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General Cardiology

Evaluation of Atrial Electromechanical Delay and Left Atrial Phasic Function in Individuals with Electrocardiographic Early Repolarization Pattern

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Background: Atrial electromechanical delay (EMD) and left atrial (LA) phasic function have been demonstrated to be predictors for the development of atrial fibrillation (AF). In the present study, we aimed to evaluate atrial EMD and LA phasic function in individuals with electrocardiographic early repolarization pattern (ERP).

Methods: Eighty consecutive individuals with ERP and 40 age- and gender-matched control subjects without ERP were compared in this cross-sectional study. Atrial electromechanical coupling (Pa') was measured from lateral mitral annulus ($Pa'_{lateral}$), septal mitral annulus (Pa'_{septal}), and lateral tricuspid annulus ($Pa'_{tricuspid}$) using tissue Doppler echocardiography to calculate intra- and inter-atrial EMD. LA maximal volume, LA minimal volume, and LA volume before atrial contraction were calculated using the biplane area-length method to assess LA phasic function.

Results: LA diameter, LA volume index, $Pa'_{lateral}$, Pa'_{septal}, $Pa'_{tricuspid}$ electrical activity and intra-left atrial EMD were significantly increased in the ERP patients. Mitral lateral, septal, tricuspid lateral annular tissue Doppler s' and e' waves were significantly decreased in the ERP patients. There were no significant difference between the groups in terms of interatrial EMD, intra-right atrial EMD, LA total emptying volume and LA total emptying fraction indicating LA reservoir function, LA passive emptying volume and LA passive emptying fraction indicating LA conduit function, LA active emptying volume and LA active emptying fraction indicating LA pump function.

Conclusion: Left atrial EMD parameters are affected in individuals with ERP, but LA phasic functions are not affected. Further prospective studies are needed to clarify whether individuals with ERP have an increased susceptibility to AF.

Key Words: Atrial electromechanical delay • Early repolarization pattern • Left atrial phasic function

INTRODUCTION

Early repolarization pattern (ERP) is considered to be a benign electrocardiographic (ECG) variation. However, several studies have demonstrated a higher prevalence of ERP in patients with idiopathic ventricular fibrillation (VF).[1,2] Subsequent epidemiological follow-up studies have also reported an increased risk of arrhythmic death in individuals with ERP.[3,4] The fact that this ECG pattern is seen in up to 10% of the general population[5] makes the issue more important. At present, it is very challenging to determine the subjects at high risk of potentially fatal ventricular arrhythmia, who constitute a very small proportion of those with ERP.

It is thought that ERP may also be associated with atrial fibrillation (AF). Some genetic and electrophysiological mechanisms have been commonly associated with the pathophysiology of ERP and AF.[6] Individuals with ERP may have an increased susceptibility to AF.[7] Atrial electromechanical delay (EMD) can be evaluated

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noninvasively by tissue Doppler echocardiography, and an increase in atrial EMD time has been demonstrated to be an independent risk factor for an improvement in AF.[8] Left atrial (LA) phasic function, which can be calculated during routine echocardiographic assessment, has also been shown to be a predictor for the risk of AF development.[9] The aim of this study was to assess atrial EMD and LA phasic function in individuals with ERP.

METHODS

Study population

This cross-sectional study included 80 consecutive individuals with ERP, and 40 age- and gender-matched control individuals without ERP. Twelve-lead ECGs of the study population were recorded after a resting period of 5 minutes, using a common ECG device (Cardiovit AT-102, Schiller, Switzerland) with 10 mm/mV amplitude and 25 mm/s rate. QRS-ST junction (J-point) elevation of ≥ 1 mm (0.1 mV) in at least two contiguous leads with either a QRS slurring or notching in standard 12-lead ECG was defined as ERP.[10] ERP was also classified as an elevation in J-point ≥ 1 mm (0.1 mV) slurring and notching type in II, III and aVF leads (inferior type), in I, aVL and V4 to V6 leads (lateral type) or both (inferolateral type) (Figure 1).[10]

