European Review for Medical and Pharmacological Sciences 2016; 20: 3249-3254

Two-dimensional speckle tracking echocardiography is useful in early detection of left ventricular impairment in patients with Crohn's disease

T. KIVRAK, M. SUNBUL[1], A. CINCIN[1], T. KANI[2], E. DURMUS[3], M. BANZRAGCH[4], M. BOZBAY[1], Y. AYDIN[4], N. IMERYUZ[4], I. SARI[1], H. AKIN[4], Y. BASARAN[1]

Department of Cardiology, Sivas Numune Hospital, Sivas, Turkey
[1]Department of Cardiology, Marmara University Faculty of Medicine, Istanbul, Turkey
[2]Department of Internal Medicine, Marmara University Faculty of Medicine, Istanbul, Turkey
[3]Department of Cardiology, Silifke State Hospital, Mersin, Turkey
[4]Department of Gastroenterology, Marmara University Faculty of Medicine, Istanbul, Turkey

Abstract. – OBJECTIVE: Crohn's disease (CD) is a chronic inflammatory bowel disease that can affect the entire gastrointestinal tract. Cardiac involvement is considered very rare. Pericarditis, myocarditis, endocarditis, cardiomyopathy and complete heart block are some of the cardiac extraintestinal manifestations of CD. The aim of this study was to explore the left ventricular (LV) functions with two-dimensional (2D) speckle tracking echocardiography (STE) in patients with CD with normal cardiac functions.

PATIENTS AND METHODS: We enrolled 50 consecutive patients with CD and 50 age and sex matched healthy controls. All patients underwent a transthoracic echocardiogram with evaluation of LV functions with 2D STE.

RESULTS: Baseline characteristics were similar between patients with CD (24 male, mean age: 41.0 ± 13.9 years) and controls (24 male, mean age: 40.1 ± 7.3 years). Although conventional echocardiographic parameters were similar between two groups, global longitudinal strain was significantly lower in patients with CD compared to controls (19.6 ± 3.3 versus 21.2 ± 2.9, $p = 0.014$). Correlation analysis revealed that Crohn's Disease Activity Index is inversely correlated with LV global longitudinal strain ($r = -0.703$, $p < 0.001$) in patients with CD. We also evaluated inflammatory parameters such as CRP, erythrocyte sedimentation rate, and complete blood counts in patients with CD. Correlation analysis revealed that only platelet value is weakly correlated with Crohn's Disease Activity Index ($r = 0.311$, $p = 0.083$).

CONCLUSIONS: Crohn's disease is associated with impairment in LV global longitudinal myocardial function. Crohn's Disease Activity Index is also strongly correlated with LV global longitudinal strain. 2D-STE may be an useful method for early detection of LV impairment in patients with CD.

Key Words:
Crohn's disease, Left ventricular function, Speckle tracking echocardiography.

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) characterized by local and systemic inflammation and an intermittent course of disease with periods of flares and remission[1,2]. Although the underlying mechanism of CD remains unclear, it is usually related with an uncontrolled inflammatory immune response in genetically predisposed individuals[3]. Previous studies have shown that systemic inflammation is one of the causes of increased risk of cardiovascular disease (CVD) in patients with CD[4]. Pericarditis, myocarditis, endocarditis, cardiomyopathy and complete heart block are some of the cardiac extraintestinal manifestations of CD.

Noninvasive techniques such as standard transthoracic echocardiography indirectly provide information about left ventricular (LV) global functions. It provides limited data regarding changes of LV function in CD. New echocardiographic techniques have been introduced to evaluate myocardial mechanics. Speckle tracking echocardiography (STE) is a new technique that provides a global approach to LV myocardial mechanics, giving information about the three spatial dimensions of cardiac deformation[5]. The aim of this study was to explore the left ventricular

Corresponding Author: Murat Sunbul, MD; e-mail: drsunbul@yahoo.com.tr

(LV) functions with two-dimensional (2D) speckle tracking echocardiography (STE) in patients with CD with normal cardiac functions.

