

## ORIGINAL ARTICLE

# P-wave dispersion and echocardiographic atrial indices as predictors of paroxysmal atrial fibrillation

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**Abstract: Objectives** – The aim of this study was to determine if specific electrocardiographic parameters and echocardiographic atrial indices could help in predicting the risk for developing paroxysmal atrial fibrillation (PAF). **Study population** – 49 patients (mean age of  $64.4 \pm 9.6$  years, 53% women) with a history of PAF and without any cardiac structural disease, were evaluated by ECG and standard bidimensional echocardiography. P wave duration, amplitude and dispersion ( $P_d$ ) were calculated from ECG and left and right atrial diameters, area, volumes, atrial emptying function and atrial function index were assessed by 2D echocardiography. **Results** – Compared with the control group, in the PAF patients group they had significantly larger anterior-posterior LA diameter ( $39 \pm 14$  mm vs  $33 \pm 3$  mm,  $p < 0.0001$ ), area ( $22 \pm 4$  cm<sup>2</sup> vs  $17 \pm 2$  cm<sup>2</sup>,  $p < 0.0001$ ), left atrial indexed volume ( $70 \pm 15$  ml vs  $50 \pm 11$  ml,  $p < 0.0001$ ) and electric parameters  $P_{min}$ ,  $P_d$  and  $P_a$  DII ( $47.4 \pm 4$  ms vs  $64.3 \pm 12.2$  ms,  $51.9 \pm 12$  ms vs  $28.2 \pm 7.5$  ms,  $0.99 \pm 0.029$  mm vs  $0.131 \pm 0.03$  mm,  $p < 0.0001$ ). There was an inverse correlation between increased electrical dispersion derived from  $P_d$  measurement on the ECG with right and left atrial emptying fraction ( $p < 0.0001$ ) and atrial function index ( $p < 0.0001$ ), and no correlation with right atrial index volume ( $r = 0.2167$ ,  $p = 0.0881$ ). These findings underlie the link between impaired electrical activation of the atria and atrial mechanical dysfunction as assessed by both atrial emptying fraction and atrial function index. Atrial dimensions were higher and the reservoir function was altered in patients with PAF compared with patients in sinus rhythm. **Conclusions** – P wave dispersion and 2DE atrial function indices could identify susceptible PAF patients. Atrial depolarization changes are linked to mechanical disturbances, being probably the first sign of atrial remodeling.

**Keywords:** atrial fibrillation, P wave dispersion, echocardiography.

**Rezumat: Obiective** – Scopul acestui studiu îl reprezintă identificarea contribuției unor parametri specifici derivați din electrocardiogramă (ECG) și ai unor indici atriali ecocardiografici în precizarea riscului de apariție a fibrilației atriale paroxistice (PAF). **Material și metodă** – 49 de pacienți (vârsta medie de  $64,4 \pm 9,6$  ani, 53% femei) cu istoric de PAF și fără boli cardiace structurale au fost evaluați prin ECG și ecocardiografie bidimensională. Durata undei P, amplitudinea și dispersia ( $P_d$ ) au fost calculate pe ECG, iar diametrele atriale stângi și drepte, aria atrială, volumul atrial, funcția de golire atrială și indicele funcției atriale au fost evaluate prin ecocardiografie 2D. **Rezultate** – În comparație cu grupul control, pacienții din grupul PAF au avut semnificativ mai crescute diametrul antero-posterior stâng ( $39 \pm 14$  mm vs  $33 \pm 3$  mm,  $p < 0.0001$ ), aria atrială stângă ( $22 \pm 4$  cm<sup>2</sup> vs  $17 \pm 2$  cm<sup>2</sup>,  $p < 0.0001$ ), volumul atrial stâng indexat ( $70 \pm 15$  ml vs  $50 \pm 11$  ml,  $p < 0.0001$ ), dar și parametrii electrice  $P_{min}$ ,  $P_d$  and  $P_a$  DII ( $47.4 \pm 4$  ms vs  $64.3 \pm 12.2$  ms,  $51.9 \pm 12$  ms vs  $28.2 \pm 7.5$  ms,  $0.99 \pm 0.029$  mm vs  $0.131 \pm 0.03$  mm,  $p < 0.0001$ ). S-a înregistrat o corelație inversă semnificativă între dispersia electrică crescută derivată din măsurarea  $P_d$  pe ECG cu fracția de golire atrială stângă și dreaptă ( $p < 0.0001$ ) și indexul funcției atriale ( $p < 0.0001$ ), și nu s-a găsit o corelație semnificativă cu volumul de atriu drept indexat ( $r = 0.2167$ ,  $p = 0.0881$ ). Acestea subliniază relația dintre afectarea activării electrice a atrului și disfuncția mecanică atrială, evaluate atât prin fracția de golire atrială, cât și prin indicele funcției atriale. Dimensiunile atriale crescute și funcția atrială alterată au fost regăsite în grupul cu PAF comparativ cu cei în ritm sinusal. **Concluzii** – Dispersia undei P și indicii ecocardiografici ai funcției atriale pot identifica riscul de recurență a fibrilației între pacienți. Modificările electrice atriale sunt corelate cu disfuncția mecanică atrială, constituind probabil primul semn al remodelării atriale.

