

# Delayed right atrial lateral electromechanical coupling relative to the septal one can be associated with paroxysmal atrial fibrillation

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**Abstract. – BACKGROUND:** Non-invasive prediction of paroxysmal atrial fibrillation (PAF) is one of the most recent interests of cardiology.

**AIM:** The current study investigates the relationship between the atrial electromechanical coupling time (EMCT) and PAF.

**PATIENTS AND METHODS:** A group of 35 patients with PAF was compared with a group of 37 subjects without PAF. Pulsed wave tissue Doppler evaluations of atrial walls were performed from apical four chambers view under ECG monitoring. The time intervals from the onset of P wave to the onset of late diastolic wave (A') at right atrial wall (P-RA), interatrial septum (P-IAS), and left atrial wall (P-LA, maximum EMCT) were measured. The right atrial EMCT (P-RA minus P-IAS), left atrial EMCT (P-LA minus P-IAS) and interatrial EMCT (P-LA minus P-RA) were computed. A' wave velocities were measured from each atrial wall.

**RESULTS:** RA ( $16.0 \pm 13.1$  vs.  $-8.7 \pm 18.6$  ms,  $p < 0.001$ ) and maximum ( $91.5 \pm 32.6$  vs.  $72.0 \pm 23.1$  ms,  $p = 0.001$ ) EMCT were longer, RA A' velocity was higher in the patient group. There were no differences between the groups in LA and interatrial EMCT, and septal and LA A' velocities. Regression analysis revealed that only RA [OR: 1.148 (1.041-1.267),  $p = 0.006$ ] and maximum [OR: 1.099 (1.009-1.197),  $p = 0.031$ ] EMCT were independent variables for PAF. In order to predict patients with PAF, we have chosen  $+7.5$  msn for the RA EMCT which yielded 69% sensitivity and 71.4% specificity to predict patients.

**CONCLUSIONS:** Delayed RA lateral EMCT relative to septal one and delayed maximum EMCT detected by tissue Doppler could be a valuable method for identifying patients with PAF.

## Key Words:

Paroxysmal atrial fibrillation, Atrial electromechanical coupling time, Tissue Doppler imaging.

## Introduction

One of the most common arrhythmia, atrial fibrillation, may cause morbidities such as thromboemboli, heart failure and side effects of treatment modalities<sup>1</sup>. Studies with holter monitoring have demonstrated that the majority of paroxysmal atrial fibrillation (PAF) episodes are initiated by premature atrial beats<sup>2</sup>. In most patients ectopic foci are commonly located around the pulmonary veins. The mechanism of AF is thought to involve a combination of multiple reentrant wavelets, mostly initiated by focal triggers at or near pulmonary veins and possibly maintained by high-frequency reentrant rotors in the posterior left atrium. Also, the conduction properties of the atrium are influenced by underlying structural disease which affects cardiac autonomic tone, the size of the atria, and the degree of atrial fibrosis<sup>3</sup>. Paroxysmal atrial fibrillation consists of self-terminating episodes, each usually lasting fewer than 7 days and often less than 24 hours<sup>4</sup>. Therefore, its diagnosis is usually missed and delayed due to intermittent nature of the disease. Ambulatory electrocardiography (ECG), a widely used tool for PAF diagnosis, but may not always helps us. Besides, it has some drawbacks such as necessity for at least overnight recording and relatively higher costs. Transthoracic echocardiography (TTE) is an important and widely used diagnostic and follow-up tool for a number of cardiovascular diseases. In addition, it may help us reveal the structural and functional state of heart and thus the patients who are under risk of AF development. Noninvasive prediction of AF is of importance in the practice and under investigation. Some parame-

ters like left atrium (LA) diameter, LA volume, mitral inflow velocities, late diastolic velocities of annuli and left atrial appendage Doppler velocities were investigated whether they carried a value as a predictor of AF<sup>5,6</sup>. In patients with PAF, it was electrophysiologically shown that the atrial electrical conduction got disturbed; else, increase of P wave duration and dispersion was shown by surface ECG<sup>7</sup>. This study investigated the association between the atrial electromechanical coupling time (EMCT) and PAF by pulsed wave tissue Doppler imaging (TDI).