Both groups included individuals aged less than 60 years of age without any known cardiovascular or systemic diseases. The patients' age, body weight, height, cardiovascular risk factors, history of family sudden cardiac death, current medications, basic laboratory parameters and other systemic diseases were recorded. Body mass index (BMI) and body surface area (BSA) were estimated using the appropriate formulae. The exclusion criteria were as follows: age < 18 or ≥ 60 years, athletes, arterial hypertension, diabetes mellitus, obesity (BMI ≥ 30 kg/m^2), coronary artery disease, heart failure, moderate to severe valvular heart disease, prosthetic heart valve, pericardial disease, anemia, thyroid dysfunction, pulmonary disease, chronic kidney disease, liver failure, malignancy, systemic diseases, regular medication use, pregnancy, presence of AF or history of paroxysmal AF attack, J-point elevation in leads V1 to V3 (Brugada ECG pattern), QRS time ≥ 120 ms, paced rhythm, atrioventricular conduction irregularities, left ventricular (LV) wall motion abnormalities, LV ejection fraction < 50%, and poor echocardiographic image quality.

The study was approved by the Ethics Committee of the Faculty of Medicine, Ondokuz Mayis University (No: 2021/4) and adhered to the Declaration of Helsinki (2013 version). All individuals were informed about study and provided written permission.

Standard echocardiographic evaluation

All echocardiographic examinations were performed by the same physician in a blinded fashion using a Vivid E9 echocardiography device (GE Vingmed Ultrasound,

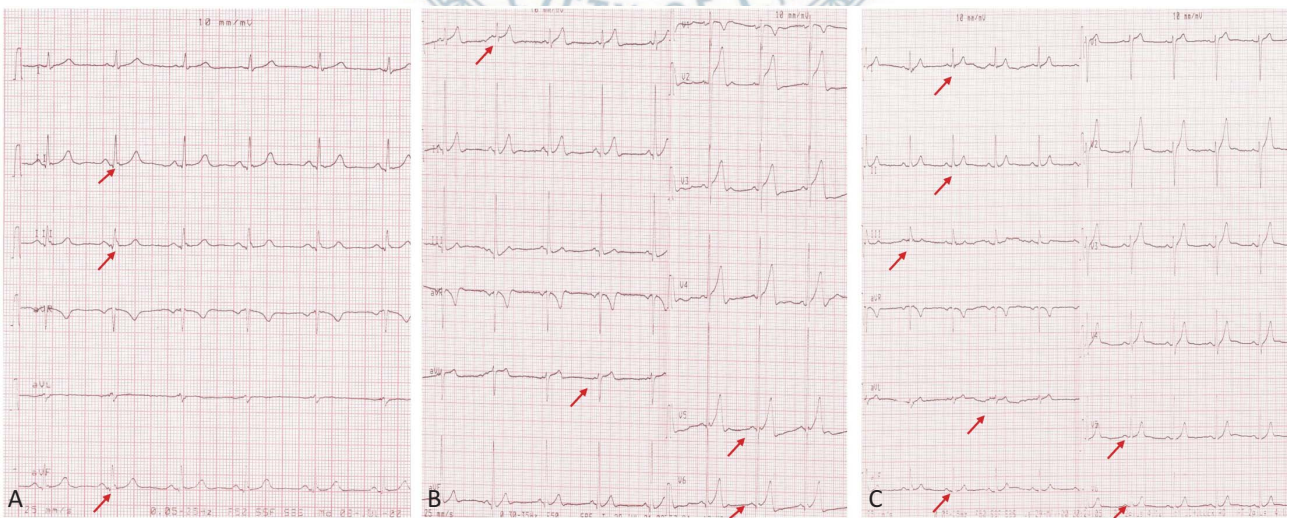

Figure 1. *Imaging of electrocardiographic ST-segment elevation of J-point ≥ 1 mm (0.1 mV) slurring and notching type in II, III and aVF leads (inferior type) (A), in I, aVL and V4 to V6 leads (lateral type) (B) or both (inferolateral type) (C).*

Horten, Norway) and M5S ultrasound probe (1.5-4.5 MHz). A single-lead ECG was connected simultaneously with the ultrasound image during echocardiography. Measurements of cardiac chamber dimensions were made according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[11] LV diastolic and systolic diameter, septal and posterior wall thickness, LA anteroposterior diameter, and proximal right ventricle (RV) outflow diameter were measured directly from two-dimensional echocardiographic images obtained in the parasternal long-axis view. LV mass was calculated using Devereux's formula and indexed to BSA. LV ejection fraction was measured using the modified Simpson technique. Mitral inflow velocities were acquired using pulsed-wave (PW) Doppler among mitral leaflet tips in the apical 4-chamber view. Mitral annular velocities were calculated using PW tissue Doppler imaging (TDI) at the septal and lateral borders of the mitral annulus in the apical 4-chamber view and averaging these parameters.