**Cuvinte cheie:** fibrilație atrială, dispersia undei P, ecocardiografie.

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## BACKGROUND

Atrial fibrillation (AF) is the most common arrhythmia and is the primary cause of cardioembolic events. The most important issue regarding AF is related to the increased thromboembolic risk in the absence of adequate anticoagulant therapy. Moreover, paroxysmal AF (PAF) carries a similar risk as persistent or permanent AF, while its diagnosis can be particularly challenging in some cases. The correlation between atrial conduction abnormalities and paroxysmal atrial fibrillation has been previously described<sup>1</sup>. While the P wave duration is linked to prolonged intra and interatrial conduction, more insight can be obtained if the variation in P wave duration is measured between different ECG leads as a marker of non-homogeneous atrial conduction. In support of this, a previous study has showed that the electrical activity recorded on the surface ECG has a good correlation with the conduction time in specific parts of the atria<sup>2</sup>. Some reports showed that the measurement in sinus rhythm of P wave dispersion (Pd) and P wave duration together with atrial echocardiographic indices might be a useful, easy and noninvasive clinical tool to identify patients at risk of developing PAF<sup>3</sup>.

Aim of the study To determine whether specific ECG parameters and transthoracic echocardiographic atrial measurements could help in predicting the risk for developing PAF in patients without structural cardiac disease.

## MATERIAL AND METHODS

### Study population

We prospectively searched for enrollment consecutive patients referred to the "Prof. Dr. C.C. Iliescu" Emergency Institute for Cardiovascular Diseases with a history of PAF without any cardiac structural disease, who were at the moment of evaluation in sinus rhythm. Exclusion criteria were: acute myocardial in-

farction, LV ejection fraction <55%, hypertrophic cardiomyopathy, significant left ventricular hypertrophy, thyroid dysfunction, uncontrolled diabetes mellitus and arterial hypertension, chronic liver or renal disease, valvular heart disease, preexcitation syndromes, electrolyte imbalance, drug use that affects atrial conduction, or alcohol use. 49 patients were included in the final study population. The control group consisted of 30 individuals without any cardiovascular diseases, with similar age and gender distribution. The approval of the Ethics Committee was obtained before conducting the study and each patient signed the consent form. The following clinical data were obtained for each patient: age, sex, BMI, associated comorbidities, cardiac rhythm and current medication. Each patient had a standard 12 lead electrocardiogram taken in sinus rhythm and a comprehensive echocardiography.

### Electrocardiogram study

Standard twelve leads ECG was performed in all patients. All ECGs were recorded at a paper speed of 50 mm/s with a calibration of 2 mV/cm and were manually measured with hand-held calipers and use of magnification for calculation of P wave maximum duration ( $P_{max}$ ), P wave minimum duration ( $P_{min}$ ),  $P_d$ , and P amplitude (Pa) in DII and VI, during sinus rhythm (Figure 1).

P-wave duration was defined as the time measured from the onset to the end of the P-wave deflection. The onset of the P-wave is determined as the initial deflection from the isoelectric baseline defined by the T-P segment and the P-wave offset is defined as the junction of the end of the P wave and its return to baseline<sup>4</sup>.  $P_d$  was defined as the difference between maximum and minimum P-wave duration taking into account all of the 12 ECG leads.

