

Assessment of Atrial Electromechanical Delay by Tissue Doppler Echocardiography in Obese Subjects

Julide Yagmur¹, Mehmet Cansel¹, Nusret Acikgoz¹, Necip Ermis¹, Murat Yagmur¹, Halil Atas¹, Hakan Tasolar¹, Yasin Karakus¹, Hasan Pekdemir¹ and Ramazan Ozdemir¹

Our aim was to evaluate whether atrial electromechanical delay measured by tissue Doppler imaging (TDI), which is an early predictor of atrial fibrillation (AF) development, is prolonged in obese subjects. A total of 40 obese and 40 normal-weight subjects with normal coronary angiograms were included in this study. P-wave dispersion (PWD) was calculated on the 12-lead electrocardiogram (ECG). Systolic and diastolic left ventricular (LV) functions, inter- and intra-atrial electromechanical delay were measured by TDI and conventional echocardiography. Inter- and intra-atrial electromechanical delay were significantly longer in the obese subjects compared with the controls (44.08 ± 10.06 vs. 19.35 ± 5.94 ms and 23.63 ± 6.41 vs. 5.13 ± 2.67 ms, $P < 0.0001$ for both, respectively). PWD was higher in obese subjects (53.40 ± 5.49 vs. 35.95 ± 5.93 ms, $P < 0.0001$). Left atrial (LA) diameter, LA volume index and LV diastolic parameters were significantly different between the groups. Interatrial electromechanical delay was correlated with PWD ($r = 0.409$, $P = 0.009$), high-sensitivity C-reactive protein (hsCRP) levels ($r = 0.588$, $P < 0.0001$). Interatrial electromechanical delay was positively correlated with LA diameter, LA volume index, and LV diastolic function parameters consisting of mitral early wave (E) deceleration time (DT) and isovolumetric relaxation time (IVRT; $r = 0.323$, $P = 0.042$; $r = 0.387$, $P = 0.014$; $r = 0.339$, $P = 0.033$; $r = 0.325$, $P = 0.041$; respectively) and, negatively correlated with mitral early (E) to late (A) wave ratio (E/A) ($r = -0.380$, $P = 0.016$) and myocardial early-to-late diastolic wave ratio (E_m/A_m) ($r = -0.326$, $P = 0.040$). This study showed that atrial electromechanical delay is prolonged in obese subjects. Prolonged atrial electromechanical delay is due to provoked low-grade inflammation as well as LA enlargement and early LV diastolic dysfunction in obese subjects.

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INTRODUCTION

Obesity is one of the independent risk factors for development of cardiovascular disease (1,2). Besides, it is also a major risk factor for the development of atrial fibrillation (AF). Multiple studies have documented a strong and independent association between BMI and incidence of AF (3,4). Given the increasing incidence of both AF and obesity in the general population, obesity may be an important factor for the increasing burden of AF (5).

Electrophysiologic and electromechanical abnormalities resulting from intra- and interatrial conduction disorders are associated with a higher risk of AF (6). The prolongation of intra- and interatrial electromechanical delay and the inhomogeneous propagation of sinus impulses are well-known electrophysiological characteristics of the atrium prone to fibrillate (6–8). With recent developments in tissue Doppler imaging (TDI), it is possible to evaluate electrical events

of different regions with high temporal resolution. Atrial electromechanical delay can be measured from the onset of the P-wave on electrocardiogram (ECG) to the onset of atrial contraction determined by TDI (8). Atrial electromechanical delay has been demonstrated to be longer in patients with paroxysmal AF than in controls (9).

To our knowledge, TDI has not been used for the detection of atrial electromechanical delay in obese subjects. In this study, we investigated whether atrial electromechanical delay detected by TDI was prolonged in obese subjects.