Evaluation of atrial electromechanical delay

TDI was performed by setting the Nyquist limit to 15-20 cm/s and the monitor scanning rate to 50-100 mm/s in order to optimize the spectral view of myocardial velocities. Atrial electromechanical coupling (PA'), defined as the time interval from the onset of P wave on ECG to the beginning of tissue Doppler late diastolic wave, was measured from the lateral mitral annulus ($Pa'_{lateral}$), septal mitral annulus (Pa'_{septal}), and lateral tricuspid annulus ($Pa'_{tricuspid}$) (Figure 2). Pa' values were recorded as the average of three serial beats. The duration between $Pa'_{lateral}$ and Pa'_{septal} was described as intra-left atrial EMD, the difference between Pa'_{septal} and $Pa'_{tricuspid}$ was described as intra-right atrial EMD, and the difference between $Pa'_{lateral}$ and $Pa'_{tricuspid}$ was described as inter-atrial EMD.

Evaluation of left atrial phasic function

LA maximal volume (LAV_{max}), LA minimal volume (LAV_{min}), and LA volume before atrial contraction ($LAV_{pre\text{-}A}$) were calculated using the biplane area-length technique in the apical 4-chamber view and indexed to BSA. LAV_{max} was determined just before the opening of the mitral valve, LAV_{min} was determined just at the closure of the mitral valve, and $LAV_{pre\text{-}A}$ was determined at the onset of P wave on ECG (Figure 3).[8] The following formulae were used to evaluate LA phasic feature by the volumetric technique:

- LA reservoir functions
  LA total emptying volume = $LAV_{max} - LAV_{min}$
  LA total emptying fraction = $(LAV_{max} - LAV_{min}) / LAV_{max}$

- LA conduit functions
  LA passive emptying volume = $LAV_{max} - LAV_{pre\text{-}A}$
  LA passive emptying fraction = $(LAV_{max} - LAV_{pre\text{-}A}) / LAV_{max}$

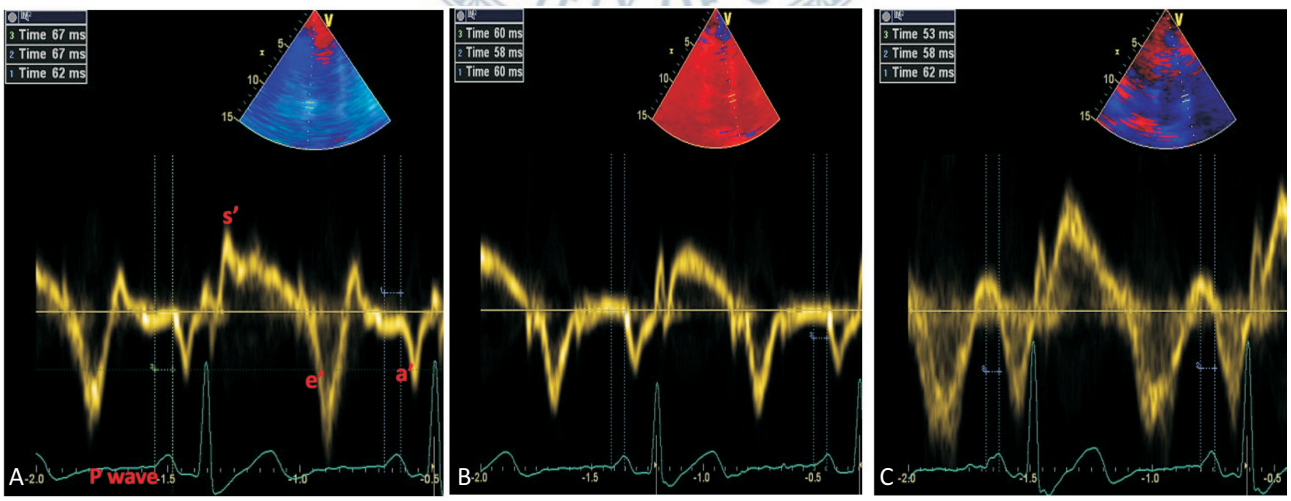

Figure 2. *Atrial electromechanical coupling (Pa'), the period from the beginning of the P-wave on the surface electrocardiographic (ECG) to the starting of the late diastolic wave a' on tissue Doppler echocardiography [Mitral lateral annulus (A), Septal annulus (B) and Tricuspid lateral annulus (C)].*

