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Echocardiography

Assessment of Atrial Electromechanical Delay and Left Atrial Mechanical Functions in Patients with Ulcerative Colitis

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Objective: Ulcerative colitis (UC) is a common inflammatory bowel disease causing systemic inflammation, which may also affect the cardiovascular system, as well as other organ systems. The aim of the current study was to evaluate left atrial (LA) mechanical functions and duration of atrial electromechanical delay (AEMD) with echocardiography in patients with UC. Method: A total of 91 patients, 45 with UC (Group 1) and 46 healthy individuals as control (Group 2) were included in the study. The demographic and laboratory data were recorded, and echocardiographic measurements were taken for all patients. Results: In the evaluation of basal clinical and laboratory findings, no difference was detected between the two groups, except for white blood cell count (WBC) (8.26 ± 2.71 vs. 7.06 ± 1.70, $P = 0.013$) and high-sensitivity C-reactive protein (Hs-CRP; 3.4 ± 1.7 vs. 1.0 ± 0.8, $P < 0.001$). The echocardiographic assessment revealed that the diastolic parameters such as E-, E/A-, and E- waves decreased in the UC group when compared to the control group. LA mechanical functions were different between groups, except for left atrial (LA) maximal volume: LA minimum volume (22.2 ± 12.9 vs. 15.3 ± 4.7, $P = 0.001$), LA volume before atrial systole (29.9 ± 14.2 vs. 24.2 ± 4.9, $P = 0.021$), LA ejection fraction (27.4 ± 16.5 vs. 38.6 ± 10.1, $P < 0.001$), LA total emptying volume (17.9 ± 6.9 vs. 21.9 ± 5.9, $P = 0.004$), LA active emptying fraction (27.4 ± 16.5 vs. 38.6 ± 10.1, $P < 0.001$), LA active emptying volume (7.7 ± 3.6 vs. 9.4 ± 2.9, $P = 0.013$), LA passive emptying fraction (26.8 ± 10.2 vs. 33.2 ± 9.2, $P = 0.002$), and LA passive emptying volume (10.3 ± 4.9 vs. 12.5 ± 4.5, $P = 0.029$). There was a significant difference between the groups in terms of AEMD durations, except time interval from the onset of the P-wave on the surface ECG to the peak of the late diastolic wave (PA) of the tricuspid valve. The correlation analysis revealed that age and duration of disease were correlated with AEMD. Conclusion: The current study reported that LA volume and mechanical functions degenerated and AEMD increased in patients with UC when compared to the control group. These findings demonstrate that UC may have effects on LA electromechanical functions related to duration of disease. (Echocardiography 2016;33:970–976)

Key words: atrial electromechanical delay, atrial fibrillation, ulcerative colitis

Ulcerative colitis (UC) is an inflammatory bowel disease with superficial colonic mucosal involvement and with a course of remissions and exacerbations. UC is characterized by multiple extraintestinal manifestations believed to be caused by concomitant systemic inflammation, similar to Crohn's disease, which is the other inflammatory bowel disease (IBD).[1] Data on cardiac disturbances due to UC are limited to myocarditis, pericarditis, and cardiomyopathies from case reports,[2–4] whereas recent studies have revealed an increase in early atherosclerosis and ischemic heart disease associated with inflammation and endothelial dysfunction in patients with UC[5,6] and even development of subclinical cardiac damage due to UC.

It is well known that inflammation and oxidative stress play important roles in the pathogenesis of atrial fibrillation (AF).[7] Increased risk of AF has been shown in diseases such as rheumatoid arthritis, systemic lupus erythematosus, and psoriasis, which all involve systemic inflammation. The association between UC and AF is not yet clearly understood. Electrophysiological and electromechanical abnormalities originating from

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intraatrial and interatrial conduction disturbances are associated with an increased risk of AF,[8,9] and tissue Doppler echocardiography is used in the evaluation of intraatrial and interatrial conduction disturbances. An increase in atrial electromechanical delay (AEMD) duration measured with this method was shown to be an independent variable for AF development.[8,10,11]

Chronic and relapsing inflammation due to UC, as well as metabolic changes, vitamin deficiencies, and conditions like hypercoagulability, may affect left atrial mechanical functions and AEMD duration.[5,6] The aim of this study was to evaluate left atrial (LA) mechanical functions and AEMD duration in patients with UC.