## Patients and Methods

### Study Population

Consecutive records of 24-hours ambulatory ECG monitoring results were analyzed prospectively from September to December 2007. We included patients with paroxysmal atrial fibrillation that was detected in 24 hour ambulatory ECG which lasting for  $\geq 30$  s with sinus rhythm spontaneously resumed before the end of recording. From these analyses, 35 patients with PAF (Group 1) and 37 subjects with normal 24 hours ambulatory ECG monitoring (Group 2) were recruited for the study. History of any heart disease and risk factors associated with heart disease like hypertension, diabetes mellitus, and family history for coronary artery disease, smoking and thyroid dysfunction were recorded. Patients with known coronary artery disease, overt heart failure, and chronic pulmonary disease were not included in the study. Physical examination, ECG and chest X-ray screen analysis and TTE examinations were done by a specialist. Subjects with other than sinus rhythm such as pacemaker rhythm, persistent and permanent AF, using antiarrhythmic drugs, with more than mild mitral stenosis (Mitral valve area  $< 2.0$  cm<sup>2</sup>) or more than mild mitral regurgitation, with congenital heart disease like atrial septal defect were excluded. Further, patients with acute AF which converted the sinus rhythm either electrically or medically were also excluded from the study. The protocol was approved by the local Ethics Committee and written informed consents were obtained from all the subjects to take part in the study.

