Original Article

P Wave Indices to Predict Atrial Fibrillation Recurrences Post Pulmonary Vein Isolation

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Abstract

Background: P-wave indices are appealing markers for predicting atrial fibrillation (AF) recurrences post ablation.

Objective: This study evaluates the value of P wave indices to predict recurrences post pulmonary vein isolation (PVI) in patients with paroxysmal AF.

Methods: We selected 198 patients (57 ± 8 years, 150 males) with symptomatic drug-refractory paroxysmal AF undergoing PVI in our hospital. A 12-lead electrocardiogram was used to measure P wave duration in lead II, P wave terminal force (PWTF) in lead V1, P wave axis and dispersion.

Results: During a follow-up of 9 ± 3 months, recurrences occurred in 60 (30.3%) patients. The patients that had AF recurrence had longer mean P wave duration (122.9 ± 10.3 vs 104.3 ± 14.2 ms, p < 0.001), larger P wave dispersion (40.7 ± 1.7 ms vs 36.6 ± 3.2 ms, p < 0.001). P wave duration ≥ 125 ms has 60% sensitivity, 90% specificity, positive predictive value (PPV) of 72% and negative predictive value (NPV) of 83.7%, whereas P wave dispersion ≥ 40 ms has 78% sensitivity, 67% specificity, PPV of 51% and NPV of 87.6% 48/66 (72.7%) patients with PWTF ≤ -0.04 mm/second vs 12/132(9%) with PWTF > -0.04 mm/second showed recurrence of AF (p < 0.001). P wave axis was not different between two groups. On multivariate analysis, P wave indices were not independent from left atrial size and age.

Conclusions: P wave duration ≥ 125 ms, P wave dispersion ≥ 40 ms and PWTF in V1 ≤ -0.04 mm/sec are good clinical predictors of AF recurrences post PVI in patients with paroxysmal atrial fibrillation; however they were not independent from left atrial size and age. (Arq Bras Cardiol. 2013; 101(6):519-527)

Keywords: Atrial Fibrillation; P Wave; Ventricular Fibrillation; Pulmonary Veins.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, of which importance derives from the fact that it is one of the most common leading causes of circulatory instability and stroke. The main goals in the management of AF are heart rate or rhythm control and anticoagulation. If rhythm control is desired and cannot be maintained by medication or cardioversion, then catheter ablation may be attempted.

Radiofrequency catheter ablation (RFCA) of AF is effective in 70-80% of the cases, but recurrences are frequent and at the present time, accurate markers of recurrences are lacking[1-4]. The natural history of AF is characterized by self-perpetuating mechanisms, rate-induced electrophysiological changes and structural remodeling that involves the atrial myocardium[5].

Atrial remodeling is both electrical and structural; it causes slow electrical conduction and enlargement of the atria, which is reflected by changes in the morphology of the P wave in the electrocardiogram (ECG). Predictors to discriminate who will benefit from ablation are needed to save money, time and effort. Using ECG parameters as a predictor is very useful, as it is low-cost, feasible and can yield a lot of information. In our study we evaluated the use of P-wave indices to predict the recurrence of atrial fibrillation post pulmonary vein isolation (PVI) in patients with paroxysmal atrial fibrillation.

Methods

Population

After informed consent, 198 consecutive patients (57 ± 8 years, 150 males, and 48 females) with symptomatic drug-refractory paroxysmal AF, undergoing RFCA were enrolled in our study. AF was classified as paroxysmal when episodes were generally self-terminating and lasted no longer than 7 days, according to the European Society of Cardiology guidelines[6].

Prior to the procedure, all patients underwent a comprehensive transthoracic echocardiographic examination to assess left atrial (LA) size and function, left ventricular (LV) function and to exclude structural heart disease; additionally,

all patients underwent transesophageal echocardiography immediately before the ablation procedure to exclude LA thrombi. Clinical characteristics are summarized in Table 1.

