients using myocardial perfusion scintigraphy and have found the average EF to be 58% in these patients. Gullu *et al.*[18] have also shown perfusion defects in 19.4% of BD patients by using myocardial scintigraphy. Whereas most of the conventional and tissue Doppler echocardiography studies have demonstrated only impaired diastolic function, but normal systolic function.[9–11] This discrepancy might have arised because of the insufficiency of conventional and TDI-derived echocardiographic systolic parameters in determining the early abnormalities in systolic function. STE seems to be a reliable method in detecting subclinical cardiac involvement in different clinical settings, such as systemic sclerosis, thalassemia, and diabetes mellitus.[15,16,24]

In our study, we detected impaired longitudinal systolic strain on STE despite the normal systolic parameters measured by TDI and conventional echocardiography in BD patients. However, circumferential systolic strain values did not differ in BD patients when compared with the controls. Actually, it has been found by a previous cardiac anatomy study that subendocardial and epicardial regions have a longitudinal and the mid-wall has a circumferential arrangement of the LV fibres.[25] Early manifestations of cardiac abnormalities are usually observed in the subendocardial layer.[24,26] For this reason, we think that subendocardial longitudinal fibres will be the first affected region in BD patients before the development of overt cardiac failure due to the detoriation in coronary microvascular function, which is probably caused by vasculitis in the small arteries. This opinion is supported by the detection of impaired LV longitudinal systolic function, but no distortion in circumferential function in BD patients.

Another important finding of our study is that we found increased NT-proBNP levels in BD patients compared with healthy controls. BNP and NT-proBNP, being peptide hormones released from the cardiac ventricles in response to myocyte stretch, have generated considerable attention in recent years and have been proposed as potential diagnostic and prognostic markers for cardiac disease.[27,28] Takase *et al.*[29] have suggested BNP measurements for detecting asymptomatic cardiac abnormalities in healthy populations. Recently, it has been demonstrated that NT-proBNP levels have been higher in patients with RA[30,31] and systemic lupus erythematosus[32] without cardiac symptoms, in comparison with healthy controls. Also, Yagci *et al.*[33] have demonstrated the elevation of BNP levels in patients with BD and suggested that it might have been related with an elevated risk of cardiovascular involvement in BD. We also found in our study that LV mean longitudinal strain value was closely related to NT-proBNP levels, which suggested that impaired subendocardial longitudinal fibre contraction in BD might stimulate NT-proBNP release. Yoneyama *et al.*[34] have recently demonstrated that LV longitudinal systolic function correlates best with BNP in patients with heart failure. This finding strongly supports our results.

Conclusion

Longitudinal myocardial systolic function assessed by STE, which is a sensitive marker of ventricular dysfunction is impaired in BD. Increased NT-proBNP level may be a sign of subclinical ventricular dysfunction in these patients.

Study limitations

The major limitation of our study is the small sample size and, we believe that further studies in larger populations will help us to define the eventual role of NT-proBNP and STE in the determination of LV functions in BD. The accuracy of STE largely depends on image quality and, six patients were excluded because of inadequate image quality.

Conflict of interest: none declared.

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