Normal values accepted in adults for Pmax is between 60-110 ms (less than 120 ms), for Pa between 0.05 mV to 0,25mV (less than 2.5 mm), but we must take

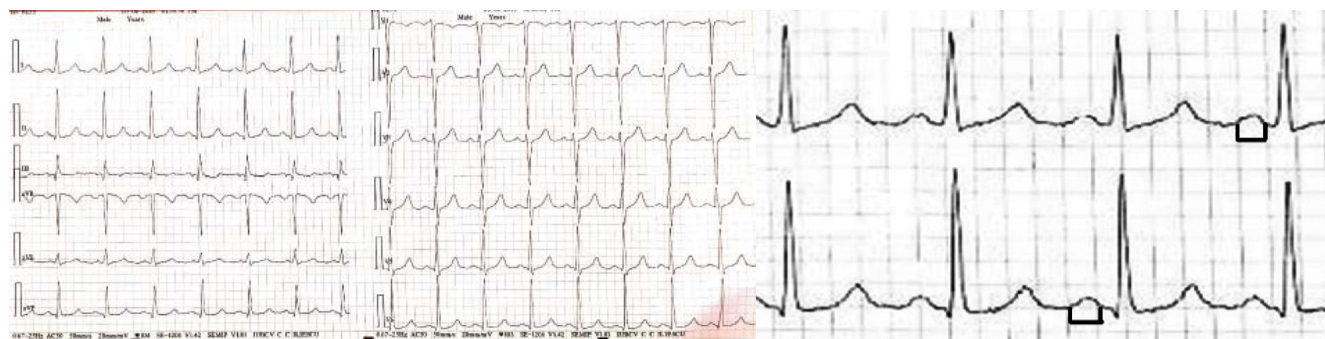


Figure 1. 12 leads normal electrocardiogram, speed of 50 mm/s, calculation of P wave duration.

into account that over the years P wave duration can progressively increase. The normal reported value of Pd is  $29 \pm 9$  ms with a maximum cut-off Pd value of 36 ms. Pd 40 ms indicates the evidence of heterogeneous electrical activity in different regions of the atrium that might determine atrial tachyarrhythmias<sup>5</sup>.

### Echocardiographic study

We performed the echocardiographic studies on VIVID 7 and VIVID 9 stations (GE Healthcare Horten Norway). We digitally stored the acquisition for offline analysis. Standard echographic views adjusted for frame rate optimization (similar frame rate and image settings were kept for the whole acquisition) were obtained to measure chamber dimensions and evaluate global and regional left ventricular function. We measured each of the four cardiac chambers according to the latest guidelines<sup>6</sup>.

Standard 2D Echocardiography: From long axis parasternal view, we measured the anteroposterior left atrium diameter, while we used the four-chamber view and two-chamber view to assess the left atrial (LA) area and volume (Figure 2). Area and volume values were indexed to the body surface area (BSA).

Assessment of left atrial volume (LAV) was done in the apical four and two chamber views, using the Simpson biplane method. During a cardiac cycle, the following measurements were made: - maximal LA volume (LAV max) - measured at the end of ventricular systole, just before mitral valve opening (the end of the T wave of the ECG), indexed LAVI, and minimal LA volume (LAV min) measured at the end of diastole at mitral valve closure.

The same measurements were done for the right atrium (RA) - diameter, area and volumes obtained from apical four chamber view and afterwards we di-

vided the volumes to the body surface area (RAVI – right atrium indexed volume) (Figure 3).

Filling pressures were estimated using the ratio between the peak early-diastolic transmitral flow velocity (E) and the average E' (the mean between septal e' and LV lateral e') (Figure 4).

LA and RA phasic function was assessed using volumetric parameters with previously measured volumes during the cardiac cycle.

The reservoir function – LA emptying fraction (LAEF) =  $(LAV_{max} - LAV_{min}) / LAV_{max}$ .

--RA emptying fraction (RAEF) =  $(RAV_{max} - RAV_{min}) / RAV_{max}$ .

For LA function index (LAFI) we measured in addition the LV outflow tract velocity time integral (LVOT VTI – we used the mean on 3 consecutive beats) (Figure 5)<sup>8</sup>.

LAFI was calculated using the following formula<sup>7</sup>:

$$LAFI = (LAEF \times LVOT) \times VTI / LAVI$$

We used a similar method to calculate RA functional index (RAFI), using the measurement of VTI at the level of right ventricular outflow tract (the mean from 3 consecutive beats).

### Statistical analysis

Measurements are presented as mean $\pm$ SD. Variables were compared using Student's t-test, ANOVA, or  $\chi^2$  test when appropriate. The relationships between different parameters were assessed by correlation analysis: Pearson's method for continuous, normally distributed variables and Spearman's rho method for ordinal or continuous but skewed variables. All statistical analyses were performed using SPSS 14.0 software for Windows (SPSS, Inc., Chicago, Illinois). A two-sided P-value of 0.05 was considered significant.