Standard 12 Lead Electrocardiogram (ECG)

Standard 12 lead ECG was performed in all patients during sinus rhythm just before the ablation procedure using commercially available equipment (MAC 1200 ST General Electric Medical Information Technology). The ECG recorded before ablation procedure was the one used for statistical analysis, while another ECG recorded after ablation was used to confirm that the patient was in sinus rhythm post-procedure. Before ablation ECGs were recorded for 10 seconds first at a sweep speed of 25 mm/s and calibrated to 1 mV/cm in the standard leads and then at a sweep speed of 50 mm/s and calibrated to 2 mV/cm in the standard leads to obtain further precise measurements. Scanning and digitizing of ECG signals from paper records using an optical scanner were performed for all ECG recordings; the onset and offset of the P wave were defined as the start of the upward deflection of the P-wave pattern and its return to the isoelectric baseline in lead II[7]. All the following parameters were assessed; P-wave duration in lead II, P wave terminal force (PWTF) in lead V1, P wave axis and dispersion.

P-wave dispersion was measured manually by subtracting the minimal P wave (Pmin) duration from the maximal P wave (Pmax) duration (Pmax - Pmin), measured by multiple surface ECG leads, from a single beat and mean values for three complexes were calculated.

Calculation of the PWTF was performed by measuring the P wave duration in seconds multiplied by the P wave amplitude of the negative terminal portion of the P wave in V1 in millimeters as shown in Figure 1. The patients were further divided in to two groups, the first group in which the PWTF was > -0.04 mm/sec. (smaller than one small square) and the second group in which the PWTF was ≤ -0.04 mm/sec. (larger than one small square).

A control group including 120 normal subjects (80 males; 40 females; mean age 44 ± 17 years) without any history of AF, structural heart disease or hypertension was used to define normal values for P-wave characteristics.

After the ablation, all patients were systematically evaluated at the outpatient clinic during a mean follow up of 9 ± 3 months. ECG recordings were acquired on each visit and 24-h Holter recordings were scheduled after 3, 6 and 9 months of follow-up. Importantly, all patients were encouraged to immediately obtain an ECG registration when experiencing palpitations. Antiarrhythmic medications were interrupted after the ablation procedure and AF recurrence was defined as any recording of AF on ECG or an episode longer than 30 s on 24-h Holter recording.

P-wave indices in each ECG trace was evaluated by two independent blinded investigators and Bland–Altman analyses were performed to assess the inter- and intra-observer reproducibility of P-wave duration, P-wave dispersion, P-wave axis and P-wave terminal force in V1. Measurements showed minimal biases (1.2±11 and 1.3±10 ms, respectively for P wave duration), (1.6±10 and 1.5±10 ms, respectively for P wave dispersion), (2±8 and 2±9 degree, respectively for P wave axis), (1.8+10 and 1.7+10 mm/sec., respectively for P wave terminal force in V1)[8].

Radiofrequency Catheter Ablation Procedure

The ablation procedure was performed in a fasting state. The right femoral vein was used for the insertion of catheters, a single transseptal puncture was performed using FAST-CATH trans-septal guiding introducer (SL1 8.5 F St. Jude medical). Two catheters were inserted: one duodecapolar lasso catheter for PV recording (introduced through the SL0 long sheath and positioned at the ostium of each PV sequentially) and a 4-mm irrigated-tip ablation catheter for pulmonary veins isolation. The right internal jugular vein was used for the insertion of one decapolar (2 mm spacing) steerable catheter in the distal

Table 1 - Clinical characteristics of the total population and the two groups

Clinical characteristics of the two groups	Total	Recurrence	Non-recurrence	p value
Number	198	60	138	
Mean age (years)	57 ± 7.5	64.6 ± 5.12	53.9 ± 5.98	< 0.001
Male/female	150/48	48/12	102/36	0.23
History of DM	13/198	6/60	7/138	0.16
History of SAH	86/198	30/60	56/138	0.14
History of Stroke	1/198	1/60	0/138	0.3
Duration of atrial fibrillation (months)	11.4 ± 6.4	16.4 ± 8.1	9.34 ± 4	< 0.001
Body mass index (mean Kg/m²)	27.5 ± 1.1	27.7 ± 1.09	27.4 ± 1.2	0.06
Mean P wave duration(ms)	109.9 ± 15.6	122.9 ± 10.3	104.3 ± 14.2ms	< 0.001
Mean P wave dispersion(ms)	37.9 ± 3.4	40.7 ± 1.7ms	36.6 ± 3.2ms	< 0.001
Mean ejection fraction (%)	59.6 ± 4.7	59.4 ± 4.3	59.7 ± 5	0.08
Mean LA diameter(mm)	42.9 ± 4.5	47.5 ± 2.8	40.9 ± 3.6	< 0.001

