

# Assessment of atrial conduction times in patients with mild diastolic dysfunction and normal atrial size

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## ABSTRACT

**Objective:** Abnormalities in atrial electromechanical delays (EMDs) are considered independent predictors of atrial fibrillation and can reflect atrial remodeling. The main purpose in this study was to compare inter-left and right intra-atrial EMDs of patients with mild left ventricular (LV) diastolic dysfunction, without left atrial (LA) structural remodeling in the absence of high filling pressure, with healthy individuals.

**Methods:** In this prospective study, a total of 41 consecutive outpatients who were referred to our echocardiography laboratory with mild diastolic dysfunction (age:  $60.9 \pm 9.6$  years) and 45 healthy control subjects who were referred from an outpatient clinic for check-up (age:  $32.2 \pm 10.3$  years) with normal diastolic function were enrolled into this study. All subjects had normal LA volume and normal right atrial area and did not have high filling pressure. Diastolic dysfunction were determined per American Society of Echocardiography recommendations; so, the following indices were measured: peak early (E) and atrial (A) flow velocities (cm/s), E/A ratio, and deceleration time (DT) (ms) of mitral inflow, systolic (S) and diastolic (D) pulmonary vein wave velocities (cm/s) by pulse wave Doppler, and  $e'$  in septal and lateral mitral annulus by pulse wave tissue Doppler. Time interval from the onset of P wave on the ECG to the beginning of the late diastolic wave (Am wave) on tissue Doppler trace, which is named PA, was obtained from the lateral and septal mitral annulus and right ventricular (RV) tricuspid annulus as atrial conduction times (ACTs) and were named lateral PA, septal PA, and RV PA, respectively. The difference between lateral PA and septal, PA septal and RV PA was defined as left and right intra-atrial EMD, respectively. The difference between lateral PA and RV PA was defined as inter-atrial EMD. Data analysis was done by independent student's t-test, Mann-Whitney U test,  $\chi^2$  test, Spearman rank order, Pearson's correlation coefficient, and multivariate regression analysis in the appropriate site.

**Results:** A, DT, S/D ratio, and  $E/e'$  (average) were significantly lower in the control group, and E, D, E/A ratio,  $e'$  septal, and  $e'$  lateral wall were significantly lower in the patient group. Atrial conduction times were longer in the patient group, but in the multivariate analysis, there was no correlation between ACTs and diastolic dysfunction. There was no significant difference in left intra-atrial EMD ( $14.2 \pm 9.7$  ms vs.  $16.4 \pm 11.4$  ms;  $p=0.336$ ), right intra-atrial EMD ( $12.8 \pm 12.2$  ms vs.  $15.4 \pm 12.1$  ms;  $p=0.321$ ), and inter-atrial EMD ( $26.9 \pm 13.7$  ms vs.  $31.7 \pm 13.7$  ms;  $p=0.108$ ) between the two groups. Multivariate analysis showed no correlation between inter- and intra-atrial EMDs and diastolic dysfunction.

**Conclusion:** There was no significant difference in ACTs and inter-atrial and left and right intra-atrial EMD in patients with mild LV diastolic dysfunction and normal LA volume in the absence high filling pressure compared with normal subjects.

(*Anatol J Cardiol*; 2015; 15: 925-31)

**Keywords:** atrial electromechanical delay, atrial conduction time, diastolic dysfunction, tissue Doppler echocardiography

## Introduction

Atrial fibrillation (AF) is associated with increased mortality and morbidity, such as heart failure, increased hospitalization, stroke, and decreased quality of life and exercise capacity (1). There is much evidence suggesting that left ventricular (LV) diastolic dysfunction provides a profibrillatory environment that initiates AF (2-5). One study showed a strong and independent

association of the presence and severity of diastolic dysfunction with higher risk of developing non-valvular AF after 5 years of follow-up. In that study, the age-adjusted cumulative risks of non-valvular AF were 1%, 12%, 14%, and 21% for patients with normal, mild, moderate, and severe LV diastolic dysfunction, respectively (6). In another study, the rate of new-onset postcardiac surgery AF increased with the severity of diastolic dysfunction. The odds ratio of AF occurrence after clinical and surgical