Methods:

Study Population:

A total of 45 patients with UC, over 18 years of age, who were admitted at the Kırşehir outpatient clinics of gastroenterology of Ahi Evran University Training and Research Hospital between October 2014 and May 2015 with a histopathological diagnosis of UC (Group 1) and 46 healthy individuals matched for age and gender (Group 2) were included in this study. The study was conducted in accordance with the ethical principles described by the Declaration of Helsinki.

Exclusion criteria for this study were as follows: hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), valvular heart disease of moderate severity, myocarditis, pericarditis, any cardiovascular drug use, rhythms other than sinus, other autoimmune diseases, significant valvular heart disease, chronic obstructive pulmonary disease, renal or hepatic dysfunction, hyperthyroidism, or electrolyte imbalance.

Investigation Planning and Measurements:

Initially, demographic data were recorded for patients who were eligible to be included in the study and who signed an informed consent form. Echocardiographic evaluation was carried out for all participants after the patient rested for 15 minutes. The clinical activity of patients with UC was calculated using the Mayo Clinic activity index, and endoscopic activity was calculated using the Rachmilewitz endoscopic activity index.[12,13]

Echocardiographic evaluation: Echocardiography was performed on all patients and the control group using a GE VingMed Vivid 7 (GE VingMed Ultrasound, Horten, Norway) at the echocardiography laboratory. Patients were examined while lying in the left supine position. Parasternal long-axis, short-axis, and apical four-chamber and two-chamber images were taken, and the assessment was made using M-mode, two-dimensional (2D), continuous-wave Doppler, pulsed-wave Doppler, and tissue Doppler methods according to the American Society of Echocardiography.[14] All echocardiographic procedures were performed by a single operator. Left ventricular systolic and diastolic functions were evaluated. Posterior wall (PW) thickness, interventricular septum (IVS) thickness, left ventricular end-diastolic diameter (LVEDD), and left ventricular end-diastolic diameter (LVESD) were calculated using the M-mode method. The modified Simpson method was used to calculate the left ventricular ejection fraction (EF). In the apical four-chamber view, a pulsed-wave Doppler (PWD) sample volume (3 mm) was placed between the mitral leaflet tips. Early diastolic flow (E), atrial contraction signal (A), E/A, and deceleration time (DT) were measured. Isovolumetric relaxation time (IVRT) was determined as the interval between the end of the aortic outflow and the start of the mitral inflow signal. Values were measured on three separate beats and then averaged for all parameters.

Evaluating left atrial (LA) mechanical functions by echocardiography: The LA volumes were calculated from the four- and two-chamber views using Simpson's rule. LA maximum volume (V_{max}) was recorded precisely when the mitral valve was opened, and LA minimum volume (V_{min}) was recorded precisely when the mitral valve was closed; LA presystolic volume (V_p) was recorded at the beginning of atrial systole (p-wave on ECG (D2 derivation). All LA volumes were corrected for body surface area (BSA). Left ventricular end-systolic and end-diastolic volumes, as well as BSA rates, were recorded.

LA emptying functions were calculated as follows:[15]

LA passive emptying volume (LAPEV)= $V_{max}-V_p$
LA passive emptying fraction (LAPEF)= $[(V_{max}-V_p)/V_{max}]X100\%$,
LA active emptying volume (LAAEV)= V_p-V_{min}
LA active emptying fraction (LAAEF)= $[(V_p-V_{min})/V_p]X100\%$,
LA total emptying volume (LATEV)= $V_{max}-V_{min}$
LA ejection fraction (LAEF)=$[(V_{max}-V_{min})/V_{max}]$ X100%