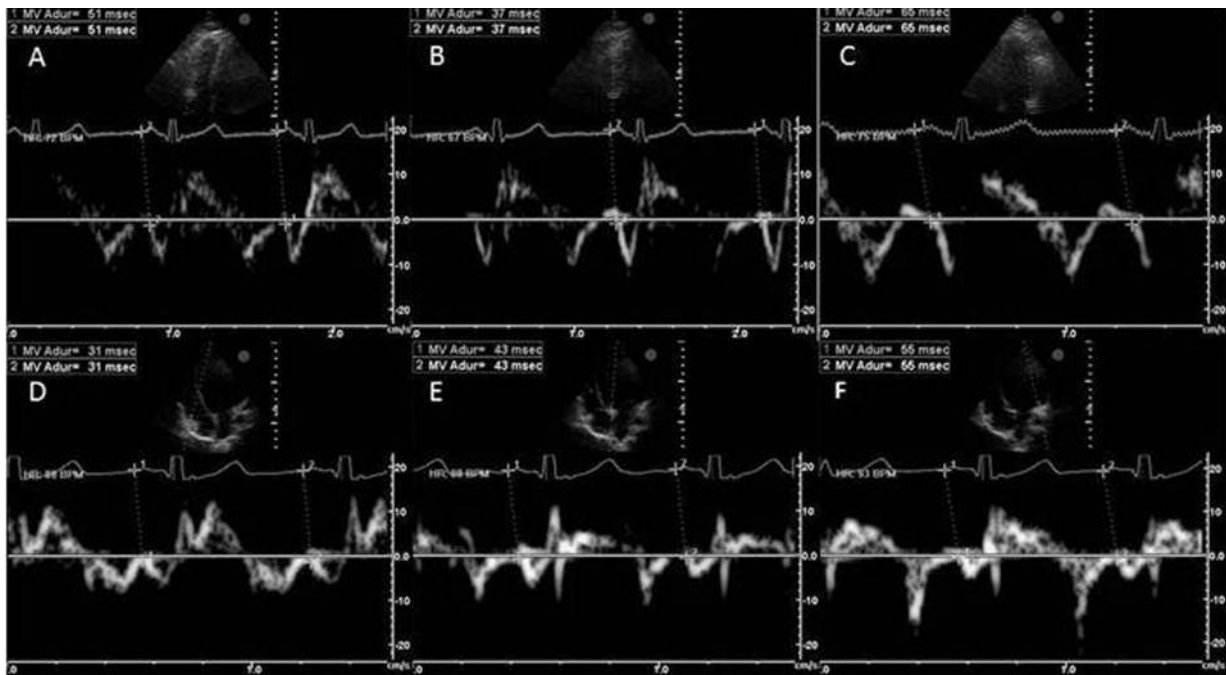
### Ambulatory ECG

All subjects underwent 12-leads 24-hours ambulatory ECG monitoring (Cardioscan Premier 12 Holter System, DMS, Stateline, NV, USA).

Recordings were analyzed with CardioScan-12 Holter ECG Systems (DMS software) on the same day by a cardiologist. Paroxysmal atrial fibrillation defined by the following ECG criteria: mean ventricular rate  $> 100$  beats per minute, QRS morphology during tachycardia that was either normal or functional bundle branch block, a grossly irregular ventricular rhythm, the absence of P waves or the presence of fibrillatory waves in the baseline when P waves had been recorded during periods of sinus rhythm, and episodic occurrence<sup>8</sup>.

### Echocardiographic Examination

Transthoracic echocardiography (TTE) was performed on the following day of the ambulatory monitoring. TTE examinations were performed at the left decubitus position using Vivid 3 system equipped with 2.5-3.5 MHz transducer (GE, Horten, Norway) by a cardiologist who was unaware of the ambulatory ECG results. ECG electrodes were positioned as a modified form of lead CB5; a negative electrode placed over the center of the right mid clavicular area and the positive electrode placed over the sixth intercostal space at the anterior axillary line to obtain larger and clearer P waves. LA anterior-posterior diameter, systolic-diastolic diameters, septal and posterior wall thickness of left ventricle (LV) were obtained by M-Mode images from parasternal long axis view. Left ventricular areas were obtained from apical four and two chamber views and ejection fraction was calculated by modified Simpson method. Also pulsed wave tissue Doppler imaging (TDI) was acquired from apical four chamber window under ECG monitoring. Depth, gain and sector size were optimized before obtaining images. And a special notice was given to the ultrasound beams to be perpendicular to the annuli. Doppler scales were optimized according to the velocities, and sweep speed was defaulted as 50-100 mm/second. Late diastolic wave velocities (A') from RA lateral wall, interatrial septum (IAS), and LA lateral wall just below the valvular annuli were acquired by TDI. The time intervals from the onset of P wave to the onset of A' wave of RA (P-RA), IAS (P-IAS), and LA (P-LA) were measured (Figure 1). Maximum electromechanical coupling time (EMCT) was defined as identical of P-LA. The RA EMCT was defined as 'P-RA minus P-IAS', and LA EMCT was defined as 'P-LA minus P-IAS' and interatrial EMCT was defined as 'P-LA minus P-RA'. Doppler measurements were ob-



**Figure 1.** The time intervals from the onset of the P wave to the onset of the A' wave at right atrium (A), interatrial septum (B), and left atrium (C) are from a patient with paroxysmal atrial fibrillation. And, same measurements are from a subject without paroxysmal atrial fibrillation (D, E, F). RA electromechanical coupling time (EMCT) is 51-37=14 ms for subject with PAF, and 31-43=-12 ms for subject without PAF. ("MV Adur" is represents time durations).

tained at end-expiratory apnea. Average values of three sequential beats were used for analysis.

### Statistical Analysis

Parametric variables presented as mean  $\pm$  standard deviation, non-parametric variables presented as frequency and percentages. Parametric variables were compared through *t*-test; nonparametric variables were compared through Wilcoxon signed rank test. Correlations were computed using Spearman's Rho correlation coefficient. The significance of the variables for the association with PAF was tested through logistic regression analysis. Receiver operating characteristic (ROC) curves of maximum EMCT and RA EMCT were drawn to determine a cutoff value to predict PAF. *p* value was set at  $< 0.05$  for significance.