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**Accepted Date:** 30.09.2014 **Available Online Date:** 11.11.2014

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DOI:10.5152/akd.2014.5816



risk factor adjustment was 5.12, 9.87, and 28.52 for mild, moderate, and severe LV diastolic dysfunction, respectively (7). Atrial size is a marker of structural atrial remodeling, but atrial conduction times (ACTs) are signs of electrical and structural remodeling of the atria. Atrial conduction delay is necessary for the initiation of AF (8-10). It has been shown that AF occurrence is related to increased atrial conduction delay (11, 12). The ACTs were shown to be markers that are associated to LA volume (13). Electromechanical intervals, the time intervals from the beginning of P wave deflection to the peak of the local lateral left atrial (LA) tissue Doppler imaging signal, have been shown, becoming progressively increased as the LV diastolic dysfunction progresses from mild to severe (14).

It has been suggested ACT can be increased in diastolic dysfunction before the appearance of structural remodeling as a marker for electrical remodeling, but this hypothesis and inter- and intra-atrial electromechanical delay (EMD) in mild diastolic dysfunction have not been evaluated (14). So, in the present study, we evaluated ACTs and inter- and left and right intra-atrial EMD in patients with LV mild diastolic dysfunction and normal LA volume, in the absence of high filling pressure, compared with those without diastolic dysfunction.

## Methods

### Study population

In this prospective study, 41 consecutive outpatients (31 males, 10 females) who were referred to the echocardiography laboratory between May 2013 and April 2013 were included in patient group (age:  $60.9 \pm 9.6$  years). Exclusion criteria were as follows: body mass index  $>30$  kg/m<sup>2</sup>, prolonged QRS duration ( $\geq 120$  ms), history of cardiac surgery, hypertrophic cardiomyopathy, AF, or atrial flutter at presentation or history of these arrhythmias, pacemaker implantation, more than mild valvular regurgitation, presence of valvular stenosis, systolic pulmonary artery pressure  $>34$  mm Hg, E/e' [(average of septum and lateral wall)]  $>13$ , history of renal or hepatic disease, LA volume index  $>28$  mL/m<sup>2</sup>, right atrial area  $>18$  cm<sup>2</sup>, and patients older than 65 years without a history of hypertension, diabetes mellitus, or coronary artery disease.

Criteria for mild LV diastolic dysfunction were according to the American Society of Echocardiography (ASE) recommendations (15). The control group was chosen from healthy persons (n=45, 20 males, 25 females), admitted for checkup to the outpatient clinic and referred to the echocardiography laboratory (age:  $32.2 \pm 10.3$  years).

A complete medical history and physical examination for all subjects were done. Subjects' height, weight, heart rate, and blood pressure on the day of echocardiography were recorded. The study was approved by the institution review board (IRB) of our hospital, and the IRB agreed that verbal patient consent sufficed.

### Standard transthoracic echocardiography

All echocardiographic examinations were performed with a Vivid S5 cardiac ultrasound scanner (GE Vingmed Ultrasound,