Interatrial and intraatrial electromechanical delay: All electromechanical delay times used to measure Interatrial and intraatrial electromechanical delay were determined using the tissue Doppler imaging (TDI) method and concurrent electrocardiographic rhythm traces. Atrial systole was considered to be the A-wave (A), which was the second negative deviation at diastole in the

tissue Doppler trace. The time interval between the beginning of the P-wave in the superficial ECG (D2 derivation) and the peak of the tissue Doppler late diastolic wave (Am wave) was defined as atrial electromechanical coupling (PA), while the measurements were taken from the lateral mitral annulus (lateral PA), septal annulus (septal PA), and right ventricular tricuspid annulus (tricuspid PA) on an apical four-chamber image such that the five cardiac cycles could be averaged. Inter-atrial electromechanical delay (inter-atrial EMD) was calculated as the time difference between lateral PA and tricuspid PA; time difference between septal PA and tricuspid PA was calculated as intra-right electromechanical delay (IRight-EMD) and time difference between lateral PA and septal PA was calculated as intra-left electromechanical delay (ILeft-EMD).[16]

Statistical Analysis:
All data were analyzed using SPSS for Windows version 15.0 software (Chicago, IL, USA). Categorical variables were presented as frequencies and percentages; continuous variables were expressed as means and standard deviation (SD). The normal distribution of continuous variables was tested using the Kolmogorov–Smirnov test. Continuous variable differences between groups were examined using the Mann–Whitney U-test. Correlation analyses were performed using Spearman's coefficient of correlation. The comparison of categorical values was carried out using the chi-square test. $P < 0.05$ was considered significant.

Results:
As described previously, a total of 91 participants were included in this study, 46 in the UC group and 45 in the control group. There were no significant differences between the groups in terms of baseline characteristics and laboratory parameters ($P > 0.05$) except for white blood cell count (WBC) (8.26 ± 2.71 vs. 7.06 ± 1.70, $P = 0.013$) and high-sensitivity C-reactive protein (Hs-CRP; 3.4 ± 1.7 vs. 1.0 ± 0.8, $P < 0.001$) (Table I).

Among conventional echocardiographic measurements, there were no differences between the groups in terms of LV systolic parameters, whereas there were significant differences between the groups in terms of E, E′, and E/A ratios from LV diastolic parameters (results shown in Table II). In the echocardiographic evaluation of LA mechanical functions, all LA mechanical functions except for LA maximal volume were decreased in the UC group in comparison with the controls (results shown in Table III).

In comparing the left atrial Doppler examination and AEMD durations of the groups, lateral PA (127.8 ± 11.1 vs. 121.8 ± 9.1 ms; $P = 0.005$), septal PA (115.3 ± 9.9 vs. 110.0 ± 8.4 ms; $P = 0.007$), IA-EMD (26.9 ± 8.3 vs. 21.6 ± 7.1 ms; $P = 0.002$), and IRight-EMD (14.4 ± 5.0 vs. 9.8 ± 4.9 ms; $P < 0.001$) were significantly higher than the control group (see Table IV). A significant correlation was found for cases between AEMD and age and duration of illness (see Table V and Fig. 1).

TABLE I

Baseline Clinical and Laboratory Characteristics

	Group 1 (n = 45)	Control Group (n = 46)	P-Value
Age (years)	46.8 ± 13.1	49.5 ± 10.3	0.279
Body mass index (BMI)	27.6 ± 4.6	26.5 ± 2.7	0.166
Duration at The Moment Cardiac Assessment (years)	5.55 ± 4.40		
Number of Acute Flares Patients % (n)	31 (14)		
Rachmilewitz Endoscopic Activity Index	3.9 ± 3.5		
Mayo Clinical Activity Index	1.6 ± 0.8		
Sex (male) % (n)	71 (32)	63 (29)	0.413
Smoking % (n)	33 (15)	47 (22)	0.159
History of Sleep Apnea % (n)	7 (3)	2 (1)	0.296
Systolic Blood Pressure (mmHg)	113.9 ± 14.4	112.9 ± 13.1	0.741
Diastolic Blood Pressure (mmHg)	71.7 ± 10.8	69.9 ± 11.1	0.441
Creatinine (mg/dL)	0.86 ± 0.28	0.83 ± 0.23	0.492
Serum Glucose (mg/dL)	90.3 ± 11.6	90.2 ± 11.9	0.970
Hemoglobin (g/dL)	12.9 ± 2.4	13.6 ± 1.9	0.192
White Blood Cell Count ($10^3/mm^3$)	8.26 ± 2.71	7.06 ± 1.70	**0.013**
Platelet ($10^3/mm^3$)	232.5 ± 63.0	246.3 ± 97.4	0.428
ALT (UI/L)	25.8 ± 13.0	27.2 ± 13	0.616
AST (UI/L)	32.3 ± 22.1	40.4 ± 47.8	0.306
Hs-CRP (mg/dL)	3.4 ± 1.7	1.0 ± 0.8	**<0.001**

hs-CRP = high-sensitivity C-reactive protein.