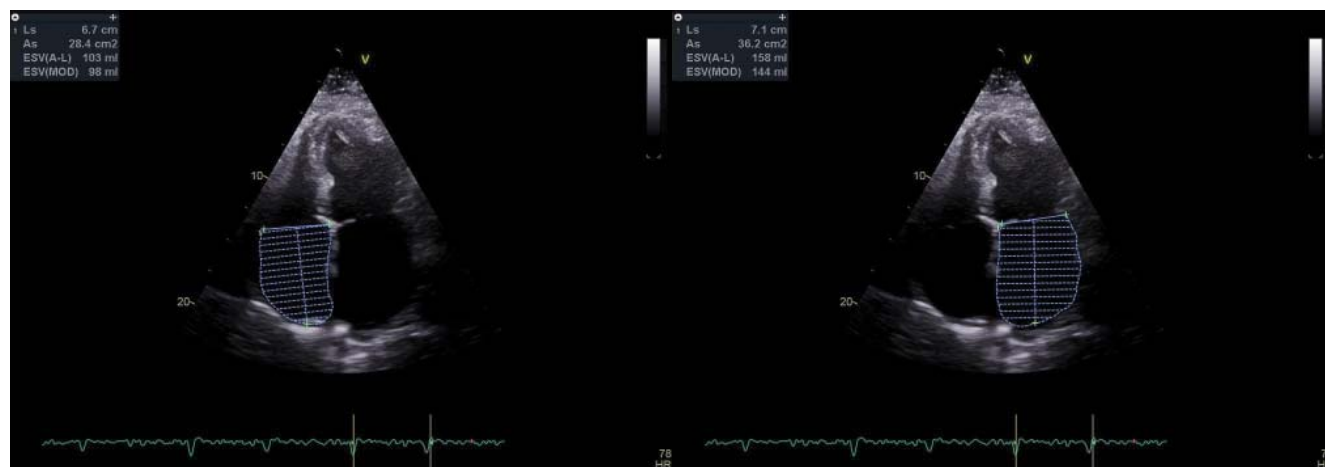


Figure 2 and 3. 2 dimensional echocardiography – LA and RA maximum volume in the apical 4 chamber view. LA – left atrium RA – right atrium.

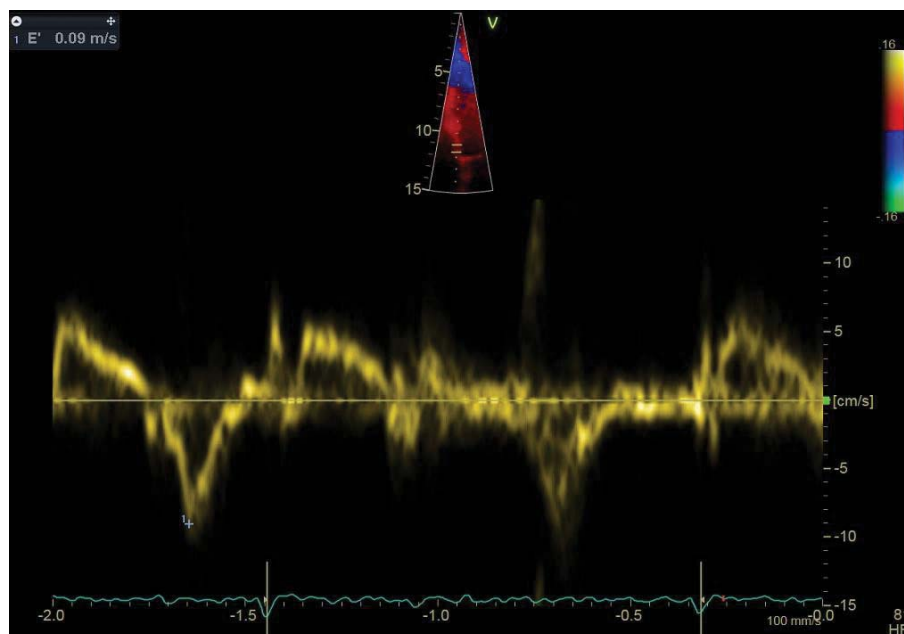


Figure 4. Tissue Doppler interrogation of the septal wall at the level of the medial mitral annulus – measurement of the septal E' wave (9 cm/s).