METHODS AND PROCEDURES

Study population

We included 40 obese (mean age 54.88 ± 9.60 years and, mean BMI 35.42 ± 3.49 kg/m²) and 40 normal-weight control subjects (mean age 53.18 ± 12.07 years and, mean BMI 22.91 ± 1.58 kg/m²) in our study, all of whom were selected from the subjects who underwent coronary angiography in our center and had angiographically proven normal epicardial

¹Department of Cardiology, Faculty of Medicine, Inonu University, Malatya, Turkey. Correspondence: Julide Yagmur (julideyagmur@hotmail.com)

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coronary arteries. BMI was calculated as weight in kilograms divided by the height in meters squared (kg/m^2) and, normal weight was defined as $\text{BMI} \leq 25 \text{ kg}/\text{m}^2$ and obesity as $\text{BMI} \geq 30 \text{ kg}/\text{m}^2$. Patients and controls with a history or clinical evidence of left ventricular (LV) wall motion abnormality, LV ejection fraction $< 50\%$, primary cardiomyopathy, valvular heart disease, bundle branch block (QRS duration $> 120 \text{ ms}$), atrioventricular conduction abnormalities on electrocardiogram, pericarditis, thyroid dysfunction, anemia, electrolyte imbalance, renal failure (serum creatinine level $> 1.5 \text{ mg}/\text{dl}$), pulmonary disease, systemic inflammatory disease, and use of medications known to affect the electrocardiographic parameters were excluded from the study. All of the subjects had sinus rhythm. The study was carried out according to the principles of the Declaration of Helsinki and approved by Inonu University, School of Medicine, investigational review board. Using standard laboratory methods, blood samples were drawn after an overnight 12-h fasting to determine levels of blood glucose, electrolytes, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides. High-sensitivity C-reactive protein (hsCRP) was calculated by the nephelometric method (Behring Nephelometer Analyzer; Dade Behring, Marburg, Germany) and expressed as mg/l .

Echocardiography

In all subjects, echocardiographic examinations (HDI-5000; ATL Bothell, Washington) were performed by a cardiologist who was blinded to the clinical details and results of the other investigations of each patient and control. During echocardiography examination, a 1-lead ECG was recorded continuously. M-mode measurements were performed according to the criteria of American Society of Echocardiography. Three consecutive cycles were averaged for every parameter. Left atrial (LA) dimension, LV end-systolic, and end-diastolic diameters were measured. LV ejection fraction was estimated by Simpson's rule. LA volume was calculated at end-systole of the LV in the apical 4- and 2-chamber views using the methods of discs (Simpson's rule). LA volume was indexed to height and expressed in ml/m^2 . Transmitral pulsed-wave Doppler velocities were recorded from the apical 4-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. For TDI, the same echocardiography machine was used to acquire TDI data at high frame rates. The Nyquist limit was set at 15–20 cm/s and, minimal optimal gain was used. The myocardial systolic (S_m), early diastolic (E_m), and late diastolic (A_m) velocities were obtained at the septal and lateral mitral annulus by placing a tissue Doppler sample volume. The E/E_m and E_m/A_m ratios were subsequently calculated. The pulsed sample volume was placed at the level of LV lateral mitral annulus, septal mitral annulus, and right ventricular tricuspid annulus in order to obtain electromechanical parameters. The time interval from the onset of the P-wave on surface ECG to the beginning of the late diastolic wave (A_m wave) on TDI, which is named PA, was obtained from the lateral mitral annulus (lateral PA), septal mitral annulus (septal PA), and right ventricular tricuspid annulus (tricuspid PA); respectively (Figure 1). The difference between lateral PA and tricuspid PA (lateral PA – tricuspid PA) was defined as interatrial electromechanical delay and, the difference between septal PA and tricuspid PA (septal PA – tricuspid PA) was defined as intra-atrial electromechanical delay (8).

Reproducibility of electromechanical parameters was assessed by coefficients of variation (standard deviation of differences between the repeated measurements divided by the mean value and expressed as percent) between measurements. Intraobserver variability was calculated from 20 randomly selected subjects among the obese group. Intraobserver variability was 5.5% for PA lateral, 5.8% for PA septal, and 5.3% for PA tricuspid, respectively.

PWD measurements on 12-lead ECG

The 12-lead surface ECGs were obtained for each subject in the supine position at a paper speed of 50 mm/s . The P-wave durations were