DM: diabetes mellitus; SAH: systemic arterial hypertension; ms: millisecond; LA: left atrium.
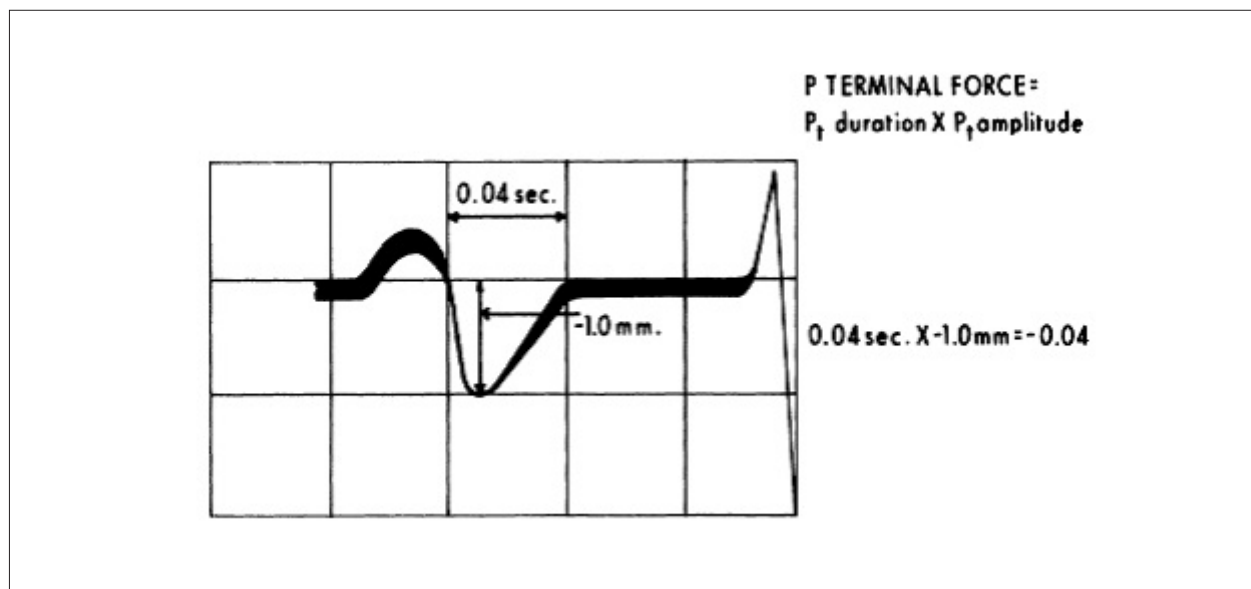
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Figure 1 - *Calculation of the P wave terminal force in lead V1.*

coronary sinus. After transseptal puncture, a bolus of 5000 U of intravenous heparin was administered and activated clotting time was maintained above 280 s throughout the procedure.

Three-dimensional electro-anatomical mapping was performed in all cases using the CARTO3 system (Biosence Webster, Johnson & Johnson). Radiofrequency catheter ablation was aimed at creating circular lesions initially applied in the whole circumference in the antral region of the veins (ipsilateral vein-to-vein), with subsequent electrical isolation provided it was not achieved in the circumferential application of the lesions. Isolation of all four PVs was performed using the ablation catheter guided by the circumferential mapping catheter in the PV [maximum power 30-35 W; maximal temperature 40; duration of the radiofrequency (RF) application 60 s]. The endpoint of RF application was complete PVI, demonstrated by the absence of PV potentials in the PV during sinus rhythm or coronary sinus pacing, by the absence of PV-left atrium conduction during PV pacing, and by recording of very-low (0.5 mV) voltage inside the PVs in the final voltage map. Reconfirmation of PV isolation was performed 30 min after ablation for each PV. Patients were followed with continuous ECG monitoring for 24 h and were discharged from the hospital two days after the procedure.

Statistical Analysis

Data are expressed as mean ± standard deviation for continuous variables and frequencies for categorical variables. Differences between groups were assessed using Chi-square statistics for categorical variables and analysis of variance for continuous variables. A p value < 0.05 was considered significant. Pearson's correlation coefficient and multivariate Cox regression analysis using significant variables was also performed. Statistical analyses were performed using SPSS version 16.0 statistical software (SPSS Inc., Chicago, IL).