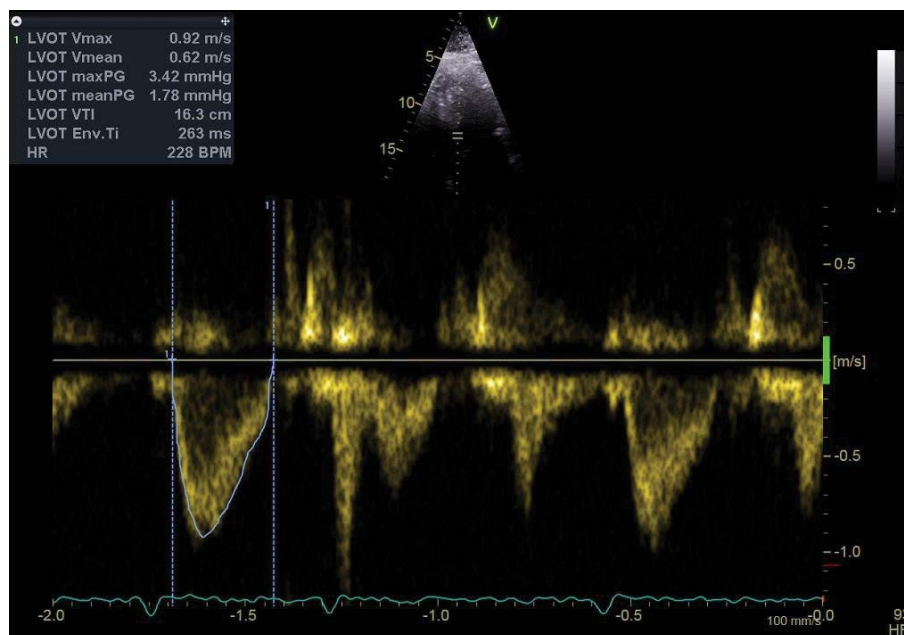


Figure 5. Pulsed wave doppler interrogation at the level of LVOT (Left ventricular outflow tract velocity time integral measure) – measurement of VTI (velocity time integral).

## RESULTS

The demographic characteristics of the two groups are listed in Table 1. The mean age was  $64.4 \pm 9.6$  years, 53% were women and mean BMI was  $28.6 \text{ kg/m}^2 \pm 4.7$  in all patients. These patients had at least one episode of atrial fibrillation.

## P wave parameters in study groups

In patients with PAF, the maximum P wave duration was  $99.4 \text{ ms} \pm 16.7$ ; minimum P wave duration was  $47.4 \text{ ms} \pm 9.8$ , the PD was  $51.9 \text{ ms} \pm 12$  and the P wave amplitude in DII was  $0.99 \text{ ms} \pm 0.029$ . In the control group, the same measurements were done and all

**Table 1. Baseline characteristics and chamber parameters in AF (atrial fibrillation) patients compared with controls**

	Controls N=30	Patients N=49	p value
<b>Clinical</b>			
Age (years)	61.3±8.4	64.4±9.6	0.1425
Women	63%	53%	0.3773
BMI (kg/m <sup>2</sup> )	26.2±4.4	28.6±4.7	0.0266
<b>P wave</b>			
P max (ms)	92.5±12.6	99.4±16.7	0.0551
P min (ms)	64.3±12.2	47.4±9.8	<0.0001
Pd (ms)	28.2±7.5	51.9±12	<0.0001
ADII (mm)	0.131±0.033	0.99±0.029	<0.0001
AVI (mm)	0.103±0.111	0.092±0.018	0.0037
<b>Left atrium</b>			
AP diam (mm)	33±3	39±14	<0.0001
LA area (cm <sup>2</sup> )	17±2	22±4	<0.0001
Max Vol LA (ml)	50±11	70±15	<0.0001
LAEF	61.4±9.4	44.6±13.4	<0.0001
LAFI	51.6±13.5	26.8±11.6	<0.0001
<b>Right atrium</b>			
ML diam (mm)	34±3	37±5	0.0005
RA area (cm <sup>2</sup> )	17±2	18±4	0.1635
Max Vol RA(ml)	50±11	52±14	0.6379
RAEF	61.3±9.3	47.1±13.6	<0.0001
RAFI	51.5±13.5	33±16.7	<0.0001

BMI – body mass index, Pmax – maximal duration of the P wave, Pmin – minimum duration of the P wave, Pd – P wave dispersion, ADII – P wave amplitude in DII lead, AVI – P wave amplitude in VI lead, AP diam – anteroposterior diameter of the left atrium, LA Area – Left atrium maximal area, Max vol LA – maximal volume of the left atrium, LAEF – left atrial emptying fraction, LAFI – left atrial function index, ML diam – mediolateral diameter of the right atrium, RA area – maximal area of the right atrium, Max Vol RA – maximal volume of the right atrium, RAEF – right atrial emptying fraction, RAFI – right atrial function index.

are summarized in Table 1. In each of these instances, the difference between the 2 groups reached the level of significance (high significance for P<sub>min</sub>, P<sub>d</sub> and P<sub>a</sub> DII p<0.0001) and no significance for P<sub>max</sub>.