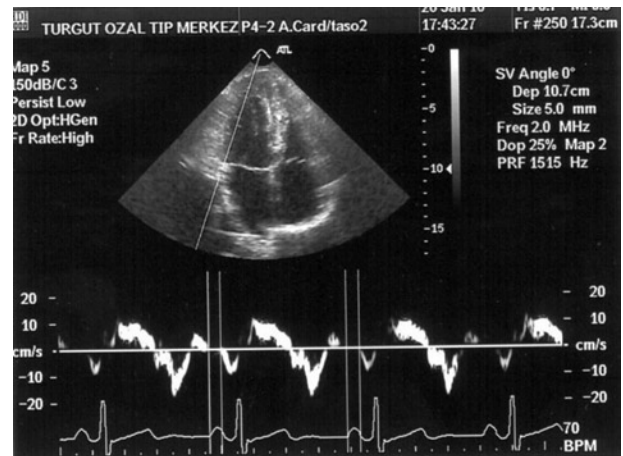


Figure 1 Measurement of the time interval from onset of the P wave on surface electrocardiogram to beginning of the A_m wave (PA) with tissue Doppler echocardiography.

measured manually by two investigators unaware of patient assignment by using calipers and a magnifying lens (tenfold magnification) to define the electrocardiogram deflections. The onset of the P-wave was defined as the junction between the isoelectric line and the beginning of P-wave deflection. The offset was defined as the junction between the end of the P-wave deflection and the isoelectric line. The longest atrial conduction time measured on any of the 12 leads was defined as P maximum (P_{\max}) and, the shortest time was defined as P minimum (P_{\min}). The difference between P_{\max} and P_{\min} was calculated and defined as P-wave dispersion ($\text{PWD} = P_{\max} - P_{\min}$). The patients who had indiscernible P-waves in more than four leads on a baseline 12-lead ECG were not enrolled in the study.

Intraobserver and interobserver coefficients of variation were 3.1 and 3.4% for maximum P-wave duration, and 3.6 and 3.8% for PWD, 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 \pm s.d., and categorical variables were defined as percentages. Categorical data were compared using the χ^2 -test. 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 < 0.05 was considered to be statistically significant.

RESULTS

Clinical characteristics and laboratory data of 40 obese and 40 normal-weight subjects are listed in Table 1. Mean BMI for the obese and the control groups were 33.35 ± 3.37 and 22.91 ± 1.58 ($P < 0.0001$). Obese subjects and the controls were similar regarding the age, gender, diabetes mellitus, hypertension, dislipidemia, and smoking. Plasma levels of hsCRP were significantly higher in the obese subjects than in the controls (3.14 ± 2.27 vs. $1.15 \pm 1.06 \text{ mg}/\text{l}$, $P < 0.0001$). The results of the echocardiographic measurements are shown in Table 2. LV end-diastolic and end-systolic diameters, LV ejection fraction, interventricular septum thickness, LV posterior wall thickness, and *E* velocity were also similar between the groups. LA diameter, LA volume, LA volume index, IVRT, *A* velocity, and DT were significantly higher (35.63 ± 3.31 vs. $32.00 \pm 3.05 \text{ mm}$,

Table 1 Clinical characteristics of the study population and laboratory data

	Obese (n = 40)	Controls (n = 40)	P value
Age (years)	54.88 ± 9.60	53.18 ± 12.07	NS
Female, n (%)	26 (65)	23 (57.5)	NS
BMI (kg/m ²)	35.42 ± 3.49	22.91 ± 1.58	<0.0001
Diabetes mellitus, n (%)	10 (25)	6 (15)	NS
Hypertension, n (%)	8 (20)	6 (15)	NS
Smokers, n (%)	13 (32.5)	11 (27.5)	NS
Total cholesterol (mg/dl)	201.03 ± 34.08	192.68 ± 30.47	NS
LDL cholesterol (mg/dl)	127.46 ± 27.39	120.03 ± 21.92	NS
HDL cholesterol (mg/dl)	40.73 ± 8.18	43.53 ± 8.39	NS
Triglycerides (mg/dl)	182.05 ± 83.69	155.78 ± 53.57	NS
Fasting blood glucose (mg/dl)	116.95 ± 43.36	105.16 ± 20.64	NS
Creatinine (mg/dl)	0.87 ± 0.18	0.84 ± 0.16	NS
CRP (mg/l)	3.14 ± 2.27	1.15 ± 1.06	<0.0001

CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

$P < 0.0001$; 48.40 ± 7.67 vs. 38.35 ± 4.67 ml, $P < 0.0001$; 29.80 ± 5.14 vs. 23.43 ± 3.01 ml/m, $P < 0.0001$; 94.00 ± 10.01 vs. 82.50 ± 9.33 ms, $P < 0.0001$; 66.41 ± 6.72 vs. 61.97 ± 7.92 cm/s, $P = 0.009$; 222.75 ± 34.38 vs. 179.50 ± 22.18 ms, $P < 0.0001$, respectively), and E/A ratio was significantly lower (1.34 ± 0.22 vs. 1.47 ± 0.22 , $P = 0.012$) in obese subjects. There was no significant difference between the groups with respect to S_m and E_m values and E/E_m ratio. However, A_m value was significantly higher (9.79 ± 1.11 vs. 8.83 ± 1.40 cm/s, $P = 0.001$) and E_m/A_m ratio was significantly lower (1.23 ± 0.13 vs. 1.47 ± 0.35 , $P < 0.0001$) in obese subjects.