### Results

Groups were comparable for age and gender. The frequencies of active smoking, diabetes mellitus and hyperthyroidism were similar between the two groups. Hypertension was more frequent in the Group 1, but systolic and diastolic blood pressures were similar. LA antero-posterior diam-

eter, LV ejection fraction, diastolic diameter and septal and posterior wall thickness, mitral regurgitation frequencies were similar between the groups (Table I). Maximum EMCT and RA EMCT of Group 1 were significantly longer than those of group 2 (Figure 2). But, LA EMCT and interatrial EMCT were not different between the groups. RA A' wave velocity of group 1 was higher than that of group 2, but IAS and LA A' velocities were similar (Table II). In correlation analysis PAF was significantly correlated with RA EMCT ( $r: 0.606, p < 0.001$ ), maximum EMCT ( $r: 0.347, p = 0.001$ ), HT ( $r: 0.419, p < 0.001$ ), interatrial EMCT ( $r: 0.211, p = 0.046$ ) and RA A' velocity ( $r: 0.258, p = 0.014$ ). Logistic regression analysis revealed that only RA EMCT [OR: 1.148 (1.041-1.267),  $p = 0.006$ ] and maximum EMCT [OR: 1.099 (1.009-1.197),  $p = 0.031$ ] were independent predictors of PAF (Table III). ROC curve of RA EMCT was drawn and, curve showed  $\geq +7.5$  milliseconds yielded 69% sensitivity and 71.4% specificity for the prediction of PAF (Area under the curve 0.852, Figure 3). Else, ROC curve of maximum EMCT was drawn and, curve showed  $\geq +80.5$  milliseconds yielded 62.5% sensitivity and 67.6% specificity for the prediction of PAF (Area under the curve 0.685).

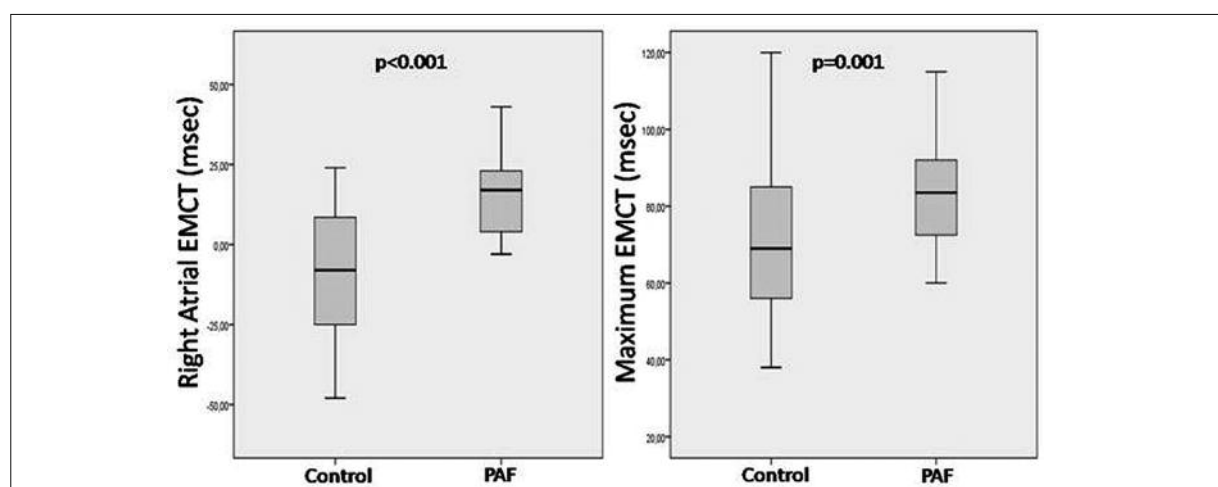
**Table I.** Demographic, clinical and echocardiographic findings of the groups.