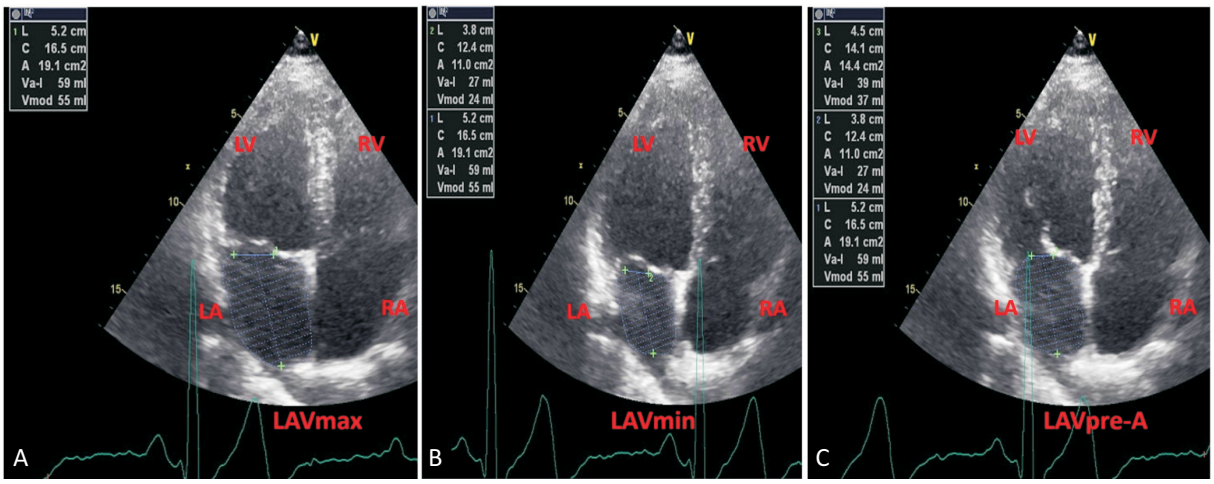

Figure 3. *Maximum (A), the minimum (B) and atrial precontraction (C) volume measurements of left atrium were made by transthoracic echocardiography on apical four-chamber window. LA, left atrium; LA_{pre-A}, LA volume before atrial contraction; LAV_{max}, LA maximal volume; LAV_{min}, LA minimal volume; LV, left ventricle; RA, right atrium; RV, right ventricle.*

- LA pump functions

  LA active emptying volume = $LAV_{pre-A} - LAV_{min}$

  LA active emptying fraction = $(LAV_{pre-A} - LAV_{min}) / LAV_{pre-A}$

Reproducibility

Intraobserver and interobserver variability in the Pa′ values and LA volumes were evaluated by repeating the measurements of 22 randomly selected individuals, with 14 subjects from the ERP group and 8 subjects from the control group. These parameters were re-evaluated by the same physician at least 1 month later to assess intraobserver variability and by another physician blinded to the data of the subjects to assess interobserver variability.

Statistical analysis

The research data were uploaded and analyzed using IBM SPSS version 22. Categorical parameters were represented as numbers and percentages. Pearson's chi-squared and Fisher's exact tests were used to compare categorical parameters. The Kolmogorov-Smirnov test was used to determine the suitability of continuous parameters with normal distribution. Continuous parameters with normal distribution were represented as mean ± standard deviation (SD). The Student's *t*-test was used for normally distributed parameters to identify important variations between the groups. Continuous variables without normal distribution were represented as median (minimum-maximum). The Mann-Whitney *U* test was used to compare parameters without normal distribution. Intraobserver and interobserver variability were evaluated by coefficient of variation among the measurements, which was measured as the SD of the variations among the repeated parameters divided by the averages of the repeated values. A p value less than 0.05 was accepted as the statistical significance level.

RESULTS

Baseline clinical characteristics

The groups were similar in terms of age, gender, BMI, heart rate, systolic and diastolic blood pressure (Table 1). In the ERP group, J-point elevation was present in inferior leads in 35 individuals (44%), lateral leads in 15 subjects (19%), and inferolateral leads in 30 subjects (37%).