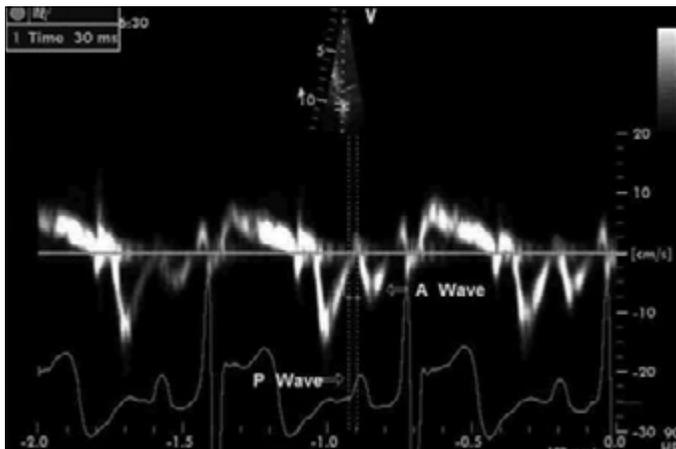
Horten, Norway) and a 2 to 4 MHz transducer. All subjects were examined by one echocardiologist in the left lateral and supine position by M-mode, 2-dimensional, Doppler, color Doppler, and tissue Doppler echocardiography. One lead electrocardiogram was recorded continuously. The position of the electrocardiogram leads was altered for maximizing the P wave height. LA anterior-posterior diameter, systolic-diastolic diameters, and septal and posterior wall thickness of LV were obtained by M-mode images from the parasternal long-axis view, and 2-dimensional maximal LA volume by the biplane area-length method was determined according to the standards of the ASE (16). LA area was measured by tracing the maximum area of the LA during systole in the apical 4-chamber and 2-chamber view, and the averaged value was recorded. Right atrial area was measured by tracing the maximum area of the right atrium during systole in the apical 4-chamber view. LV end-diastolic volume, LV end-systolic volume, and LV ejection fraction were measured by modified biplane Simpson's method.

### Diastolic measurements

Flow velocity indexes were obtained using pulsed-wave Doppler from apical projections, and measurements were made using the ultrasound equipment software. Mitral diastolic flow was obtained after the pulsed Doppler sample volume was positioned perpendicularly to the tips of the mitral valve leaflets. The following indices were measured from the mitral valve diastolic wave form: peak early (E) and atrial (A) flow velocities (cm/s), E/A ratio, and deceleration time (DT) (ms) of the early LV diastolic filling. Also, systolic (S) and diastolic (D) pulmonary vein wave velocities (cm/s) were measured from the apical 4-chamber view. All measurements were averaged from three cardiac cycles. Diastolic dysfunction was determined per ASE recommendations (15).

### Tissue Doppler echocardiography

Tissue Doppler echocardiography was performed by transducer frequencies of 2 to 4 MHz, adjusting the spectral pulsed Doppler signal filters until a Nyquist limit of 15 to 20 cm/s and using the minimal optimal gain. The monitor sweep speed was set to 100 mm/s to optimize the spectral display of myocardial velocities. The ultrasound beam was positioned as parallel as possible to the myocardial segment to acquire the optimal angle of imaging. In the apical 4-chamber view, the pulsed Doppler sample volume was subsequently placed at the level of the septal and lateral mitral annulus and right ventricular tricuspid annulus. The E/[e' (average of lateral and septal wall)] ratio was measured for the mitral annulus. The time interval from the onset of P wave on the surface electrocardiogram to the beginning of the late diastolic wave (Am wave), which is named PA, was obtained from the lateral and septal mitral annulus and right ventricular (RV) tricuspid annulus and was named lateral PA, septal PA, and RV PA, respectively. The measurement of PA interval is shown in Figure 1. The difference between lateral PA and septal PA (lateral PA-septal PA) was defined as left intra-



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

atrial EMD, the difference between septal PA and RV PA was defined as right intra-atrial EMD (septal PA-RV PA), and the difference between lateral PA and RV PA (lateral PA-RV PA) was defined as inter-atrial EMD (17). Average values of three sequential beats were used for the analysis.

### Statistical analysis

All analyses were performed using the SPSS (SPSS for Windows 18.0) software package, and a 2-sided p value of <0.05 was considered significant. Distribution of data was assessed using one-sample Kolmogorov-Smirnov test. Data are demonstrated as mean±standard deviation for normally distributed continuous variables, median (minimum-maximum) for skew-distributed continuous variables, and frequencies for categorical variables.  $\chi^2$  test was performed for the comparison of categorical variables. Independent student's t-test was performed for normally distributed variables, and Mann-Whitney U test was performed for skew-distributed continuous variables. Correlation was tested with Spearman rank order or Pearson's correlation coefficient. The associations between ACTs, inter- and intra-atrial delay, and other variables were analyzed with linear regression analysis. In the evaluation of the interrelation of between ACTs and inter- and intra-atrial EMD with Doppler diastolic indices, variables that correlated with a p value <0.2 were entered into the multivariate analysis.