	Group 1 (n: 35)	Group 2 (n: 37)	p value
Age (years)	55 ± 13	55 ± 15	NS
Male % (n)	49 (17)	38 (14)	NS
Active smoker % (n)	23 (8)	24 (9)	NS
Hypertension % (n)	74 (26)	41 (15)	< 0.001
Diabetes Mellitus % (n)	9 (3)	14 (5)	NS
Hyperthyroidism % (n)	6 (2)	3 (1)	NS
Systolic blood pressure (mmHg)	124 ± 11	121 ± 10	NS
Diastolic blood pressure (mmHg)	77 ± 12	75 ± 13	NS
Left atrial anteroposterior diameter (mm)	35 ± 5	34 ± 6	NS
Left ventricle ejection fraction (%)	63 ± 4	64 ± 5	NS
Left ventricle diastolic diameter (mm)	48 ± 4	46 ± 5	NS
Ventricular septal thickness (mm)	9 ± 1	9 ± 1	NS
Posterior wall thickness (mm)	8 ± 1	8 ± 2	NS
Mitral regurgitation (mild) % (n)	20 (7)	16 (6)	NS

### Discussion

This study documented that RA EMCT and maximum EMCT are longer in patients with PAF compared to those with no PAF. The likelihood of PAF increases with presence of prolonged period of maximum EMCT, and prolonged period of RA lateral coupling time (P-RA) compared to the septal coupling time (P-IAS). Transthoracic echocardiography (TTE) is widely used to investigate structural heart diseases which are predispose AF. It is also useful to investigate AF associated complications such as thrombus and its risk factors<sup>5,9</sup>. Atrial conducting times are prolonged and non-homogen in PAF<sup>10-14</sup>. Noninvasive determination of this condition either with ECG or/and TTE is one of the most recent inter-

ests of cardiology. It was shown that atrial EMCTs could be measured by TTE<sup>15-17</sup>. These studies showed that atrial EMCT which defined by TTE could be useful for noninvasive evaluation of atrial conduction disturbance. Tissue Doppler imaging (TDI) is a novel method which determined tissue velocities with exact time resolution. It gives us an opportunity to measure tissue velocities from various atrial regions. When P wave on surface ECG (represents atrial electrical activation) and A' wave on TDI (represents atrial mechanical activation) monitored at the same time, periods of atrial electromechanical coupling times (ECMTs) could be measured<sup>18</sup>. The current study investigated the relationship between the atrial EMCT and PAF by pulsed wave TDI. We found that the RA and maximum EM-



**Figure 2.** Comparisons of RA electromechanical coupling time (EMCT) (A) and maximum EMCT (B) between the paroxysmal atrial fibrillation and control groups.

**Table II.** Comparison of atrial electromechanical coupling time (EMCT) and A' wave velocities of groups.

	Group 1 PAF (n: 39)	Group 2 control (n: 54)	p value
Heart rate (beats/min)	68 ± 11	70 ± 13	NS
P-LA (Maximum EMCT) (ms)	91.5 ± 32.6	72.0 ± 23.1	= 0.001
P-RA (ms)	51.1 ± 15.6	40.8 ± 18.5	NS
P-IAS (ms)	34.9 ± 10.7	49.2 ± 20.4	NS
Interatrial EMCT (ms)	40.3 ± 12.3	32.0 ± 24.7	NS
Left atrial EMCT (ms)	24.9 ± 10.6	24.0 ± 20.1	NS
Right atrial EMCT (ms)	16.0 ± 13.1	-8.7 ± 18.6	< 0.001
Left atrial A' wave velocity (cm/s)	10.3 ± 2.8	10.2 ± 3.3	NS
Interatrial septum A' wave velocity (cm/s)	9.0 ± 2.1	9.6 ± 2.9	NS
Right atrial A' wave velocity (cm/s)	14.3 ± 3.8	12.5 ± 3.4	= 0.022