Patients and Methods

Study Population

Fifty-five consecutive patients followed by the Department of Gastroenterology with diagnosis of CD were enrolled in the study. All patients were evaluated for Crohn's disease activity according to the Crohn's Disease Activity Index[6]. Inflammatory parameters such as C-reactive protein levels, erythrocyte sedimentation rate levels, and complete blood counts were recorded from the patient's data. Patients with impairment of left ventricular systolic function (ejection fraction < 55%), significant valvular heart disease, cardiomyopathy, history of coronary artery disease, malignancy, hypertension, hyperlipidemia, diabetes mellitus and patient with poor echogenicity were excluded. The remaining 50 patients with CD were included in the study. The control group included 50 healthy age and sex matched volunteers free of cardiovascular risk factors and without any cardiac and systemic disease. All subjects underwent a resting two dimensional (2D) transthoracic echocardiographic examination to evaluate cardiac function. The investigation complies with the principles outlined in the Declaration of Helsinki. The study was approved by the local Ethics Committee and written informed consent was taken from all participants.

Standard Echocardiography and 2D Speckle Tracking Echocardiography

Standard echocardiographic examinations were performed in accordance with the recommendations of the American Society of Echocardiography guidelines[7] using an ultrasound system (Vivid 7, General Electric, Horten, Norway). Two-dimensional speckle tracking echocardiographic data for LV was obtained from the apical-four chamber view. A single cardiac cycle was stored in cineloop format with a frame rate of 40-80 Hz for the analysis. The strain data analysis was performed as previously described[8]. The endocardium of LV was manually drawn in end-systolic single frame, a region of interest was automatically mapped to the endocardial border (Figure 1). Only the images that demonstrated appropriate tracking in all myocardial segments in echocardiograms were used in the analysis.

Statistical Analysis

Statistical analyses were performed using SPSS 20.0 statistical software package (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean ± standard deviation while categorical data were presented as number and percentage of patients. Chi-square and Fisher's

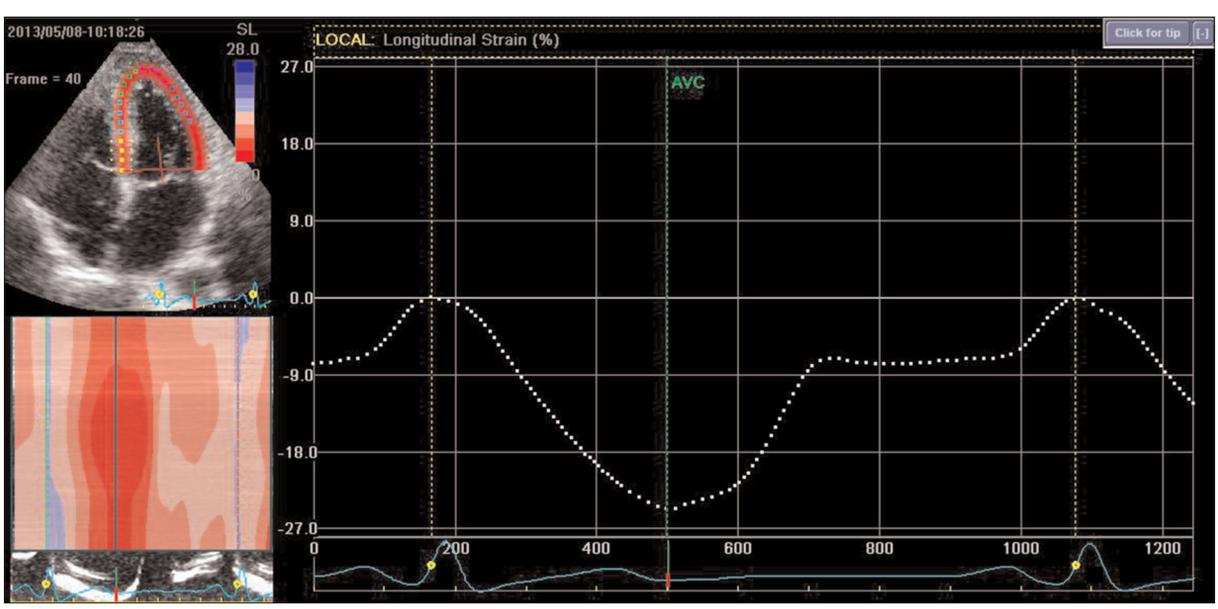

Figure 1. Left ventricular two-dimensional speckle tracking echocardiographic pattern in a patient with Crohn's disease.

Table I. Comparison of conventional echocardiographic parameters between patients with Crohn's disease and controls.