P-wave measures are shown in **Table 3**. Statistically significant differences were found in P_{\max} and PWD values between the obese and the control groups (115.25 ± 7.12 ms vs. 100.10 ± 6.14 ms, $P < 0.0001$; 53.40 ± 5.49 ms vs. 35.95 ± 5.93 ms, $P < 0.0001$).

The atrial electromechanical parameters are reported in **Table 3**. PA lateral and PA septum durations were significantly higher in the obese subjects compared with the controls (79.18 ± 11.08 vs. 54.88 ± 6.69 ms, $P < 0.0001$; 58.73 ± 8.53 vs. 40.65 ± 4.86 ms, $P < 0.0001$, respectively). However, PA tricuspid duration was similar between both groups (35.10 ± 5.56 vs. 35.53 ± 3.63 ms, $P > 0.05$). Moreover, inter and intra-atrial electromechanical delay were significantly higher in the obese subjects when compared with the controls (44.08 ± 10.06 vs. 19.35 ± 5.94 , $P < 0.0001$ and 23.63 ± 6.41 vs. 5.13 ± 2.67 , $P < 0.0001$, respectively).

A significant correlation was detected between PWD and interatrial electromechanical delay ($r = 0.409$, $P = 0.009$).

Table 2 Echocardiographic parameters of the study population

	Obese (n = 40)	Controls (n = 40)	P value
LV ejection fraction (%)	65.35 ± 3.93	65.00 ± 4.84	NS
Left atrial diameter (mm)	35.63 ± 3.31	32.00 ± 3.05	<0.001
Left atrial volume (ml)	48.40 ± 7.67	38.35 ± 4.67	<0.0001
Left atrial volume index (ml/m)	29.80 ± 5.14	23.43 ± 3.01	<0.0001
LVEDD (mm)	45.93 ± 3.40	44.70 ± 2.65	NS
LVESD (mm)	29.15 ± 3.03	28.18 ± 3.17	NS
Septal thickness (mm)	10.35 ± 0.89	9.95 ± 1.19	NS
PW thickness (mm)	10.05 ± 0.84	9.88 ± 1.41	NS
Mitral E velocity (cm/s)	88.56 ± 12.46	90.31 ± 11.41	NS
Mitral A velocity (cm/s)	66.41 ± 6.72	61.97 ± 7.92	0.009
E/A	1.34 ± 0.22	1.47 ± 0.22	0.012
DT (ms)	222.75 ± 34.38	179.50 ± 22.18	<0.0001
IVRT (ms)	94.00 ± 10.01	82.50 ± 9.33	<0.0001
S_m (cm/s)	11.07 ± 1.86	10.89 ± 1.61	NS
E_m (cm/s)	12.03 ± 1.62	12.66 ± 1.70	NS
A_m (cm/s)	9.79 ± 1.11	8.83 ± 1.40	=0.001
E_m/A_m	1.23 ± 0.13	1.47 ± 0.35	<0.0001
E/E_m	7.46 ± 1.29	7.24 ± 1.20	NS

A , mitral late diastolic velocity; A_m , LV myocardial late diastolic velocity; DT, mitral E -wave deceleration time; E , mitral early diastolic velocity; E_m , LV myocardial early diastolic velocity; IVRT, isovolumetric relaxation time; LV, left ventricular; LVEDD, LV end-diastolic dimension; LVESD, LV end-systolic dimension; PW, posterior wall; S_m , LV systolic myocardial velocity.