Standard echocardiographic parameters

LV diastolic and systolic diameter, septal and posterior wall thickness, LV mass index, LV ejection fraction, and proximal RV outflow diameter were not significantly different between the two groups. However, LA anteroposterior diameter and left atrial volume index were significantly increased in the ERP group (Table 1).

Mitral E, mitral A, mitral E/A, mitral a′, and mitral E/e′ did not significantly differ between the groups ei-

Table 1. Distribution of baseline clinic, laboratory and echocardiographic parameters between the early repolarization pattern and control groups

	ERP group (n = 80) Mean ± SD Median (min-max.)*	Control group (n = 40) Mean ± SD Median (min-max.)*	p value
Age (year)	30.7 (18-54)*	30.9 (23-52)*	0.27
Gender			0.12
Men, n (%)	64 (80%)	26 (65%)	
Women, n (%)	16 (20%)	14 (35%)	
BMI (kg/m^2)	25.3 ± 4.5	24.9 ± 3.1	0.70
BSA (m^2)	1.91 ± 0.19	1.90 ± 0.19	0.86
Systolic BP (mmHg)	120 (100-135)*	120 (100-130)*	0.71
Diastolic BP (mmHg)	70 (50-85)*	70 (60-85)*	0.34
Heart rate (bpm/min)	69.2 ± 9.1	72.1 ± 6.8	0.06
Cigarette smoking, n (%)	19 (23.8%)	11 (27.5%)	0.66
History of family sudden cardiac death	15 (18.8%)	4 (10%)	0.29
ERP region			
Inferior leads	35 (44%)		
Lateral leads	15 (19%)		
Inferior-lateral leads	30 (37%)		
Glucose (mg/dl)	92 ± 11.2	90.9 ± 8.1	0.54
Creatinine (mg/dl)	0.91 ± 0.92	0.80 ± 0.16	0.42
Hemoglobin (g/dl)	14.6 ± 1.2	14.3 ± 1.4	0.36
White blood cell (10^3/ml)	7.0 (4.5-15.7)*	7.4 (4.5-16)*	0.12
Platelet (10^3/ml)	245 ± 54.2	241.4 ± 59.1	0.78
AST (Ul/L)	19.5 (11-45)*	19 (8-45)*	0.12
ALT (Ul/L)	20 (8-70.2)*	17.5 (8-70)*	0.07
Left ventricular ejection fraction (LVEF) (%)	60 (57-65)*	60 (58-65)*	0.26
LVEDD (mm)	44.7 ± 5.0	46.5 ± 4.1	0.06
LVESD (mm)	28.8 ± 4.3	28.6 ± 3.2	0.82
LVMI (g/m^2)	94.5 ± 23.6	96.2 ± 21.2	0.77
IVS (mm)	10 (6-14)*	10 (7-13)*	0.06
PW (mm)	10 (6-14)*	9.5 (8-12)*	0.62
LA diameter (mm)	35.2 ± 4.4	33.9 ± 3.6	0.04
LAVI (ml/m^2)	18.8 ± 2.1	17.8 ± 1.5	0.05
RV (mm)	23 (16-30)*	24 (13-30)*	0.20

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BP, blood pressure; BSA, body surface area; ERP, early repolarization pattern; IVS, interventricular septum; LA, left atrium-parasternal long axis; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVMI, left ventricular mass index; PW, posterior wall; RV, right ventricle; SD, standard deviation.
The (*) sign shows median, minimum, and maximum values.

ther, however mitral lateral, septal, mean annular s', e' waves and tricuspid annular s', e' waves were significantly lower in the ERP group ($p < 0.05$) (Table 2).

Atrial electromechanical delay

$Pa'_{lateral}$, Pa'_{septal}, $Pa'_{tricuspid}$ electrical activity and intra-left atrial EMD were significantly increased in the ERP group, however there were no significant differences between the two groups in terms of intra-right atrial EMD and inter-atrial EMD (Table 3).

Left atrial phasic function

LAV_{max}, LAV_{min}, $LAV_{pre\text{-}A}$, LA total emptying volume and LA total emptying fraction indicating LA reservoir function, LA passive emptying volume and LA passive emptying fraction indicating LA conduit function, LA active emptying volume and LA active emptying fraction indicating LA pump function were comparable between the groups (Table 4).