	Patients with CD (n= 50)	Controls (n= 50)	p
LAD (mm)	31.4 ± 4.2	32.8 ± 3.5	0.071
Aortic Diameter (mm)	29.0 ± 4.2	28.7 ± 3.5	0.756
LVEDD (mm)	44.3 ± 3.5	45.2 ± 3.3	0.180
LVESD (mm)	27.7 ± 3.1	27.8 ± 3.7	0.906
EF (%)	67.3 ± 7.3	67.1 ± 6.6	0.898
LAA (cm^2)	12.7 ± 2.5	12.8 ± 1.8	0.924
RAA (cm^2)	11.9 ± 2.4	11.1 ± 1.4	0.374
E Velocity (m/s)	0.72 ± 0.16	0.75 ± 0.11	0.232
A Velocity (m/s)	0.64 ± 0.15	0.64 ± 0.11	0.988
Deceleration Time (msn)	198.1 ± 53.2	193.4 ± 35.3	0.610
e' velocity (cm/s)	13.7 ± 4.3	12.8 ± 3.1	0.212
a' velocity (cm/s)	10.2 ± 2.6	9.2 ± 2.7	0.075
Aortic Velocity (m/s)	1.11 ± 0.17	1.12 ± 0.17	0.729

*Data are presented as mean ± standard deviation. CD: Crohn's disease, LAD: Left atrial diameter; LVEDD: Left ventricular end diastolic diameter; LVESD: Left ventricular end systolic diameter; EF: Ejection fraction; LAA: Left atrial area; RAA: Right atrial area.

Exact test was used for comparison of categorical variables while Student-*t* test or Mann-Whitney U test were used to compare parametric and non-parametric continuous variables, respectively. The correlation of continuous variables was analyzed by Spearman and Pearson correlation analysis. Correlation analysis was performed by Spearman's correlation test. A value of $p < 0.1$ was considered statistically significant.

Results

The study population was consisted with 50 patients with CD and 50 healthy controls. Age and sex distributions were similar between patients with CD and controls (24 male versus 24 male, mean age: 41.0 ± 13.9 years versus 40.1 ± 7.3 years, $p = 1.0$, 0.979, respectively). Mean disease duration of patients was 3.3 ± 2.4 years. Mean Crohn's Disease Activity Index score of patients was 111.6±109.7. While ileal involvement was determined in 18 patients (36%), iliacolonic involvement was determined in 22 patients (44%) and colonic involvement was determined in 10 patients (20%). We also classified patients according to behavior of disease as: inflammatory status in 31 patients (62%), stenosing in 7 patients (14%), and fistulizing in 12 patients (24%). Half of patients were treated with anti TNF drugs and 9 patients underwent surgery due to intestinal complication.

All study population was evaluated with transthoracic echocardiography for assessment of cardiac functions. Conventional echocardiographic parameters were similar between two groups (Table I). We also performed two dimensional speckle tracking echocardiography to further evaluation of left ventricular global functions in study population. Although conventional echocardiographic parameters were similar between two groups, LV global longitudinal strain value was significantly lower in patients with CD (Figure 2). Correlation analysis revealed that Crohn's Disease Activity Index is inversely correlated with LV global longitudinal strain in patients with CD ($r = –0.703$, $p < 0.001$).

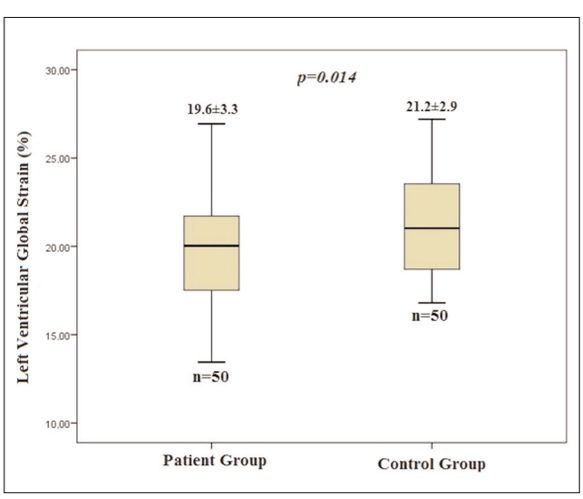

Figure 2. Comparison of left ventricular global longitudinal strain values between patients with Crohn's disease and controls.

We evaluated inflammatory parameters such as CRP, sedimentation, and complete blood counts in patients with CD. Mean levels of inflammatory parameters were shown in Table II. Correlation analysis revealed that only platelet value is weakly correlated with Crohn's Disease Activity Index (r = 0.311, $p = 0.083$).