### Echocardiographic atrial indices comparison

Compared with the control group, patients with PAF had significantly larger anterior-posterior LA diameter, area and indexed volume. Patients with PAF had a significantly worse LA reservoir function (44.6 cm<sup>2</sup>±13.4 vs 61.4 cm<sup>2</sup> ±9.4, p<0.0001) and LA functional index (26.8±11.6 cm<sup>2</sup> vs 51.6±13.5 cm<sup>2</sup>, p<0.0001). In a similar way, the PAF group had worse right atrial indices – both the reservoir and the atrial function derived from RAFI were significantly altered compared with controls (47.1±13.6 vs 61.3±9.3 respectively 33±16.7 vs 51.5±13.5, p<0.0001). There were no significant differences between patients and controls regarding the RA volume and area, but patients with PAF had a larger RA mediolateral diameter.

### Pd and echocardiographic atrial indices correlation

We used Pearson's correlation to evaluate the relationship between Pd and echographic atrial parameters (Table 2) and we found a strong positive correlation

with antero-posterior LA diameter, area and indexed volume (p<0.0001) and an inverse strong correlation with LA and RA function and index (p<0.0001). In addition, higher atrial electrical dispersion positively correlated with LV filling pressures. No correlation was found between Pd and RAVI, while Pd had a moderate positive correlation with RA area and mediolateral RA diameter (Table 2).

### DISCUSSIONS

Atrial fibrillation is associated with structural and electrical remodeling in the atria and ventricular myocardium. The heterogeneity in impulse conduction as a consequence of atrial fibrosis is one of the most important electrical mechanism leading to AF. The progression of atrial fibrosis is the result of structural remodeling and factors as a substrate for AF recurrence - advanced atrial fibrosis is associated with increased risk for both paroxysmal and persistent or permanent AF. Our study aimed to evaluate the potential for simple and reproducible electrical parameters (P-wave variability) derived from standard 12 leads ECG to potentially identify patients at risk of developing PAF and their correlation with echocardiographic atrial parameters to identify secondary atrial changes.

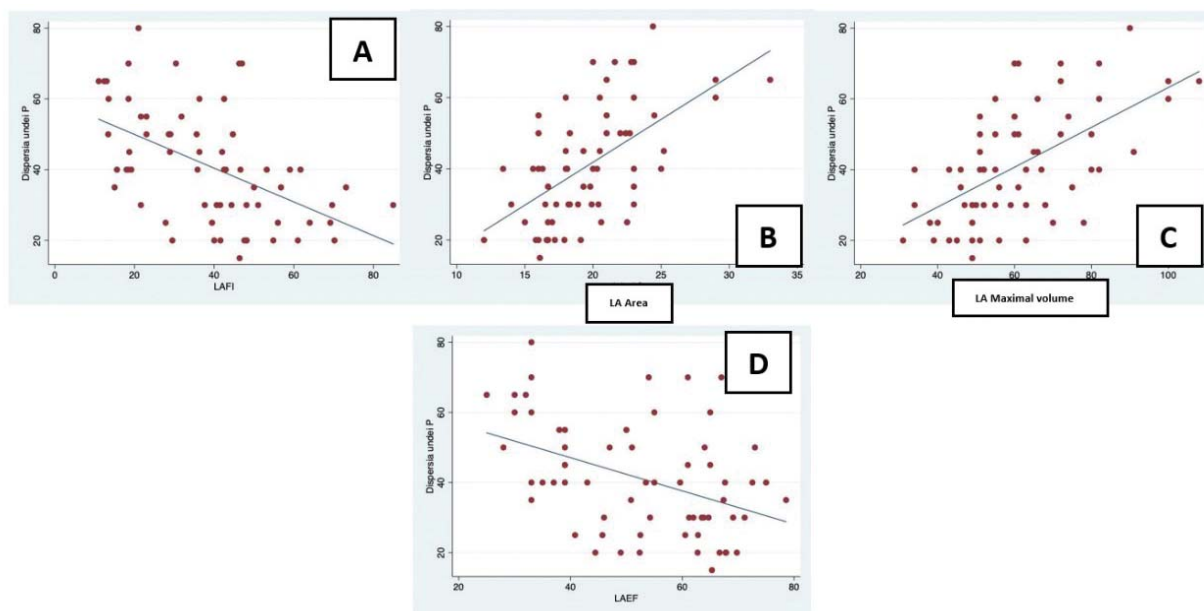
**Table 2. Correlations between P<sub>d</sub> (Pwave dispersion), left ventricular filling pressures and echocardiographic atrial measurements and indices**