A receiver operating characteristic (ROC) curve was generated to evaluate P wave indices as a predictor of AF recurrences post PVI and different cut-off values for P wave duration and P wave dispersion were chosen to evaluate probability of AF recurrences. The AF-free rates according to P wave duration of < 125 ms and ≥ 125 ms along with P wave dispersion < 40 ms and ≥ 40 ms were calculated using Kaplan-Meier analysis with the log-rank test.

Results

Paroxysmal AF patients in comparison to control cases had longer P wave duration (109.9 ± 15.6 ms vs 99.5 ± 11.6 ms, p < 0.001), larger P wave dispersion(37.9 ± 3.4 ms vs 24.9 ± 9.1 ms, p < 0.001), larger left atrial diameter (42.9 ± 4.5 mm vs 30 ± 6.3 mm, p < 0.001); 66 of 198 patients showed PWTF ≤ -0.04 mm/second, while the entire control group had PWTF > -0.04 mm/second (p < 0.0001).

All patients had successful pulmonary vein isolation and all patients were in sinus rhythm at the end of the procedure. No AF recurrence was observed during the first 24 h after the ablation procedure. During a mean follow-up of 9 ± 3 months, recurrences occurred in 30.3% (60/198). The clinical characteristics of the total paroxysmal AF patients and the two groups are summarized in Table 1.

Patients with AF recurrence had longer mean P-wave duration (122.9 ± 10.3 vs 104.3 ± 14.2 ms, p < 0.001), larger P-wave dispersion (40.7 ± 1.7 ms vs 36.6 ± 3.2 ms, p < 0.001) when compared with patients without recurrence of atrial fibrillation (Figures 2 and 3). Further subgroup analysis for patients with normal LA size showed that patients with normal LA size and recurrence of AF post PVI had longer P-wave duration (119.5 ± 13.5 ms vs 100.6 ±11.38 ms, p = 0.01) and larger P-wave dispersion (38.09 ± 2.7 ms vs 35.86 ± 3.38 ms, p = 0.03) in comparison with normal LA size patients without recurrence of AF.

Forty-eight of 66 (72.7%) patients with P wave terminal force $\leq$ -0.04 mm/second showed recurrence of AF when compared with 12/132 (9%) patients with P-wave terminal force > -0.04 mm/second (p < 0.001). P-wave axis was not significantly different between patients with and without AF recurrences (p > 0.09).

Receiver operating characteristic (ROC) curve analysis was performed for different P-wave duration and P wave dispersion cutoff points (Figures 4 and 5). The area under the ROC curve for P wave duration was 0.858 (95% confidence interval 0.805–0.912) (p < 0.001). The area under the ROC curve for P wave dispersion was 0.852 (95% confidence interval 0.8–0.904) (p < 0.001). By observing different cutoff values, P wave duration $\geq$ 125/ms and P wave dispersion $\geq$ 40 ms were found to discriminate patients prone to AF recurrences over time according to log-rank test (Figures 6 and 7). P wave duration of 125 ms has the best combined sensitivity and specificity (60% and 90% respectively) along with positive predictive value of 72% and negative predictive value of 83.7%, whereas P wave dispersion of 40 ms has the best combined sensitivity and specificity (78% and 67% respectively) along with positive predictive value of 51% and negative predictive value of 87.6%.

Multivariate cox regression analysis showed that P wave indices were not independent from left atrial size and age; however, P wave duration was moderately correlated with age (r = 0.3, p < 0.001) and a good correlation with left atrial size (r = 0.5, p < 0.001). No significant correlation was found between P-wave duration and P-wave axis (r = 0.03, p = 0.6). P-wave dispersion had a moderate positive correlation with age (r = 0.41, p < 0.001) and left atrial volume (r = 0.42, p < 0.001). P-wave duration and P-wave dispersion had a moderate positive correlation (r = 0.3, p < 0.001).

Discussion

AF is one of the most important arrhythmias found in the field of cardiology, as it is the most prevalent and causes many complications. Several strategies have been used in its management and the importance of AF ablation has increased as it is believed it can cure arrhythmia. The challenge of post ablation atrial fibrillation recurrence is still high, so the present study proposes a non-invasive and easy-to-apply predictor for AF recurrence, which are the P wave indices obtained from standard 12 lead ECG.