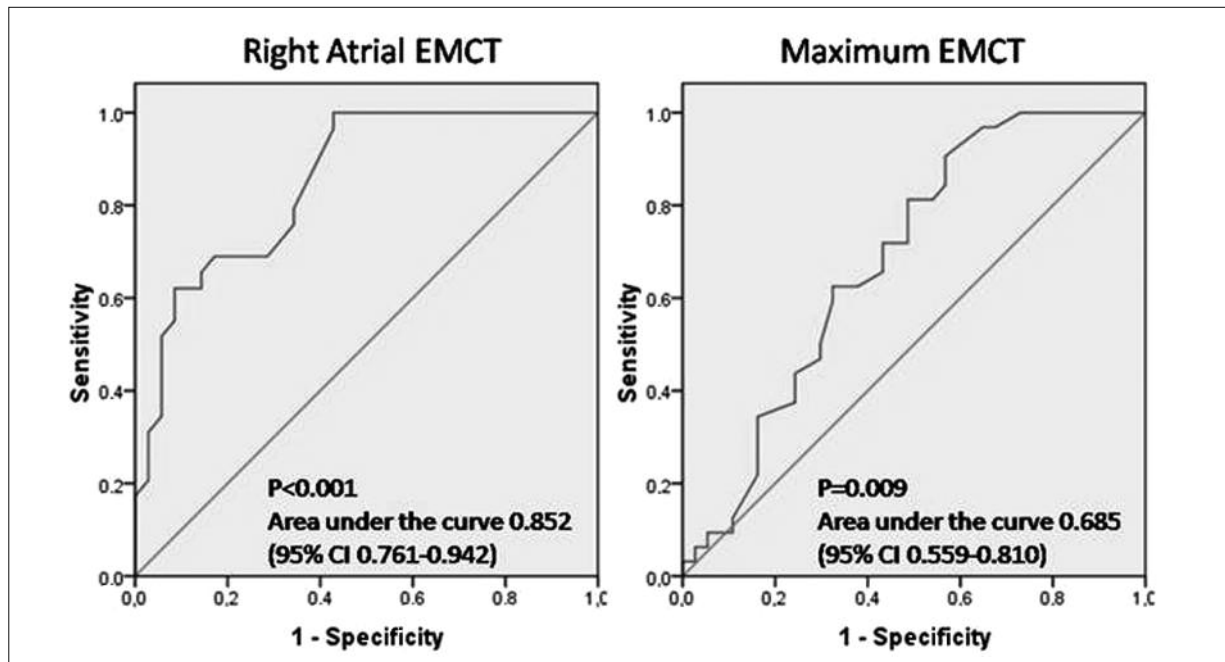
**Table III.** Independent correlates of paroxysmal atrial fibrillation by logistic regression analysis.

Independent variable	Odds ratio (95% CI)	p value
Hypertension (0 = no, 1 = yes)	7.547 (0.718-79.351)	0.092
A' velocity of RA lateral wall (cm/sec)	1.339 (0.941-1.160)	0.058
Maximum EMCT (msec)	1.099 (1.009-1.197)	0.031
RA EMCT (msec)	1.148 (1.041-1.267)	0.006

Footnote: RA = Right atrium, EMCT = Electro-mechanical coupling time.

CT significantly delayed in patients with PAF. Delayed maximum EMCT means increased P-LA. Delayed RA EMCT means P-RA much longer than P-IAS. We found the RA EMCT and maximum EMCT to be independent predictors of

PAF. Predictive value of RA EMCT has moderate sensitivity and specificity. Predictive value of maximum EMCT was less than RA EMCT. Our research agrees with the earlier reports that used similar methods for maximum EMCT<sup>19,20</sup>. How-



**Figure 3.** Receiver operating characteristic (ROC) curves for RA electromechanical coupling time (EMCT) (A) Maximum EMCT (B) of diagnostic accuracy of patients with and without paroxysmal atrial fibrillation.