### Results

The clinical and echocardiographic characters for the two groups are shown in Table 1. Age ( $32.2\pm 10.3$  vs.  $60.9\pm 9.6$ ,  $p<0.001$ ), ratios of male sex, hypertension, diabetes, dyslipidemia, cigarette smoking, and coronary artery disease prevalence were significantly lower in the control group.

Septal and posterior wall thickness, LV mass, and LV mass index were significantly lower in the control group, but LV ejection fraction, RV diameter, tricuspid annular plane systolic excursion (TAPSE), and RV systolic motion (RV Sm) were significantly lower in the patient group.

**Table 1. Clinical and echocardiographic characters of control and patient group\***

Variables	Control (n=45)	Patient (n=41)	P
Age, years	32.2±10.3	60.9±9.6	<0.001
Sex (M) % (n)	44.4 (20)	75.6 (31)	0.003
HTN % (n)	2.2 (1)	48.8 (20)	<0.001
DM % (n)	2.2 (1)	26.8 (11)	<0.001
C/S % (n)	4.4 (2)	31.7 (13)	<0.001
DLP % (n)	2.2 (1)	48.8 (20)	<0.001
CAD % (n)	0 (0)	87.7 (36)	<0.001
HR, bpm	70.7± 11.3	71.3 ±9.1	0.795
SBP, mm Hg	123.2±14.9	127.7±11.7	0.124
DBP, mm Hg Range	80 (60-95)	80 (60-95)	0.120
BSA, m <sup>2</sup> Range	1.8 (1.5-2.1)	1.8 (1.5-2.25)	0.381
SWT, mm Range	7 (5-9)	8 (5-13)	<0.001
PWT, mm Range	7 (5-9)	8 (6-11)	<0.001
LV mass, gr	99.4±20.9	127.8±31.6	<0.001
LV mass index, gr/m <sup>2</sup>	55.0±11.0	71.8±17.6	<0.001
LVEDV mL	107.8±18.8	107.3±29.8	0.928
LVESV mL Range	44.1 (24-61)	47.5 (22-123.8)	0.125
LVEF % Range	60 (55-69)	55.4 (24-68)	<0.001
LA diameter Range	31 (17-39)	32 (22-39)	0.123
LA area, cm <sup>2</sup>	14.3±2.6	14.3±2.0	0.966
LA volume, mL	36.0±8.7	35.0±7.7	0.363
LA volume index, mL/m <sup>2</sup>	19.9±4.6	19.7±4.5	0.495
RV diameter, mm	29.4±2.9	27.6±3.6	0.012
TAPSE, mm	22.0±3.7	20.3±3.7	0.038
RV Sm, cm/s	12.0±1.5	11.1±1.7	0.019
RA area, cm <sup>2</sup>	13.0 ±2.1	13.1±3.6	0.822
E, cm/s	78.0±14.8	52.4±12.1	<0.001
A, cm/s	49.3±14.3	74.1±15.9	<0.001
DT, ms	175.5± 41.9	236.3±55.4	<0.001
S, cm/s	46.6±10.9	47.6±10.0	0.667
D, cm/s	47.2±9.1	31.9±7.1	<0.001
E/A ratio	1.7±0.6	0.7±0.2	<0.001
S/D ratio	1.0±0.3	1.5±0.4	<0.001
e' septum, cm/s	11.3±2.3	5.2±1.4	<0.001
e' lateral, cm/s Range	14 (10-25)	7 (3-9)	<0.001
E/e' (average) ratio *	6.2±1.3	8.9±3.3	<0.001

\*Data are demonstrated as mean±standard deviation for normally distributed continuous variables, median (minimum-maximum) for skew-distributed continuous variables, and frequencies (%) for categorical variables.