Multiple independent predictors of AF recurrences after RF ablation have been identified, such as age, persistent AF[1], hypertension, hyperlipidemia, left atrial diameter, white blood cell count before ablation[2,3], and atrial remodeling by delayed-enhancement MRI[4], but quantitative non-invasive markers are still lacking.

Prolonged P-wave duration denotes inter- and intra-atrial abnormal conduction. Dogan et al[9] reported that maximum P wave duration and P wave dispersion were predictors for the maintenance of sinus rhythm after AF cardioversion and that increased P wave dispersion could be used to identify patients at risk of such post procedural recurrence.

Previous studies were performed to evaluate different P wave duration and dispersion values to predict occurrence of atrial fibrillation post cardioversion, post myocardial infarction and also post-cardiac surgery. Rosiak et al[10] demonstrated that P-wave duration >125 ms and P-wave dispersion >25 ms, when measured very early after an acute myocardial infarction, were independently associated with AF. [10]

The association between P-wave duration and atrial electromechanical delay assessed by tissue Doppler echocardiography by Dabrowska-Kugacka et al[11] concluded that P-wave duration of the surface ECG is highly correlated with the atrial electromechanical delay and based on this association, one can verify the importance of P-wave duration on the surface ECG as a predictor of atrial fibrillation recurrence post pulmonary vein isolation.

Other studies that used P-wave signal averaging to predict atrial fibrillation recurrences after pulmonary vein isolation concluded that Filtered P wave duration > 140 ms on the P-wave signal averaged electrocardiogram is a useful marker of AF recurrences over time after pulmonary vein isolation. Although this technique is still not widely used, it confirms that prolonged P-wave duration probably reflects inter- and/or intra-atrial conduction delays and could be related to the extent of atrial scarring and fibrosis, as shown by the longer P-wave duration in patients with recurrent AF[12].

P-wave morphology represents atrial electrical activation, which depends mainly on the distance traveled by the electric current from the first to the last point of depolarization, along with the velocity of the electric current. Atrial remodeling, which is the main substrate of AF, is divided mainly into structural and electrical remodeling and in most cases, both will occur together. Structure remodeling is mainly represented by atrial enlargement detected by echocardiography, while electrical remodeling is represented by prolonged electromechanical time demonstrated by tissue Doppler imaging or invasively by measuring total atrial activation time between the first atrial potential detected by an intracardiac electrode positioned in high right atrium and the last atrial potential detected by an intracardiac electrode positioned in distal coronary sinus. The main characteristics of the electrical remodeling process are the shortening of the refractory period with increased dispersion and atrial conductivity reduction. Based on this point of view about atrial electrical remodeling, one can clarify our findings regarding patients with normal LA size, as we found that even in patients with normal LA size patients with recurrence of AF post PVI had longer P wave duration and larger P wave dispersion in comparison with normal LA size patients without AF recurrence.