Interatrial electromechanical delay had a positive correlation with LA diameter, LA volume index, DT, and IVRT ($r = 0.323$, $P = 0.042$; $r = 0.387$, $P = 0.014$; $r = 0.339$, $P = 0.033$; $r = 0.325$, $P = 0.041$, respectively) and a negative correlation with interatrial electromechanical delay and E/A ($r = -0.380$, $P = 0.016$) and E_m/A_m ($r = -0.326$, $P = 0.040$). hsCRP levels were strongly correlated with interatrial electromechanical delay ($r = 0.588$, $P < 0.0001$; **Figure 2**).

DISCUSSION

Obesity is a major risk factor for the development of AF (3). In a recent population-based cohort study, it has been pointed out that obese individuals have an associated 49% increased risk of developing AF compared to nonobese individuals, and the risk arose in parallel with increased BMI (10). There are several possible responsible mechanisms for the development of AF in obesity and LA enlargement is probably the main cause responsible for this association (3,11). Elevated plasma volume, ventricular diastolic dysfunction, and enhanced neurohormonal activation accompany obesity and may contribute to LA

enlargement and electrical instability (12). Also, inflammation, increased oxidative stress and lipoapoptosis, which are associated with increasing adiposity, may contribute to structural atrial changes increasing the risk of AF (13–15).

Recent studies have assessed atrial electromechanical delay with TDI echocardiography, which is a noninvasive method alternative to invasive electrophysiological studies (8,9). Omi and colleagues have recently evaluated the ability of the atrial electromechanical interval to detect atrial impairment in paroxysmal AF. They found that the atrial electromechanical interval was prolonged in paroxysmal AF (16). Roshanali *et al.* found that atrial electromechanical interval was a predictor of AF emerging after coronary artery bypass graft and showed that the preoperative administration of amiodarone to patients having longer atrial electromechanical interval decreased the postoperative AF incidence (17). These studies showed that prolonged

electromechanical interval seemed to reflect atrial remodeling for an arrhythmogenic substrate (16,17). Also, atrial electromechanical delay has been assessed as a predictor of AF in patients with mitral stenosis, ankylosing spondylitis, and type 1 diabetes mellitus (8,18,19). In this study, we have demonstrated that the intra- and interatrial electromechanical delay, which is a noninvasive technique providing estimate risk of AF, were significantly longer in obese subjects than in normal-weight controls.

It is accepted that increased P-wave duration on the standard surface ECG indicates an atrial conduction disorder. PWD appears to correlate with P-wave duration, and to be a useful predictive marker for the development of AF (7). Recently, PWD has been studied in patients with hypertension, metabolic syndrome, and diabetes mellitus as a simple and noninvasive predictor of AF development (20–22). Also, Kosar *et al.* found PWD and P-wave duration high in the obese subjects and found out the relationship of these parameters with echocardiographic parameters (23). Our results are consistent with their findings demonstrating that values of PWD and P_{\max} were higher in the obese subjects than in normal-weight controls. We also found a significant correlation between PWD and interatrial electromechanical delay.

LA dilatation and LV diastolic dysfunction have already been reported in the obese subjects in previous studies (24,25). The resulting electroanatomical substrate in dilated atria is characterized by increased nonuniform anisotropy and macroscopic slowing of conduction. Atrial conduction disorders and the resultant abnormalities are associated with a higher risk of paroxysmal atrial tachyarrhythmias (9). In this study, we also detected a greater LA diameter and LA volume index, a higher DT and IVRT and a lower E/A ratio and E_m/A_m ratio in the obese subjects. We found that interatrial electromechanical delay had a significant correlation with LV diastolic parameters, LA volume index, and LA dimension. Our findings support that increased LA enlargement and LV early diastolic dysfunction accompanying obesity may contribute the prolongation of interatrial electromechanical delay.

Table 3 Comparison of the electrocardiographic and atrial electromechanical parameters

	Obese (n = 40)	Controls (n = 40)	P value
Heart rate (beat/min)	78.5 ± 10.82	77.5 ± 9.02	NS
P_{\max} (ms)	115.25 ± 7.12	100.10 ± 6.14	<0.0001
P_{\min} (ms)	61.85 ± 5.64	64.15 ± 7.15	NS
PWD (ms)	53.40 ± 5.49	35.95 ± 5.93	<0.0001
Lateral PA (ms)	79.18 ± 11.08	54.88 ± 6.69	<0.0001
Septal PA (ms)	58.73 ± 8.53	40.65 ± 4.86	<0.0001
Tricuspid PA (ms)	35.10 ± 5.56	35.53 ± 3.63	NS
Lateral PA – tricuspid PA ^a (ms)	44.08 ± 10	19.35 ± 5.94	<0.0001
Septal PA – tricuspid PA ^b (ms)	23.63 ± 6.41	5.13 ± 2.67	<0.0001

PA, time interval from the onset of the P-wave on surface electrocardiogram to the beginning of the late diastolic wave; P_{\max} , P maximum; P_{\min} , P minimum; PWD, P-wave dispersion.