TABLE II

Conventional Echocardiographic Parameters

	Group 1 (n = 45)	Control Group (n = 46)	P-Value
IVS thickness (mm)	10.4 ± 1.7	10.0 ± 1.4	0.195
PW thickness (mm)	10.2 ± 1.5	9.9 ± 1.2	0.386
LVEDD (mm)	45.8 ± 4.2	46.4 ± 3.7	0.429
LVESD (mm)	28.4 ± 4.3	28.5 ± 3.6	0.924
LA dimension (mm)	34.0 ± 4.2	33.1 ± 4.8	0.322
LVEF (%)	62.0 ± 5.7	60.4 ± 4.5	0.140
RV dimension (mm)	27.3 ± 4.3	27.3 ± 2.2	0.944
PAB(s) (mmHg)	24.6 ± 5.4	22.9 ± 3.4	0.066
DT (ms)	187.4 ± 32.5	179.8 ± 30.9	0.261
IVRT (ms)	84.1 ± 14.3	82.5 ± 15.5	0.626
E (m/s)	0.67 ± 0.18	0.74 ± 0.20	0.090
A (m/s)	0.64 ± 0.18	0.56 ± 0.06	**0.017**
E/A	1.1 ± 0.4	1.3 ± 0.7	**0.013**
E′	0.7 ± 0.2	0.8 ± 0.2	**0.008**

IVS = ventricular septal thickness; PW = posterior wall thickness; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimensions; LA = left atrium; LVEF = left ventricular ejection fraction; RV = right ventricular; PAB(s) = systolic pulmonary artery pressure; DT = deceleration time; IVRT = isovolumetric relaxation time; E = early diastolic flow; E/A = early diastolic flow/atrial contraction signal; E′ = tissue doppler early diastolic flow.

TABLE III

LA Volume Measurements and Mechanical Function

	Group 1 (n = 45)	Control Group (n = 46)	P-Value
LA Vmax (mL/m²)	40.2 ± 16.6	37.2 ± 6.9	0.252
LA Vmin (mL/m²)	22.2 ± 12.9	15.3 ± 4.7	**0.001**
LA Vp (mL/m²)	29.9 ± 14.2	24.2 ± 4.9	**0.021**
LA EF (%)	27.4 ± 16.5	38.6 ± 10.1	**<0.001**
LATEV (mL/m²)	17.9 ± 6.9	21.9 ± 5.9	**0.004**
LAAEF (%)	27.4 ± 16.5	38.6 ± 10.1	**<0.001**
LAAEV (mL/m²)	7.7 ± 3.6	9.4 ± 2.9	**0.013**
LAPEF (%)	26.8 ± 10.2	33.2 ± 9.2	**0.002**
LAPEV (mL/m²)	10.3 ± 4.9	12.5 ± 4.5	**0.029**

LA Vmax = left atrium maximum volume; LA Vmin = left atrium minimum volume; LA Vp = left atrium volume before atrial systole; LAEF = left atrium ejection fraction; LATEV = left atrium total emptying volume; LAAEF = left atrium active emptying fraction; LAAEV = left atrium active emptying volume; LAPEF = left atrium passive emptying fraction; LAPEV = left atrium passive emptying volume.