BSA - body surface area; CAD - coronary artery disease; C/S - cigarette smoker; DBP - diastolic blood pressure; DLP - dyslipidemia; DM - diabetes mellitus; HR - heart rate; HTN - hypertension; LA - left atrium; LV - left ventricle; LVEDV - left ventricular end-diastolic volume; LVEF - left ventricular ejection fraction; LVESV - left ventricular end-systolic volume; M - male; n - number; PWT - posterior wall thickness; RA - right atrium; RV Sm - right ventricular systolic motion; RV - right ventricle; SBP - systolic blood pressure; SWT - septal wall thickness; TAPSE - tricuspid annular plane systolic excursion; \*E/e' (average) ratio: E/(mean e' septum and lateral wall)

A, DT, S/D ratio, and E/e' (average) were significantly lower in the control group, but E, D, E/A ratio, and e' septal and e' lateral wall were significantly lower in the patient group. Other echocardiographic characters of the two groups were similar.

ACTs and inter- and intra-atrial EMDs are presented in Table 2. Septal PA, lateral PA, and RV PA were significantly different in patients compared with healthy controls ( $35.6 \pm 15.0$  vs.  $44.9 \pm 11.7$ ,  $p=0.004$ ,  $49.7 \pm 12.6$  vs.  $61.1 \pm 16.3$ ,  $p<0.001$  and  $22.8 \pm 14.6$  vs.  $29.6 \pm 12.8$ ,  $p=0.024$ , respectively), but when correlating septal PA, lateral PA, and RV PA with diastolic dysfunction adjusted according to other factors, presented in Table 3, this correlation was not statistically significant ( $p=0.869$ ,  $p=0.504$ , and  $p=0.907$ , respectively). Male sex was the only determinant of septal PA ( $p=0.029$ ), age and LV mass index were determinants of lateral PA ( $p=0.011$  and  $p=0.037$ , respectively), and male sex was the only determinant of RV PA ( $p=0.019$ ).

Septal PA was related to E ( $r=-0.229$ ,  $p=0.034$ ), DT ( $r=0.245$ ,  $p=0.023$ ), and D ( $r=-0.227$ ,  $p=0.037$ ). In the multivariate analysis,

**Table 2. Atrial conduction times and inter- and left and right intra-atrial EMD in control and patient groups**

Group / Index	Control	Patient	P
Septal PA, ms	$35.6 \pm 15.0$	$44.9 \pm 11.7$	0.004
Lateral PA, ms	$49.7 \pm 12.6$	$61.1 \pm 16.3$	<0.001
RV PA, ms	$22.8 \pm 14.6$	$29.6 \pm 12.8$	0.024
Lateral PA-Septal PA, ms	$14.2 \pm 9.7$	$16.4 \pm 11.4$	0.336
Septal PA-RV PA, ms	$12.8 \pm 12.2$	$15.4 \pm 12.1$	0.321
Lateral PA-RV PA, ms	$26.9 \pm 13.7$	$31.7 \pm 13.7$	0.108

PA - the interval with tissue Doppler imaging from the onset of P wave on the surface electrocardiogram to the beginning of the late-diastolic wave (Am wave); RV - right ventricle

these correlations were not statistically significant. Lateral PA was related to E ( $r=0.317$ ,  $p=0.003$ ), A ( $r=0.291$ ,  $p=0.007$ ), DT ( $r=0.244$ ,  $p=0.023$ ), D ( $r=-0.254$ ,  $p=0.019$ ), E/A ratio ( $r=-0.285$ ,  $p=0.009$ ), e' septal ( $r=-0.304$ ,  $p=0.004$ ), and e' lateral ( $r=-0.309$ ,  $p=0.004$ ). The multivariate analysis showed only E ( $p=0.043$ ) and A ( $p=0.030$ ) to be predictors of lateral PA. RV PA was only related to DT ( $r=0.215$ ,  $p=0.047$ ). In the multivariate analysis, no statistically significant predictor was found.