^aInteratrial electromechanical delay. ^bIntra-atrial electromechanical delay.

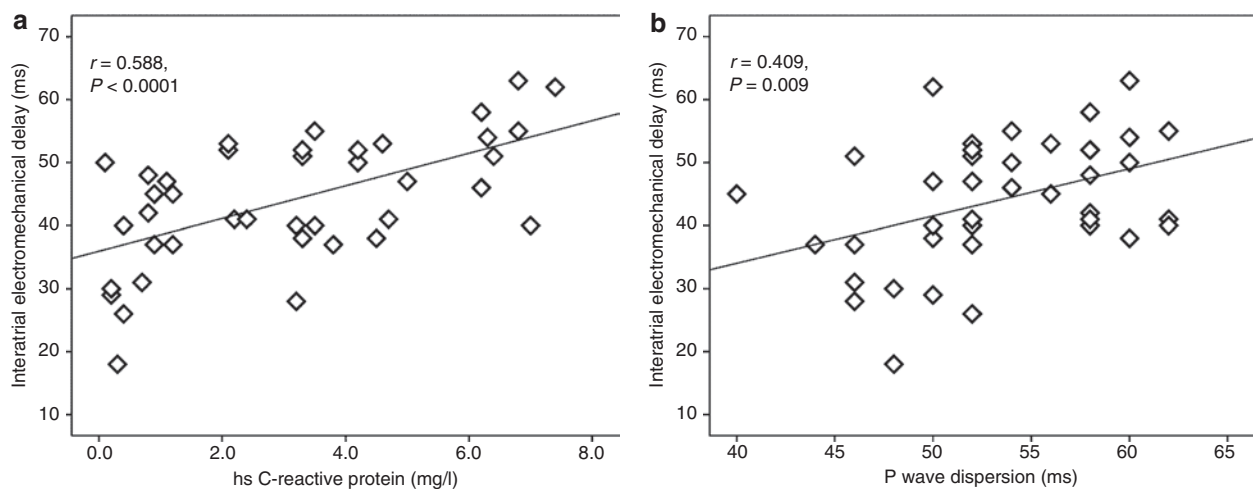


Figure 2 Positive correlation (a) between interatrial electromechanical delay and hsCRP and (b) between interatrial electromechanical delay and P-wave dispersion. hsCRP, high-sensitivity C-reactive protein.

We also detected higher hsCRP levels in obese subjects. Fat tissue is a known source of inflammatory cytokines and the correlation between obesity and elevated concentrations of CRP is well documented (13,26). Previous studies have demonstrated the presence of increased levels of CRP in patients with persistent and paroxysmal AF (27,28). Also from a histological perspective, studies have documented inflammatory infiltrates, myocyte necrosis, and fibrosis in atrial biopsies of patients with AF (29). We found a strong significant correlation between interatrial electromechanical delay and hsCRP levels. Inflammation may cause the prolongation of atrial activation time by causing structural remodeling process in atrial myocardium. Also, detection of relatively higher CRP levels as an indicator of a low-grade systemic inflammation in obese subjects may be an explanation of the increased risk for the development of AF.

In conclusion, we found inter- and intra-atrial electromechanical delay and PWD prolonged in obese subjects. Prolonged interatrial electromechanical delay had a significant correlation with hsCRP, PWD, LA diameter, LA volume index, and LV diastolic function parameters. We concluded that atrial electromechanical delay, which is a predictor of increased risk of AF development, is due to provoked low-grade inflammation as well as LA enlargement and LV diastolic dysfunction in obese subjects.

The most important limitations of our study is the small sample size and cross-sectional design of the study, in which we could not follow-up the patients prospectively for future arrhythmic events. Further long-term prospective studies are needed to determine the clinical utility and prognostic importance of interatrial electromechanical delay in obese subjects.

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DISCLOSURE

The authors declared no conflict of interest.

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