Discussion:

We showed that there is an increase in AEMD durations for patients with UC and derangements in LA mechanical and LV diastolic functions. This suggests the presence of effects on both electrical and mechanical cardiac functions

TABLE IV

Electrocardiographic and Tissue Doppler Echocardiographic Findings

	Group 1 (n = 45)	Control Group (n = 46)	P-Value
PA lateral (ms)	127.8 ± 11.1	121.8 ± 9.1	**0.005**
PA septal (ms)	115.3 ± 9.9	110.0 ± 8.4	**0.007**
PA tricuspid (ms)	100.9 ± 8.9	100.2 ± 7.3	0.628
IA-EMD (ms)	26.9 ± 8.3	21.6 ± 7.1	**0.002**
IRight-EMD (ms)	14.4 ± 5.0	9.8 ± 4.9	**<0.001**
ILeft-EMD	12.5 ± 5.2	11.8 ± 4.9	0.478
Pmax (ms)	94.4 ± 10.3	91.8 ± 14.1	0.320
Pmin (ms)	56.1 ± 7.3	52.9 ± 9.5	0.078
Pd (ms)	39.1 ± 7.8	37.2 ± 9.9	0.304

PA = time interval from the onset of the P-wave on the surface ECG to the peak of the late diastolic wave (A-wave); IA-EMD = interatrial electromechanical delay; IRight-EMD = intra-right electromechanical delay; ILeft-EMD = intra-left electromechanical delay; Pmax = maximum P-wave duration; Pmin = minimum P-wave duration; Pd = P-wave dispersion.

TABLE V

Univariate Correlation Analysis

	Age (years)		Disease Duration (years)	
	r	P	r	P
IA-EMD (ms)	0.31	0.002	0.61	<0.001
IRight-EMD (ms)	0.26	0.011	0.67	<0.001
ILeft-EMD	0.32	0.002	0.42	0.004

IA-EMD = interatrial electromechanical delay; IRight-EMD = intra-right electromechanical delay; ILeft-EMD = intra-left electromechanical delay.

in patients with UC. Another interesting aspect of the present study is the absence of associations between disease activity and clinical and endoscopic scores, although an association between disease duration and AEMD duration exists. This may be due to cardiac damage caused by long-term chronic inflammatory processes rather than disease activity and exacerbations.

As is well known, AF is the most frequently encountered arrhythmia in daily clinical practice. It increases the risk of stroke, thereby increasing mortality and morbidity.[17,18] Thus, recognizing risk factors that play a role in the development of AF is very important for preventing possible complications. Systemic inflammation has been shown to be an important predictor of AF development, and various mechanisms have been proposed to account for the association between AF

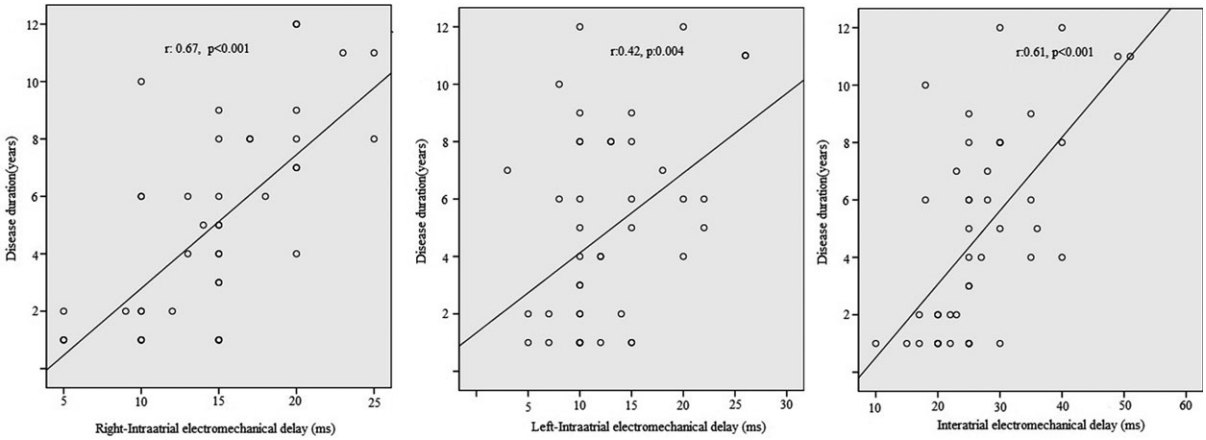

Figure 1. Correlation graphs of AEMD times with disease duration (years).