AF recurrences post PVI are mainly due to PV re-conduction in ablated myocardium or sometimes to non-PV foci[13-16]. To test the hypothesis that P-wave duration could be a marker of a successful PVI, Date et al[17] studied the contribution of PV cardiac muscles to the P-wave using standard vectorcardiography and electrocardiography recorded before and after the procedure. They found that the morphology of the P-wave changed after PVI and that the myocardial sleeves of the PV played an important role in the formation of the middle part of the P-wave.
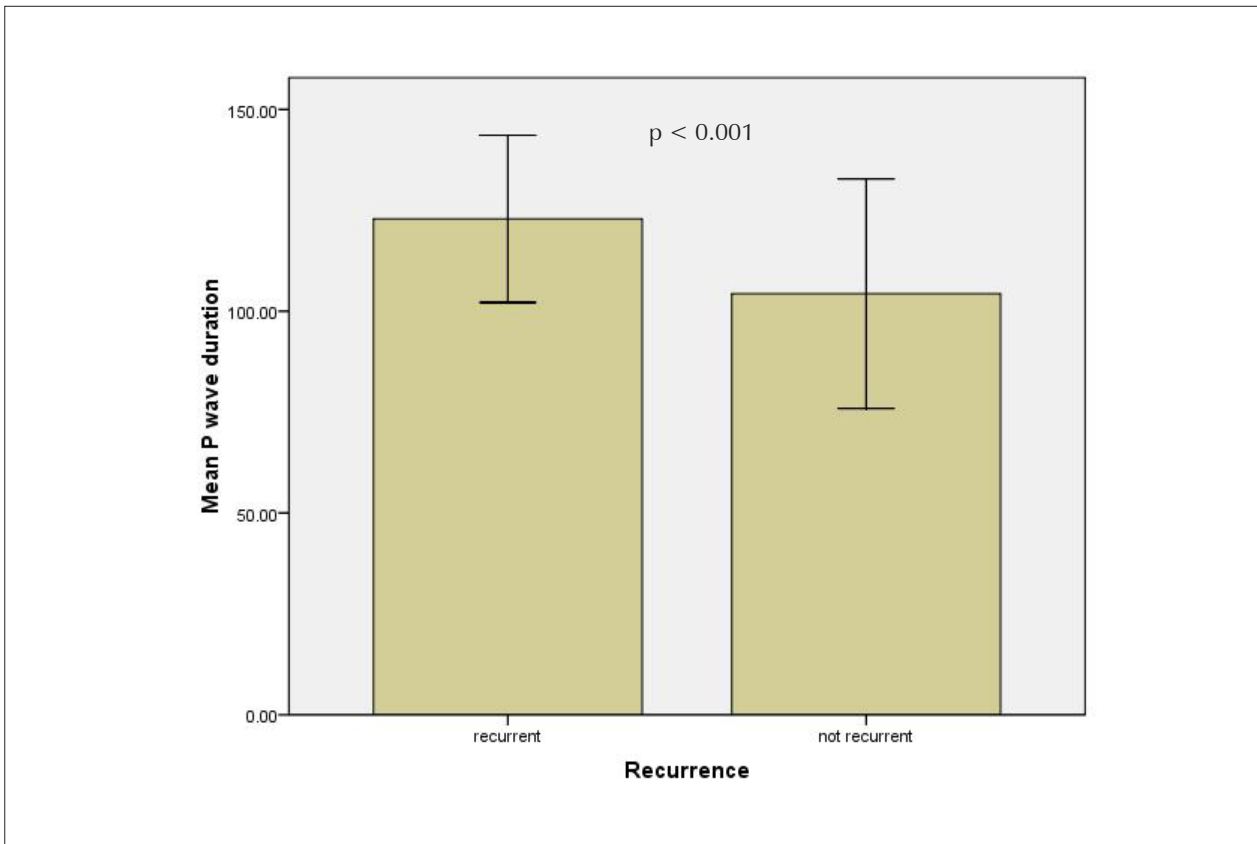
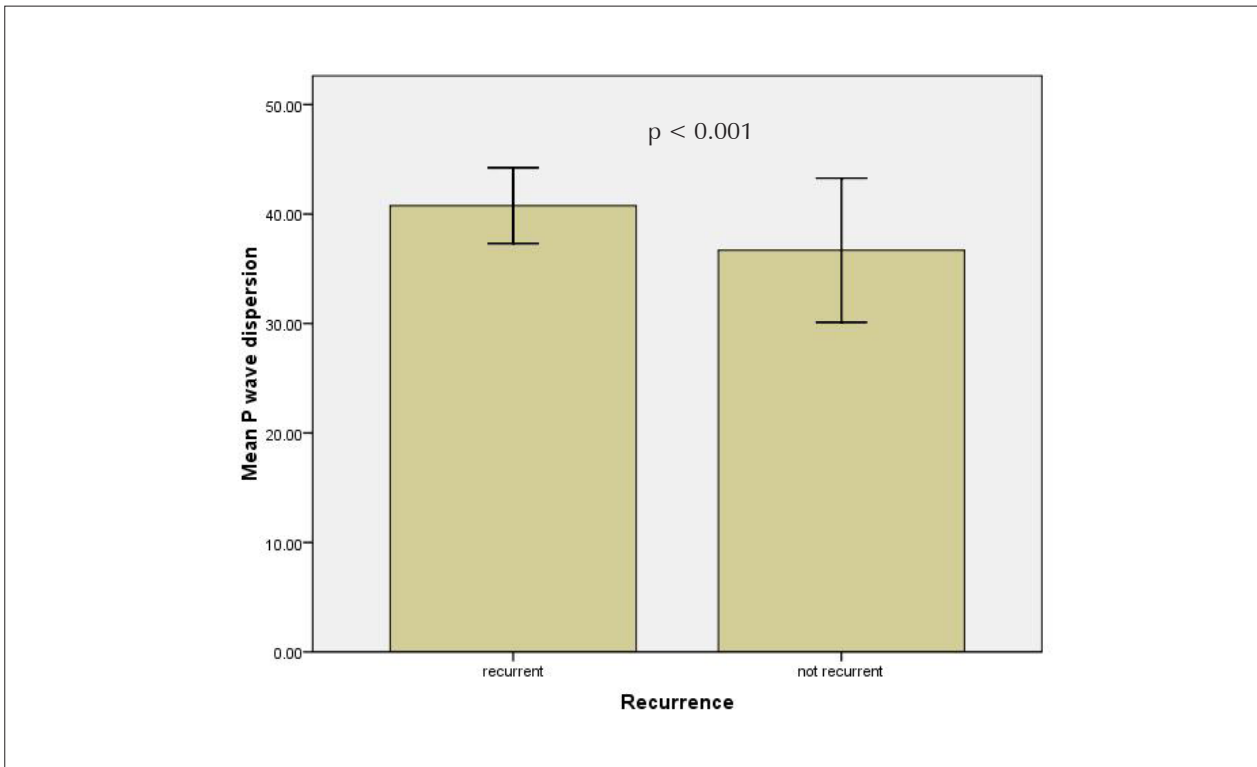**Figure 2 -** *Significant difference between mean P wave duration in the recurrence and non-recurrence groups.*