Left intra-atrial EMD, right intra-atrial EMD, and inter-atrial EMD were not significantly prolonged in patients compared with healthy controls ( $14.2 \pm 9.7$  vs.  $16.4 \pm 11.4$ ,  $p=0.336$ ,  $12.8 \pm 12.2$  vs.  $15.4 \pm 12.1$ ,  $p=0.321$  and  $26.9 \pm 13.7$  vs.  $31.7 \pm 13.7$ ,  $p=0.108$ ). When correlating left intra-atrial EMD, right intra-atrial EMD, and inter-atrial EMD with diastolic dysfunction adjusted according to some factors, presented in Table 4, these correlations were not statistically significant ( $p=0.251$ ,  $p=0.739$ , and  $p=0.520$ , respectively). Age was the only determinant of right intra-atrial EMD and inter-atrial EMD ( $p=0.012$  and  $p=0.002$ , respectively) (Table 4).

Left intra-atrial EMD was not related to diastolic Doppler indices in the bivariate and multivariate analysis. Right intra-atrial EMD was related to D ( $r=-0.267$ ,  $p=0.013$ ) in the bivariate analysis ( $r=-0.267$ ,  $p=0.013$ ) and multivariate analysis ( $p=0.036$ ). Inter-atrial EMD was related to A ( $r=0.276$ ,  $p=0.010$ ), D ( $r=-0.272$ ,  $p=0.012$ ), E/A ratio ( $r=-0.234$ ,  $p=0.032$ ), S/D ( $r=0.219$ ,  $p=0.046$ ), and e' lateral ( $r=-0.279$ ,  $p=0.009$ ). In the multivariate analysis, these correlations were not statistically significant.

## Discussion

In this study, tissue Doppler imaging was used to show ACTs and inter- and intra-atrial EMD. Septal PA, lateral PA, and RV PA

**Table 3. Linear regression analyses of variables associated with atrial conduction times**

Variables	Septal PA			Lateral PA			RV PA		
	$\beta$	t	P	$\beta$	t	P	$\beta$	t	P
Age	0.350	1.694	0.095	0.494	2.619	0.011	-0.094	-0.449	0.655
Sex, male	-0.266	-2.226	0.029	-0.211	-1.929	0.058	-0.292	-2.406	0.019
DLP	0.145	1.094	0.278	0.194	1.607	0.113	0.198	1.477	0.144
DM	0.029	0.215	0.830	-0.053	-0.422	0.672	0.122	0.880	0.382
HTN	-0.164	-1.158	0.251	-0.127	-0.981	0.330	-0.010	-0.072	0.943
C/S	0.180	1.420	0.160	0.183	1.584	0.118	0.109	0.845	0.401
CAD	-0.299	-1.135	0.260	-0.267	-1.114	0.269	0.003	0.011	0.991
LV mass index	0.109	0.784	0.436	0.270	2.129	0.037	0.099	0.698	0.487
LVEF	0.114	0.858	0.394	0.006	0.053	0.958	0.063	0.463	0.645
E/e' (average) ratio *	0.003	0.026	0.979	0.095	0.797	0.428	-0.020	-0.151	0.880
RV diameter	-0.167	-1.469	0.146	-0.007	-0.064	0.949	-0.159	-1.383	0.171
TAPSE	-0.127	-1.110	0.271	-0.063	-0.604	0.548	-0.160	-1.379	0.172
RV Sm	-0.003	-0.027	0.978	-0.054	-0.505	0.615	0.119	1.010	0.316
Diastolic dysfunction	0.046	0.165	0.869	-0.169	-0.671	0.504	-0.033	-0.117	0.907

CAD - coronary artery diseases; C/S - cigarette smoker; DLP - dyslipidemia; DM - diabetes mellitus; HTN - hypertension; LVEF - left ventricular ejection fraction; RV Sm - right ventricular systolic motion; RV - right ventricle; TAPSE - tricuspid annular plane systolic excursion; \*E/e' (average) ratio - E/ (mean e' septum and lateral wall)

**Table 4. Linear regression analyses of variables associated with inter- and left and right intra-atrial electromechanical delays**