Discussion

We demonstrated that Crohn's disease is associated with impairment in LV global longitudinal myocardial function. Crohn's Disease Activity Index is also strongly correlated with LV global longitudinal strain. 2D-STE may be useful for early detection of LV impairment in patients with CD.

Crohn's disease is a chronic recurrent gastrointestinal disease with an unknown origin and pathogenesis. It is commonly seen in adolescent and young adulthood, with peak incidence occurring between 15 and 30 years[9-11]. CD is a systemic disease associated with extraintestinal manifestations and complications[12,13] due to chronic inflammatory status and the need of a longstanding therapy. Previous studies have shown that the rate of extraintestinal complications is approximately 40%[14-17]. Various organs including skin, eye, joints, biliary tract, lung and heart can be involves in CD. Cardiac complications of IBD are rare; the most commonly reported complications are pericarditis (70% of the cases) and myocarditis (10%)[18-22]. Otherwise, a few cases of atrioventricular block, amyloidosis of the heart, cardiomyopathy and endomyocardial fibrosis have been reported in patients with IBD[23]. Although chronic inflammatory diseases associated with increased risk of atherothrombotic events, IBD remains unclear. In our work, we found that weakly correlation between Crohn's Disease Activity Index and platelet values (r = 0.311, $p = 0.083$). That finding may be responsible for increased risk of atherothrombotic events in patients with CD. On the other hand, our patients had comparatively lower disease duration (3.3 ± 2.4 years). Therefore, it may be suggested that; due to lower disease age; our group patients may had not enough time to develop overt cardiovascular disease or any cardiovascular complication related to inflammation of CD. Previous reports[24-26] have shown that some of patients have advanced thrombotic complications related with activate coagulation cascade, which can result in cardiac thrombi, pulmonary embolisms and myocardial infarction. IBD shows many features with the processes in the arterial wall during progression of atherosclerosis. Hence, it may result in atherosclerotic plaque rupture and thrombosis[27-29]. Atherosclerosis and thromboembolic complications are the most important causes of cardiovascular mortality and morbidity in patients with IBD[30]. Some drugs including steroids and 5-aminosalicylic acids have been included in the etiology of cardiac complications in patient with IBD. For example, steroids may aggravate diabetes, hypertension and congestive heart failure[31,32], and 5-aminosalicylic acids may cause of the pericarditis in patients with IBD[19].

Table II. Mean levels of inflammatory parameters of patients with Crohn's disease.

	Patients with Crohn's disease (n = 50)
C-Reactive Protein (mg/dl)	14.2 ± 31.1
Erythrocyte sedimentation rate (mm)	25.0 ± 17.0
Leukocytes (mm^{-3})	6533.3 ± 1713.6
Hemoglobin (g/dL)	12.7 ± 1.6
Mean corpuscular volume (fL)	87.6 ± 7.6
Platelet ($10^3/mm^{-3}$)	269.7 ± 90.8

Early diagnosis of cardiac involvement is crucial for perform appropriate therapeutic strategies in patients with systemic inflammatory disease[31,33]. Although standard echocardiographic measurements and tissue Doppler imaging can be useful to evaluate systolic and diastolic function of heart, diagnostic value of standard echocardiography is limited in early phase of cardiac impairment. Therefore, the use of more sensitive echocardiographic methods may allow the detection of subclinical LV systolic dysfunction. 2D STE is a quantitative technique to evaluate myocardial function by analyzing spots on the two-dimensional gray-scale ultrasound images of myocardium. It is not user dependent and not effected from angle. STE parameters are not affected by the movement of heart. STE also provides information about the segmental wall function[34]. Previous studies[35-39] have shown that STE is useful method for early detection of LV impairment in patients with systemic disease.

Our study has several clinical implications. We showed that patients with CD have subclinical LV myocardial dysfunction assessed by 2D STE while conventional echocardiographic parame-

ters were normal range. To the best of our knowledge, this is the first study in literature to evaluate left ventricular myocardial function with 2D STE in CD patients. Our results have suggested that 2D STE may be useful for early detection of myocardial involvement in patients with CD and would rather be performed in every patient with CD suspected from myocardial dysfunction.

Study Limitations

Although the study had a prospective design, we did not gather data regarding prognosis of the patient with CD. It would have been better if we had followed-up the patients and explored the relation between adverse cardiac events and decreased LV global strain parameters in patients with CD. Therefore, further large scale, prospective studies are needed to gain more information about impact of Crohn's disease on cardiovascular outcome and the best approach to treatment of such abnormalities.