Table 2. Distribution of mitral and tricuspid leaflets tissue Doppler parameters between the early repolarization pattern and control groups

	ERP group (n = 80) Mean ± SD Median (min-max.)*	Control group (n = 40) Mean ± SD Median (min-max.)*	p value
Mitral E (m/s)	0.85 ± 0.19	0.90 ± 0.13	0.09
Mitral A (m/s)	0.59 ± 0.12	0.58 ± 0.10	0.74
Lateral s′ (m/s)	0.10 ± 0.02	0.11 ± 0.02	< 0.001
Lateral e′ (m/s)	0.17 ± 0.04	0.18 ± 0.03	0.04
Lateral a′ (m/s)	0.11 ± 0.02	0.11 ± 0.02	0.61
Septal s′ (m/s)	0.09 ± 0.02	0.10 ± 0.02	< 0.001
Septal e′ (m/s)	0.13 ± 0.03	0.15 ± 0.03	< 0.001
Septal a′ (m/s)	0.10 ± 0.02	0.11 ± 0.02	0.40
Tricuspid s′ (m/s)	0.14 ± 0.02	0.15 ± 0.02	0.002
Tricuspid e′ (m/s)	0.15 ± 0.03	0.17 ± 0.04	0.007
Tricuspid a′ (m/s)	0.15 ± 0.04	0.15 ± 0.03	0.98
Mitral E/A	1.5 ± 0.42	1.59 ± 0.35	0.27
Mitral E/e′	5.9 ± 1.28	5.4 ± 0.88	0.05
Mitral mean s′ (m/s)	0.09 (0.07-0.15)*	0.10 (0.08-0.15)*	< 0.001
Mitral mean e′ (m/s)	0.15 ± 0.03	0.16 ± 0.02	0.001
Mitral mean a′ (m/s)	0.10 ± 0.02	0.10 ± 0.01	0.59

The (*) sign shows median, minimum, and maximum values. ERP, early repolarization pattern; SD, standard deviation.

Table 3. Atrial electrical activity parameters between the early repolarization pattern and control groups

	ERP group (n = 80) Mean ± SD Median (min-max.)*	Control group (n = 40) Mean ± SD Median (min-max.)*	p value
Pa′ lateral (ms)	72.1 ± 12.8	68.4 ± 13.3	0.04
Pa′ septal (ms)	65.8 ± 14.7	63.5 ± 17.1	0.05
Pa′ tricuspid (ms)	61.4 ± 10.0	57.6 ± 10.0	0.05
Interatrial-EMD (ms)	9 (0-42)*	9 (0-30)*	0.91
Intra-LA-EMD (ms)	7 (0-37)*	5 (0-27)*	0.04
Intra-RA-EMD (ms)	2 (0-45)*	4 (0-59)*	0.18

ECG, electrocardiographic; EMD, electromechanical delay; ERP, early repolarization pattern; LA, left atrium; Pa′, time interval from the onset of the P-wave on the surface ECG to the peak of the late diastolic wave (a′); RA, right atrium; SD, standard deviation.
The (*) sign shows median, minimum, and maximum values.

Table 4. Left atrial mechanical functions between the early repolarization pattern and control groups

	ERP group (n = 80) Mean ± SD Median (min-max.)*	Control group (n = 40) Mean ± SD Median (min-max.)*	p value
LAVmax (ml/m^2)	25.4 ± 6.6	25.2 ± 5.9	0.91
LAVmin (ml/m^2)	9.5 ± 3.8	9.0 ± 3.0	0.39
LAVpre-A (ml/m^2)	15.4 ± 4.8	14.9 ± 4.1	0.51
LA reservoir (ejection) function %	63.2 ± 9.6	64.9 ± 7.2	0.30
LA conduit (passive emptying fraction) function %	39.1 ± 11.7	41.2 ± 9.2	0.30
LA pumping (active emptying fraction) function %	39.0 ± 12.7	40.1 ± 10.0	0.63
LA total emptying volume (ml/m^2)	15.9 ± 4.5	16.3 ± 3.8	0.70
LA passive emptying volume (ml/m^2)	10.0 ± 4.1	10.4 ± 3.4	0.54
LA active emptying volume (ml/m^2)	5.8 (1.5-13.2)*	5.8 (2.2-14.3)*	0.91

ERP, early repolarization pattern; LA, left atrium; LAVmax, left atrium maximum volume; LAVmin, left atrium minimum volume; LAVpreA, left atrium volume before atrial systole; SD, standard deviation.
The (*) sign shows median, minimum, and maximum values.