Variables	Lateral PA-Septal PA			Septal PA-RV PA			Lateral PA-RV PA		
	$\beta$	t	P	$\beta$	t	P	$\beta$	t	P
Age	0.207	0.940	0.350	0.558	2.577	0.012	0.646	3.211	0.002
Sex	0.076	0.594	0.555	0.001	0.006	0.995	0.058	0.499	0.619
DLP	0.97	0.687	0.494	-0.047	-0.342	0.733	0.032	0.248	0.850
DM	-0.091	-0.627	0.533	-0.106	-0.737	0.464	-0.162	-1.216	0.228
HTN	0.024	0.160	0.873	-0.197	-1.328	0.189	-0.154	-1.119	0.267
C/S	0.033	0.244	0.808	0.103	0.774	0.442	0.115	0.932	0.355
CAD	0.053	0.188	0.852	-0.385	-1.396	0.167	-0.297	-1.161	0.250
LV mass index	0.238	1.6105	0.113	0.024	0.164	0.870	0.202	1.489	0.141
LVEF	-0.185	-1.308	0.195	0.073	0.521	0.604	-0.077	-0.596	0.553
E/e'(average) ratio*	0.132	0.951	0.345	0.028	0.202	0.841	0.124	0.981	0.330
RV diameter	0.228	1.892	0.063	-0.027	-0.229	0.819	0.150	1.356	0.180
TAPSE	0.092	0.754	0.454	0.025	0.205	0.838	0.091	0.820	0.415
RV Sm	-0.068	-0.549	0.585	-0.143	-1.177	0.243	-0.177	-1.566	0.122
Diastolic dysfunction	-0.341	-1.157	0.251	0.097	0.335	0.739	-0.174	-0.646	0.520

CAD - coronary artery diseases; C/S - cigarette smoker; DLP - dyslipidemia; DM - diabetes mellitus; HTN - hypertension; LVEF - left ventricular ejection fraction; PA - the interval with tissue Doppler imaging from the onset of P wave on the surface electrocardiogram to the beginning of the late-diastolic wave (Am wave); RV - right ventricle; RV Sm - right ventricular systolic motion; TAPSE - tricuspid annular plane systolic excursion; \*E/e'(average) ratio - E/(mean e' septum and lateral wall)

were significantly different in patients compared with healthy controls, but when correlating septal PA, lateral PA, and RV PA with diastolic dysfunction, adjusted to other factors, this correlation was not statistically significant. It seems that mild diastolic dysfunction in the presence of normal atrial size, in the absence of high filling pressure after adjusting for some factors, may not prolong ACTs, and ACT prolongation may be due to other effective factors. So, it seems that atrial electrical remodeling may not occur because of mild diastolic dysfunction itself. According to the multivariate analysis, it seems that the aging process and male sex may be independent determinant processes in ACT prolongation. Recently, it has been shown that androgenic hormones can have a role in the prolongation of ACTs (18). This hypothesis needs to be evaluated in further studies.

Left and right intra-atrial EMD and inter-atrial EMD were examined in multiple diseases, such as scleroderma and hypothyroidism (10, 19-21). These studies suggest that the inhomogeneity in ACTs might be related with an increased risk for AF. Also, it has been proposed that ACTs can show the process of atrial remodeling (13).

It has been suggested that LV diastolic dysfunction provides a profibrillatory environment that initiates AF (2-5). Age-adjusted cumulative risks of non-valvular AF increase with diastolic dysfunction severity (6). Increased LA size can predict the occurrence of AF in diastolic dysfunction.

Inter-atrial and left and right intra-atrial EMD was not found to be significantly different in patients compared with normal subjects, and when correlating inter-atrial and left and right intra-atrial EMD with diastolic dysfunction, adjusted to other

factors, this correlation remained statistically insignificant. Age was the only determinant of right intra-atrial EMD and inter-atrial EMD. So, it seems that atrial electrical inhomogeneity may not occur because of mild diastolic dysfunction itself. Also, it seems that aging may be one of the determinant processes in inter-atrial and right intra-atrial EMD. This hypothesis needs to be evaluated in further studies.

This was the first study evaluating inter- and intra-atrial EMD in patients with mild LV diastolic dysfunction and normal LA volume, in the absence of high filling pressure [E/e'(average of septal and lateral wall) < 13].