	r coefficient (P <sub>d</sub> )	p-value
LA AP diameter	0.5597*	<0.0001
LA area	0.5771*	<0.0001
Max Vol LA	0.5869*	<0.0001
LAEF	-0.4231*	0.0006
LAFI	-0.5244*	<0.0001
E/A	-0.5435*	<0.0001
E/E'	0.4550*	0.0002
ML diam RA	0.3826*	0.002
RA Area	0.2978*	0.0178
Max Vol RA	0.2167	0.0881
RAEF	-0.5601*	<0.0001
RAFI	-0.5617*	<0.0001

LA AP diameter – left atrial anteroposterior diameter, LA Area – Left atrium maximal area, Max vol LA – maximal volume of the left atrium, LAEF – left atrial emptying fraction, LAFI – left atrial function index, ML diam RA – mediolateral diameter of the right atrium, RA area – maximal area of the right atrium, Max Vol RA – maximal volume of the right atrium, RAEF – right atrial emptying fraction, RAFI – right atrial function index.

is probably related to the inhomogeneity of electrical atrial activity that persists in patients with PAF even after restoring normal sinus rhythm. In our study P<sub>d</sub> was significantly higher in patients with PAF compared to controls, these findings being consistent with previously reported data. For faster calculation and better reproducibility of P<sub>d</sub>, automatic methods might be more accurate.

The correlation between Pd and echocardiographic left atrial indices such as left atrial size and function<sup>11</sup>, left atrial appendage function<sup>12</sup> and the left ventricular diastolic function<sup>13,14</sup> was described by several studies and was also demonstrated in our study. Another echocardiographic index evaluating the atrial function, independent of the underlying rhythm is the LA function index (LAFI), a marker who incorporates surro-

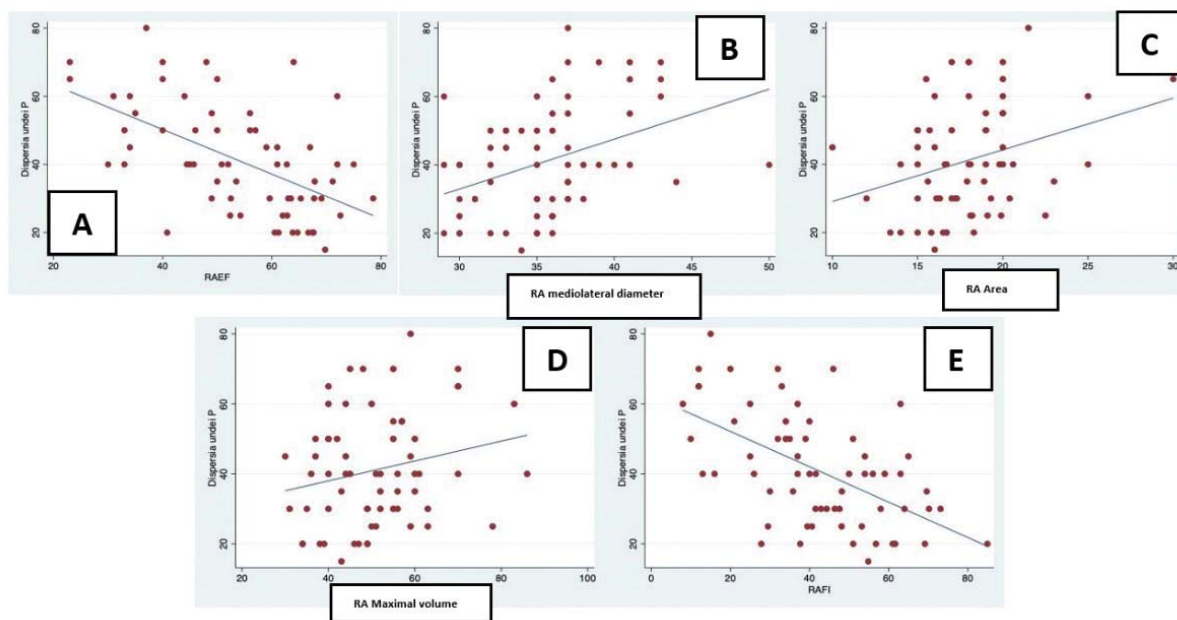


**Figure 6.** Correlation between P wave dispersion (P<sub>d</sub>) and left atrial indices. **A** – correlation between Pd and left atrial function index. **B** – correlation between Pd and left atrial maximal area. **C** – correlation between P<sub>d</sub> and left atrium maximal volume. **D** – correlation between Pd and left atrial emptying fraction.