Reproducibility

Intraobserver and interobserver variability were lower than 5% and non-significant ($p > 0.05$) for all Pa′ values and LA volumes.

DISCUSSION

In the present study, we evaluated the association between EMD and left atrial phasic function in ERP patients and compared them with healthy controls. We demonstrated that left atrial diameter, volume index and left atrial EMD parameters were significantly increased in the individuals with ERP, but that there were no significant difference in left atrial mechanical functions compared to the individuals without ERP.

ERP is a common ECG finding with a prevalence of about 10% in the general population.[5] This ECG pattern was initially considered to be completely benign, but was later demonstrated to be associated with an increased risk of VF and arrhythmic death.[1-4] In addition, some reports have suggested that ERP may also be associated with AF. The prevalence of AF in individuals with ERP has been reported to be higher than that in the general population.[12,13] In another study, ERP was more common in patients with paroxysmal lone AF compared to age- and gender-matched healthy controls.[7] On the other hand, no relationship was found between ERP and AF in population studies.[13,14] Similarly, no relationship was found between ERP and lone AF in young and middle-aged patients in another study.[15] As a result, there are conflicting data in the literature regarding the susceptibility to AF in individuals with ERP.

Certain echocardiographic parameters have been demonstrated to be useful for identifying individuals with increased susceptibility to AF. The most commonly used echocardiographic parameters for this purpose are LA diameter[16] and LA volume.[17] A decrease in mitral a′, which is a feature of LA contractile function, is another predictor for the risk of AF development.[18] Volumetric parameters of LA phasic function may also be utilized to determine those with an increased risk of developing AF. LA total emptying fraction has been shown to be an independent factor associated with future AF episodes.[19] Atrial EMD can be evaluated noninvasively by tissue Doppler echocardiography, and an increase in atrial EMD time has also been shown to be useful for determining individuals prone to AF.[20] Moreover, it may allow for the early detection of subjects with a higher risk of AF before the development of tissue remodeling.[21] In the present study, all of these echocardiographic parameters, which have been demonstrated to be useful for identifying those with increased susceptibility to AF, were comparable between the individuals with ERP and healthy control subjects.

Although there seems to be no predisposition to AF in individuals with ERP, evidence of such a relationship exists in some patient groups. It has been reported that several genetic mutations detected in individuals with ERP may also be associated with AF.[22,23] These mutations expressed in both atria and ventricles may cause increased susceptibility to AF in addition to the phenotypic expression of ERP.[24] Another example of the relationship between ERP and AF is the athlete's heart. ERP is one of the most common ECG findings in athletes,[25] and is thought to be caused by increased vagal tone.[26] Athletes have also been shown to have an increased risk of AF,[27] and the main mechanism for the development of AF in these subjects is thought to be increased vagal tone.[28] In addition, it has been reported that athletes with ERP have higher LA filling pressure, which can then cause LA remodeling over time.[29] We excluded athletes from this study, and found that LA diameter, volume index and left atrial electrical activity parameters all increased in the individuals with ERP.

In the present study, mitral lateral, septal, mean annular and tricuspid annular s′ and e′ waves were significantly lower in the ERP group. In contrast to our study, mitral s′ was similar among subjects with and without ERP in a study evaluating middle-aged runners.[30] Similar to our study, athletes with ERP had significantly lower mitral e′ compared to those without ERP in two other studies evaluating professional soccer players.[29,31] More studies are required to better understand TDI characteristics in individuals with ERP.

The present study has some limitations. It was a single-center study, and the sample size was relatively small. Since it was not a follow-up study, the effect of atrial EMD and LA phasic function on the development of AF could not be evaluated.

CONCLUSION

Left atrial EMD parameters are affected in individuals with ERP, but LA phasic functions are not affected. Further prospective studies are needed to clarify whether individuals with ERP have an increased susceptibility to AF.

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AUTHOR CONTRIBUTIONS

All authors contributed to the conception of the work and drafted the manuscript. All authors critically revised the manuscript and gave final approval.

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