Chao et al. (14) assessed ACT in the lateral wall of the LA in patients with diastolic dysfunction; 46% of the patient sample had mild diastolic dysfunction. In the multivariate analysis, ACT in the lateral wall of the LA was independently related to age, LA diameter, E, DT, E/A ratio, and E/e'. In our study, we found that age, LV mass index, E, and A were independent predictors of lateral PA. Because the patient group in our study had mild diastolic dysfunction with a normal LA size in the absence of high filling pressure, diastolic dysfunction indices had homogeneity in our patient groups; so, LA diameter, DT, E/A, and E/e' were not determinants in our study. Also, their study showed that in patients with diastolic dysfunction, ACT is related to LA size, even in patients with normal LA size. But, in our study, lateral PA was not related to atrial size. A possible explanation was that in their study, only linear LA dimension was measured, without indexing according to body surface area. In our study, we measured LA volume with indexing according to body surface area.

Yavuz et al. (21) evaluated inter- and left and right intra-atrial EMD in hypertensive patients with and without diastolic dys-

function and a healthy control group. They found that inter-atrial EMD significantly increased in hypertensive patients with diastolic dysfunction compared with those without diastolic dysfunction and controls. Also, they found that left and right intra-atrial EMD did not significantly increase in hypertensive patients with diastolic dysfunction compared with those without diastolic dysfunction, but left intra-atrial EMD increased in hypertensive patients compared with healthy controls. Also, they found a significant positive correlation between LV mass index and left intra-atrial EMD and inter-atrial EMD; although these findings were not repeated in our study in the bivariate correlation analysis, LV mass index was an independent determinant of lateral PA. In that study, grade of diastolic dysfunction was not expressed in hypertensive patients with diastolic dysfunction, but LA was significantly enlarged in the study sample, and there was no specification about filling pressure. ACTs were not reported, either.

Although the proportion of hypertensive and diabetic patients in the patient group was significantly higher than in the control group and although these factors can be causes of ACT prolongation and inter- and intra-atrial EMD (18, 22-24), in our study, inter-atrial and left and right intra-atrial EMD were not found to be significantly different in patients compared with the control group. The patient sample of those studies was young or relatively young, and most of them did not have diastolic dysfunction, and there was no specification about LA size.

In atrial volume overload with low filling pressure, the atria can be enlarged, and AF may not occur, such as during athletics (25-26). However, with increasing LA pressure, atrial stretch, myolysis, and fibrosis occur (27). This type of enlarged left atrium is pathological and may be associated with the development of AF (28). An enlarged LA reflects the effects of LV filling pressure over time; so, it represents the arrhythmogenic substrate for the development of AF (29). Due to increased LV filling pressure, LV diastolic dysfunction is associated with an increasing stretch in the pulmonary veins (30). The stretching of pulmonary veins increases the arrhythmogenic activity of the pulmonary veins due to impaired diastolic distensibility and may have a role in the pathophysiology of AF (31). Also, increasing atrial fibrosis corresponds to an increase in conduction heterogeneity and AF vulnerability (32). It has been shown that patients with paroxysmal AF and diastolic dysfunction exhibit a significant decrease in LA voltage, a sign of atrial remodeling (2). So, according to our results, it seems that in the absence of high filling pressure and LA enlargement, and after adjustment of accompanying factors, diastolic dysfunction itself may not prolong ATCs and atrial EMDs.

### Study limitations

The major limitation of this study was the conduction in a single center with a small number of participants. ACTs were determined with tissue Doppler echocardiography, and the gold standard technique, electrophysiological study, was not per-

formed. Follow-up of patients for the occurrence of AF was not done. For these reasons, long-term follow-up and large-scale, multicenter prospective studies are needed.

### Conclusion

This study demonstrated no prolongation in inter- and intra-atrial electromechanical delays in patients with mild diastolic dysfunction and normal LA volume in the absence of high filling pressure [ $E/e'$  (average of septal and lateral wall) <13]. These findings may be associated with decreasing risk of electrical remodeling and AF in these patients compared with those with more than mild diastolic dysfunction and enlarged LA size with high filling pressure. Further larger prospective studies are needed to evaluate risk factors of AF in this group.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

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