Conclusions

Crohn's disease is associated with impairment in LV global longitudinal myocardial function. Crohn's Disease Activity Index is also strongly correlated with LV global longitudinal strain. 2D-STE may be useful method for early detection of LV impairment in patients with CD and it may be part of cardiovascular examination in the outpatient clinic setting in patients with CD suspected from myocardial dysfunction. Hence, closer follow-up of patients with CD may prevent to occurrence of overt CVD.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Danese S, Fiocchi C. Ulcerative colitis. N Engl J Med 2011; 365: 1713-1725.
2) Solberg IC, Vatn MH, Hoie O, Stray N, Sauar J, Jahnsen J, Moum B, Lygren I; IBSEN Study Group. Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. Clin Gastroenterol Hepatol 2007; 5: 1430-1438.
3) Podolsky DK. Inflammatory bowel disease. N Engl J Med 2002; 347: 417-429.
4) Hansson GK. Inflammation, atherosclerosis and coronary artery disease. N Engl J Med 2005; 352: 1685-1695.
5) Sitia S, Tomasoni L, Turiel M. Speckle tracking echocardiography: A new approach to myocardial function. World J Cardiol 2010; 2: 1-5.
6) Best WR, Becktel JM, Singleton JW, Kern F. Development of a Crohn's disease activity index. Gastroenterology 1976; 70: 439-444.
7) Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas PS, Faxon DP, Gillam LD, Kimball TR, Kussmaul WG, Pearlman AS, Philbrick JT, Rakowski H, Thys DM, Antman EM, Smith SC Jr, Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Faxon DP, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). J Am Soc Echocardiogr 2003; 16: 1091-1110.
8) Dandel M, Lehmkuhl H, Knosalla C, Suramelashvili N, Hetzer R. Strain and strain rate imaging by echocardiography - basic concepts and clinical applicability. Curr Cardiol Rev 2009; 5: 133-148.
9) Hendrickson BA, Gokhale R, Cho JH. Clinical aspects and pathophysiology of inflammatory bowel disease. Clin Microbiol Rev 2002; 15: 79-94.
10) Chutkan RK. Inflammatory bowel disease. Prim Care 2001; 28: 539-556.
11) Harper PC, McAuliffe TL, Beeken WL. Crohn's disease in the elderly. A statistical comparison with younger patients matched for sex and duration of disease. Arch Intern Med 1986; 146: 753-755.
12) Danese S, Semeraro S, Papa A, Roberto I, Scaldaferri F, Fedeli G, Gasbarrini G, Gasbarrini A. Extraintestinal manifesta-tions in inflammatory bowel disease. World J Gastroenterol 2005; 11: 7227-7236.
13) Novacek G, Haumer M, Schima W, Müller C, Miehsler W, Polterauer P, Vogelsang H. Aortic mural thrombi in patients with inflammatory bowel disease: report of two cases and review of the literature. Inflamm Bowel Dis 2004; 10: 430-435.
14) Veloso FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease. A prospective study of 792 patients. J Clin Gastroenterol 1996; 23: 29-34.
15) Das KM. Relationship of extraintestinal involvements in in-flammatory bowel disease: new insights into autoimmune pathogenesis. Dig Dis Sci 1999; 44: 1-13.
16) Oshitani N, Watanabe K, Nakamura S, Higuchi K, Arakawa T. Extraintestinal complications in patients with ulcerative colitis. Nippon Rinsho 2005; 63: 874-878.
17) Mendoza JL, Lana R, Taxonera C, Alba C, Izquierdo S, Díaz-Rubio M. Extraintestinal manifestations in

inflammatory bowel disease: differences between Crohn's disease and ulcerative colitis. Med Clin (Barc) 2005; 125: 297-300.

18) Abid MA, Gitlin N. Pericarditis--an extraintestinal complication of inflammatory bowel disease. West J Med 1990; 153: 314-315.

19) Ishikawa N, Imamura T, Nakajima K, Yamaga J, Yuchi H, Ootsuka M, Inatsu H, Aoki T, Eto T. Acute pericarditis associated with 5-aminosalicylic acid (5-ASA) treatment for severe active ulcerative colitis. Intern Med 2001; 40: 901-904.

20) Molnar T, Hogye M, Nagy F, Lonovics J. Pericarditis associated with inflammatory bowel disease: case report. Am J Gastroenterol 1999; 94: 1099-1100.