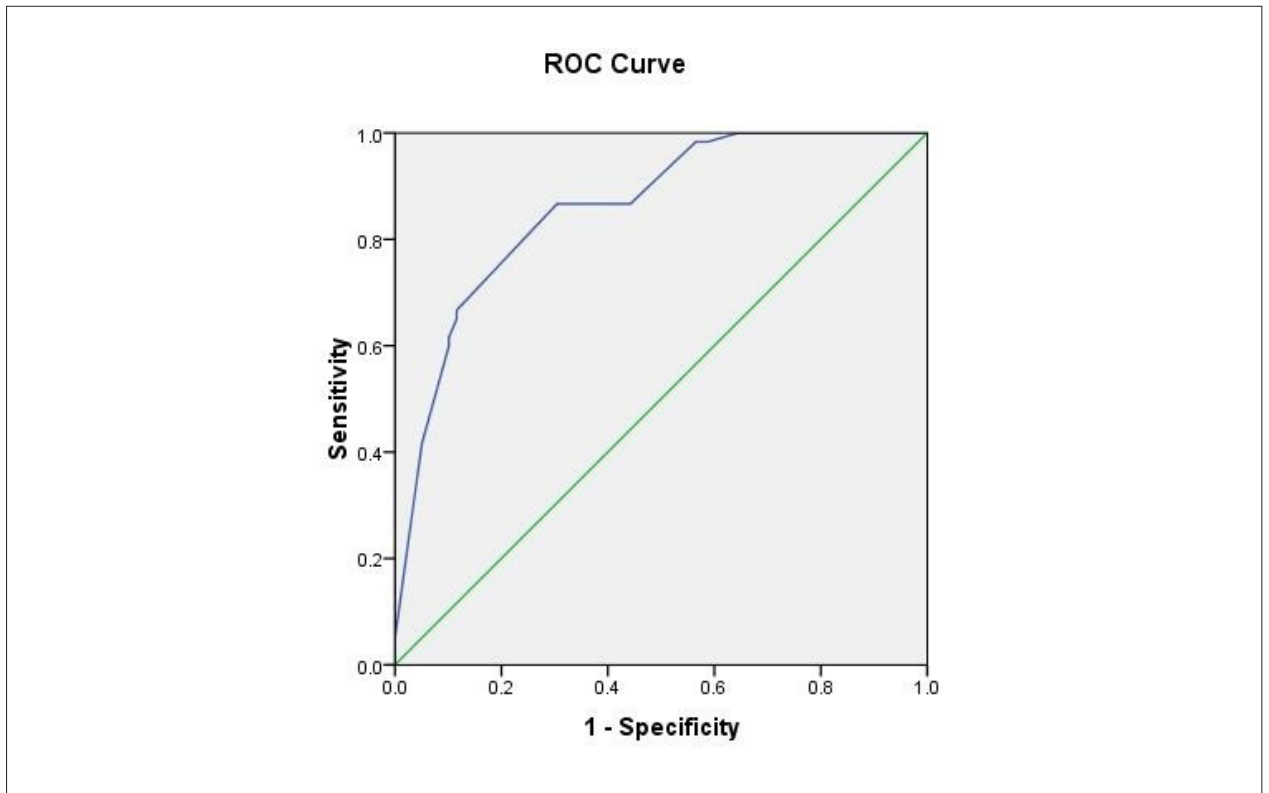**Figure 3 -** *Significant difference between mean P-wave dispersion in the recurrence and non-recurrence groups.*