and inflammation.[7] An increased risk of AF has recently been demonstrated in studies of many diseases of autoimmunity (systemic lupus erythematosus, rheumatoid arthritis, psoriasis, etc.) with concomitant systemic inflammation.[19–21] However, the association between UC and AF has not been adequately investigated. Pattanshetty et al.[22] found that AF frequency increased in all age groups for IBD compared to the normal population and proposed an association between this finding and chronic inflammation due to IBD. Similarly, Kristensen et al.[23] compared 24 499 IBD patients with >235 000 controls and followed patients with IBD between 1996 and 2011. IBD was found to be associated with an increased risk of AF and stroke, independent of age and gender.[23] However, in contrast to our study, they did not find an increased risk of AF in patients with UC in remission. Probable reasons for this inconsistency may include the following: only, patients with UC were included in our study, their study was not a prospective follow-up study for AF development, and the number of active patients included in our study was too low. In a study by Yuksel et al. evaluating ECG, P-wave dispersion was shown to be increased in patients with IBD, and IBD was shown to be associated with AF.[24] Although increased P-wave dispersion values were detected in patients with UC in our study, the results were not statistically significant. In other studies, parasympathetic functions were shown to decrease and autonomic dysfunction was shown to increase in patients with UC.[25,26] These results may inform our understanding of the increase in AEMD durations in patients with UC in our study.

Interatrial and intraatrial electromechanical delay and nonhomogenous spread are well-known characteristics of atria with a tendency for AF. AEMD may be measured using invasive and noninvasive methods. With current advances in echocardiographic techniques, TDI has become an alternative method[8] for the measurement of AEMD, and in contrast with LA measurements, atrial conduction times may reflect both structural and electrical atrial remodeling. AEMD durations were shown to be significantly increased in patients with paroxysmal AF.[9,27] The decreased mechanical LA functions and increased AEMD durations found in the present study show that UC affects atrial functions both mechanically and electrically, and UC increases the risk of AF development. No prior study has evaluated LA electromechanical functions in patients with UC. However, in an investigation evaluating patients with celiac disease, an inflammatory and autoimmune disorder of the intestinal system, AEMD durations were shown to be increased in patients with celiac disease, and AEMD and duration of disease were shown to be associated, similar to the results in our study.[28] Also, increased AEMD durations were found in autoimmune disorders with intensive systemic inflammation such as psoriasis vulgaris, rheumatoid arthritis, scleroderma, ankylosing spondylitis, and systemic lupus erythematosus in comparison with control groups.[19–21,29,30]

The effects of UC on cardiac functions have not been adequately investigated, and rare cardiac complications of UC such as pericarditis, myocarditis, and thrombotic events have been presented in case reports. However, in recent years, some published preclinical studies have demonstrated effects of IBD on cardiac functions. Cardiac functions of patients with UC were evaluated using two-dimensional speckle tracking echocardiography in a study by Cincin et al., and subclinical cardiac damage and changes in cardiac deformation values were observed.[31] In another study by Çalışkan et al., derangements

in left ventricular diastolic functions and coronary flow reserve were shown in patients with IBD.[32]

In the present study, the cause of derangements in LA electromechanical functions and LV diastolic functions in patients with UC may be structural changes that develop due to inflammation. Inflammatory cytokines, which were shown to be increased in IBD, cause structural changes in arterial vascular walls, alteration in lipid levels, oxidative stress, and insulin resistance. Collagen deposition in multiple organs in IBD due to chronic inflammation[33] and presence of an association between IBD and arterial stiffness have also been shown in previous studies.[34] Also, deficiencies of vitamins, iron, and essential trace elements due to malabsorption and malnutrition associated with UC may impact cardiac structure and functions.

Study Limitations:

The primary limitations of this study are the relatively small sample size and the cross-sectional design. A larger sample size could provide stronger statistical data. Another limitation is the possible effect of medications that were used by patients with UC between diagnosis and the start of the study on AEMD durations. We did not further evaluate our patients to detect conditions such as pulmonary embolism, portopulmonary hypertension, or pulmonary fibrosis, which may damage the pulmonary capacity and complicate ulcerative colitis.

Conclusion:

In the present study, AEMD durations were shown to be increased and LA mechanical and LV diastolic functions were shown to be decreased in patients with UC. Also, a strong correlation was found between AEMD durations and disease durations. These results suggest that chronic inflammation in patients with UC may have effects on LA electromechanical functions, dependent on the duration of disease.

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