21) Oxentenko AS, Loftus EV, Oh JK, Danielson GK, Mangan TF. Constrictive pericarditis in chronic ulcerative colitis. J Clin Gastroenterol 2002; 34: 247-251.

22) Patwardhan RV, Heilpern RJ, Brewster AC, Darrah JJ. Pleuropericarditis: an extraintestinal complication of inflammatory bowel disease. Report of three cases and review of literature. Arch Intern Med 1983; 143: 94-96.

23) Rellecke P, Strauer BE. Chronic inflammatory bowel disease and cardiovascular complications. Med Klin (Munich) 2006; 101: 56-60.

24) Ahlehoff O, Gislason GH, Charlot M, Jørgensen CH, Lindhardsen J, Olesen JB, Abildstrøm SZ, Skov L, Torp-Pedersen C, Hansen PR. Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. J Intern Med 2011; 270: 147-157.

25) Meune C, Touze E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 2009; 48: 1309-1313.

26) Svenungsson E, Jensen-Urstad K, Heimburger M, Silveira A, Hamsten A, de Faire U, Witztum JL, Frostegård J. Risk factors for cardiovascular disease in systemic lupus erythematosus. Circulation 2001; 104: 1887-1893.

27) Zitomersky NL, Verhave M, Trenor CC 3rd. Thrombosis and inflammatory bowel disease: a call for improved awareness and prevention. Inflamm Bowel Dis 2011; 17: 458-470.

28) Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. Lancet 2007; 369: 1627-1640.

29) Irving PM, Pasi KJ, Rampton DS. Thrombosis and inflammatory bowel disease. Clin Gastroenterol Hepatol 2005; 3: 617-628.

30) Dorn SD, Sandler RS. Inflammatory Bowel Disease is not a risk factor for cardiovascular disease mortality: Results from a Systematic Review and Meta-Analysis. Am J Gastroenterology 2007; 102: 662-667.

31) Baty V, Blain H, Saadi L, Jeandel C, Canton Ph. Fatal myocardial infarction in an elderly woman with severe ulcerative colitis; what is the role of steroids? Am J Gastroenterol 1998; 93: 2000-2001.

32) Quera R, Shanahan F. Thromboembolism an important manifestation of inflammatory bowel disease. Am J Gastroenterol 2004; 99: 1971-1973.

33) Efremidis M, Prappa E, Kardaras F. Acute myocardial infarction in a young patient during an exacerbation of ulcerative colitis. Int J Cardiol 1999; 70: 211-212.

34) Mondillo S, Galderisi M, Mele D, Cameli M, Lomoriello VS, Zacà V, Ballo P, D'Andrea A, Muraru D, Losi M, Agricola E, D'Errico A, Buralli S, Sciomer S, Nistri S, Badano L; Echocardiography Study Group of the Italian Society of Cardiology (Rome, Italy). Speckle-tracking echocardiography: a new technique for assessing myocardial function. J Ultrasound Med 2011; 30: 71-83.

35) Spethmann S, Dreger H, Schattke S, Riemekasten G, Borges AC, Baumann G, Knebel F. Two-dimensional speckle tracking of the left ventricle in patients with systemic sclerosis for an early detection of myocardial involvement. Eur Heart J Cardiovasc Imaging 2012; 13: 863-870.

36) Sunbul M, Durmus E, Kivrak T, Yildiz H, Kanar BG, Ozben B, Sari I, Mutlu B. Left ventricular strain and strain rate by two-dimensional speckle tracking echocardiography in patients with subclinical hypothyroidism. Eur Rev Med Pharmacol Sci 2013; 17: 3323-3328.

37) Aggeli C, Felekos I, Tousoulis D, Gialafos E, Rapti A, Stefanadis C. Myocardial mechanics for the early detection of cardiac sarcoidosis. Int J Cardiol 2013; 168: 4820-4821.

38) Tigen K, Sunbul M, Karaahmet T, Dundar C, Ozben B, Guler A, Cincin A, Bulut M, Sari I, Basaran Y. Left ventricular and atrial functions in hypertrophic cardiomyopathy patients with very high LVOT gradient: a speckle tracking echocardiographic study. Echocardiography 2014; 31: 833-841.

39) Alpaydin MS, Aksakal E, Erol MK, Sim ek Z, Açikel M, Arslan S, Gündo du F, Sevimli S, Karakelleo lu S. [Assessment of regional left ventricular functions by strain and strain rate echocardiography in type II diabetes mellitus patients without microvascular complications]. Turk Kardiyol Dern Ars 2011; 39: 378-384.