ever, these studies had no information about RA EMCT. Previous electrophysiological studies documented that RA conduction is prolonged and fractionated in patients with PAF<sup>10-14</sup>. The findings of this investigation agree with the data of recent electrophysiological works and noninvasive expressions of RA conduction disturbance which documented invasively in those studies. Sinus node is located on the superior-posterior wall of RA. Impulses generated from there spread to the RA and LA via different pathways<sup>10</sup>. It is normally expected for LA lateral wall to have delayed coupling because of the longer distance, so the increase of this delay with disturbance of conduction like in patients with PAF. Else, we observed significant difference between the PAF patients and the control group with regard to RA EMCT. Two possible theories may exist based on this finding; different localization of the conduction pathways or different degrees of conduction disturbances at different localizations of the RA<sup>10,21</sup>. Our results showed indications of support for the first<sup>10</sup> and the second options<sup>21</sup>. However, definite differentiation was not possible for the current sample because we did not perform a simultaneous electrophysiological study. Omi et al<sup>19</sup> showed the prolonged EMCT in PAF patients by color M-mode. They observed that P-RA and P-LA were significantly longer in PAF patients and also found it to be related with LA long axis diameter. We used pulsed TDI instead of color M-mode Doppler because it is widely accessible and more accurate technique with high temporal resolution. Chui et al<sup>20</sup> also used pulsed wave TDI in their investigation and observed maximum EMCT, P-IAS and P-RA different after correction by age but no difference in interatrial, left and right atrial EMCT. However, of these PAF patients, 39% was on beta blocker, 19% were on digitalis, 57% were on class I or III antiarrhythmic and 10% were on calcium channel blocker therapy. So, conduction delay might be affected by these drugs. Further, they analyzed the EMCT mean 39 months after the PAF diagnosis. We analyzed the EMCT just after day of the PAF revealed ambulatory ECG monitoring. Our study group's mean PAF duration was much shorter than Chui et al.'s case load<sup>20</sup> which was 30 hours. This may confound the data distribution and their's evaluation. Also these authors declared that the LA and RA diameters were longer in study group and found the conduction delay to be correlated with the diameters. So, they mentioned the delay might be

caused by the anatomic enlargement. Omi et al<sup>19</sup> found EMCT to be affected by LA dimensions, but we didn't observe any significant relation with LA anteroposterior diameter. However, we did not measure LA and RA volumes at least multiple diameters. So, we could not rule out effects of atrial enlargements on EMCT in recent study. Many previous studies used lead DII for ECG monitoring but we preferred to use modified form of lead MB5 which was observed to show better P wave amplitudes<sup>22</sup>. We increased the sensitivity of our measurement by providing the maximum P wave amplitude by modification of lead MB5. This modified lead may be useful in later studies with coupling time measurements. LA and LAA functions were found to be disturbed in AF by many studies<sup>5</sup> but we did not observe any significant difference of LA lateral wall and IAS A' velocity between the groups. We found the RA lateral wall A' velocity significantly higher in PAF group in univariate analysis but logistic regression model showed it was a dependent variable. The main limitation of our study was the method of PAF diagnosis. We had chosen the subjects with or without PAF by ambulatory ECG monitoring. Abovementioned ambulatory ECG might be skipped the PAF due intermittent nature of disease. So, there might be conflicts in some of the patients' diagnoses. Furthermore, we did not measure atrial volumes. So, we could not rule out the effects of atrial enlargements of prolonged EMCT. Also, coronary artery disease was not investigated invasively. Therefore, patients with asymptomatic coronary artery disease might be included in our study. We did not measure the atrial electrical conduction times invasively because of ethical considerations. Moreover, P wave dispersion and signal averaged ECG were not measured. Previous studies showed significant correlation among total EMCT and signal averaged ECG P wave duration.

## Conclusions

Atrial electromechanical delays could be showed noninvasively by tissue Doppler echocardiography. The right atrial and maximum electromechanical coupling times were delayed in patients with PAF. Electromechanical coupling time might be recognized patient with PAF with moderate specificity and sensitivity. However, these results needed to be confirmed by other large scale studies.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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