Several studies showed the relationship between P wave derived parameters and AF, like Gonna et al.<sup>9</sup> who reported that parameters that accounted for the P-wave duration were increased in the recurrent AF than in the sinus rhythm group. P wave dispersion proved to be the most specific and sensitive marker in distinguishing between the patients with PAF and normal subjects. First time described by Dilaveris et al.<sup>10</sup> in his study on 60 patients with PAF versus 40 healthy controls, the interlead variation in P wave duration

gates of cardiac output, LA size and atrial reservoir function and which is inversely proportional to LA size and directly proportional to LA reservoir function and stroke volume.

Left atrial function index was associated with an increased risk of developing incident atrial fibrillation independent of validated clinical risk prediction scores and echocardiographic measures of adverse cardiac remodeling. Left atrial function index can be easily measured using widely available 2-dimensional



**Figure 7.** Correlation between P wave dispersion ( $P_d$ ) and right atrial indices. **A** – correlation between  $P_d$  and right atrial emptying fraction. **B** – correlation between  $P_d$  and right atrium mediolateral diameter. **C** – correlation between  $P_d$  and right atrial maximal area. **D** – correlation between  $P_d$  and right atrium maximal volume. **E** – correlation between  $P_d$  and right atrial function index.

echocardiography and the studies demonstrated independent association of left atrial function index with adverse outcomes even in the presence of normal left atrial size, making it an enticing novel risk marker<sup>15</sup>. In our study, patients with PAF had worse LA mechanical function as assessed by LAFI compared to controls. Moreover, this is the first study that established an inverse correlation between increased electrical dispersion derived from  $P_d$  measurement on the ECG and LAFI/RAFI, underlying the link between impaired electrical activation of the atria and atrial mechanical dysfunction as assessed by both LAFI/RAFI and LAEF/RAEF. We have also found a moderate correlation between  $P_d$  and LV filling pressures – probably because the delay in electrical activation of the atria negatively impacts the diastole, especially if the left atrium activation is delayed, shortening the LV filling time and leading to a partially inefficient atrial contraction, conversely increasing LA pressure and in the end LV diastolic pressure.

Right atrium size is considered an independent predictor of early PAF recurrence<sup>16</sup> and a recent study by Luong C et al.<sup>17</sup> on 95 patients with AF after cardioversion showed that right atrial volume is superior to left atrial volume for prediction of PAF. Considering these facts, we also analyzed the correlation between the electrical changes with RA dimensions and the

parameters evaluating the function of the right atrium. To our knowledge, this is the first study that used RAFI to assess the performance of the right atrium, and we showed that patients with AF had poorer performance of the RA compared to controls.

In our study, echocardiographic atrial parameters (dimensions and function indices) and P wave parameters were statistically different between the PAF group and the control group (patients with PAF had increased electrical dispersion and dimensions of LA/RA, while the mechanical performance of RA/LA was worse in the PAF group), except P wave max. duration and RAVI - probably explained by the lack of specific and accurate measurement methods (automatic ECG measurement methods for  $P_d$  and  $P_{max}$ , and 3 dimensional echocardiography for a precise measurement of the right atrium) and the fact that at first, RA is less involved in maintaining and initiating AF.

These indices are easy to assess in clinical practice and can help in evaluating the risk for developing AF in apparently healthy individuals, guiding the physician to screen these patients aggressively for AF, especially in the presence of symptoms (palpitations, thromboembolic events). Unfortunately, since we didn't follow the patients prospectively, we cannot assess the predictive value of these parameters for AF recurrence, which is one of the main limitations of our study.

## LIMITATIONS

The small number of patients, the use of manual methods to measure P wave parameters, and the lack of long-term follow-up for patients in the PAF group, represent some of the limitations of this study.

## CONCLUSIONS

Structural and electrical atrial remodeling is both a consequence and a substrate for atrial fibrillation. Because of the high mortality in patients with untreated/undetected AF, identifying patients at high risk for developing AF is very important.

Easy to measure and reproducible markers are needed in clinical practice for evaluating the risk of AF occurrence. P<sub>d</sub> and atrial function indices proved to be meaningful in identifying susceptible patients, and moreover, electrical changes in atria are linked to mechanical disturbances, underlying the mechanism of atrial remodeling.

**Conflict of interest:** none declared.

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