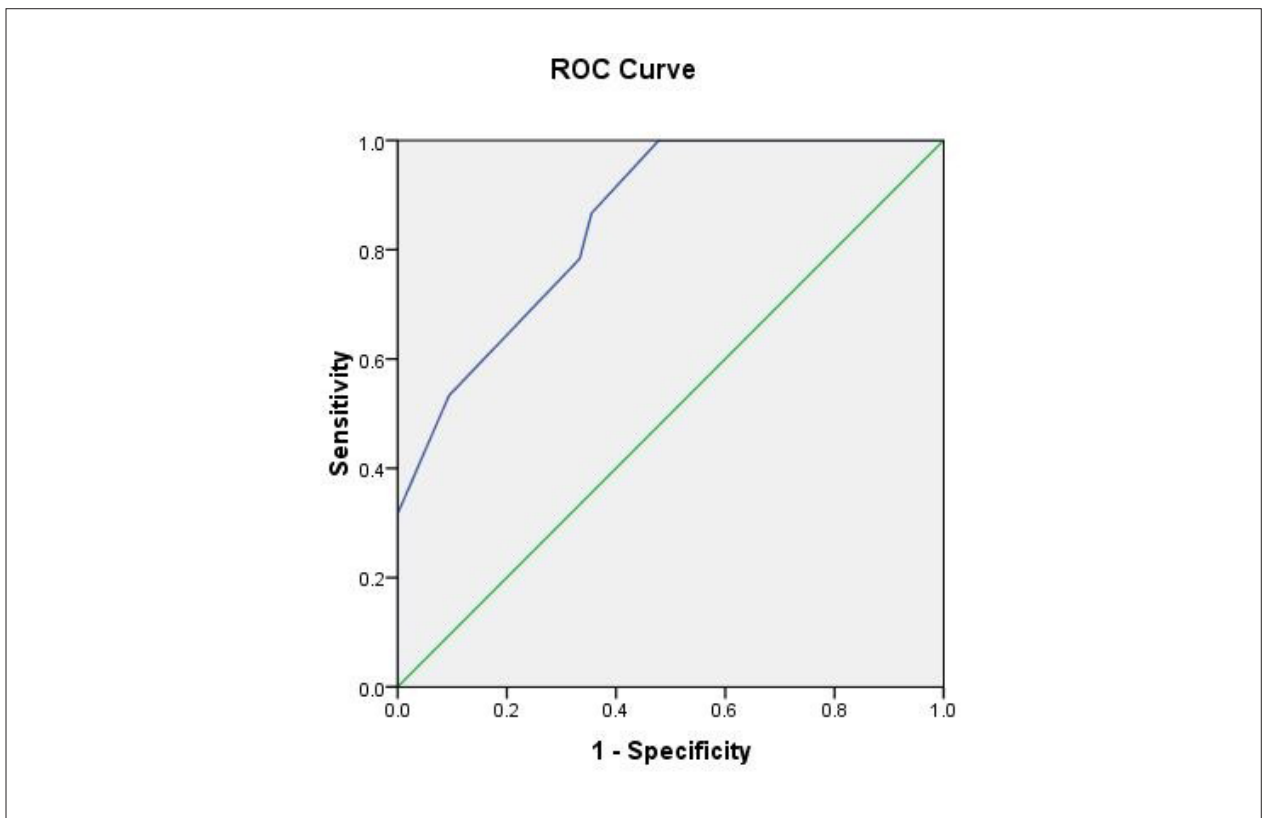**Figure 4 -** *ROC curve for different P-wave duration cut off points.*

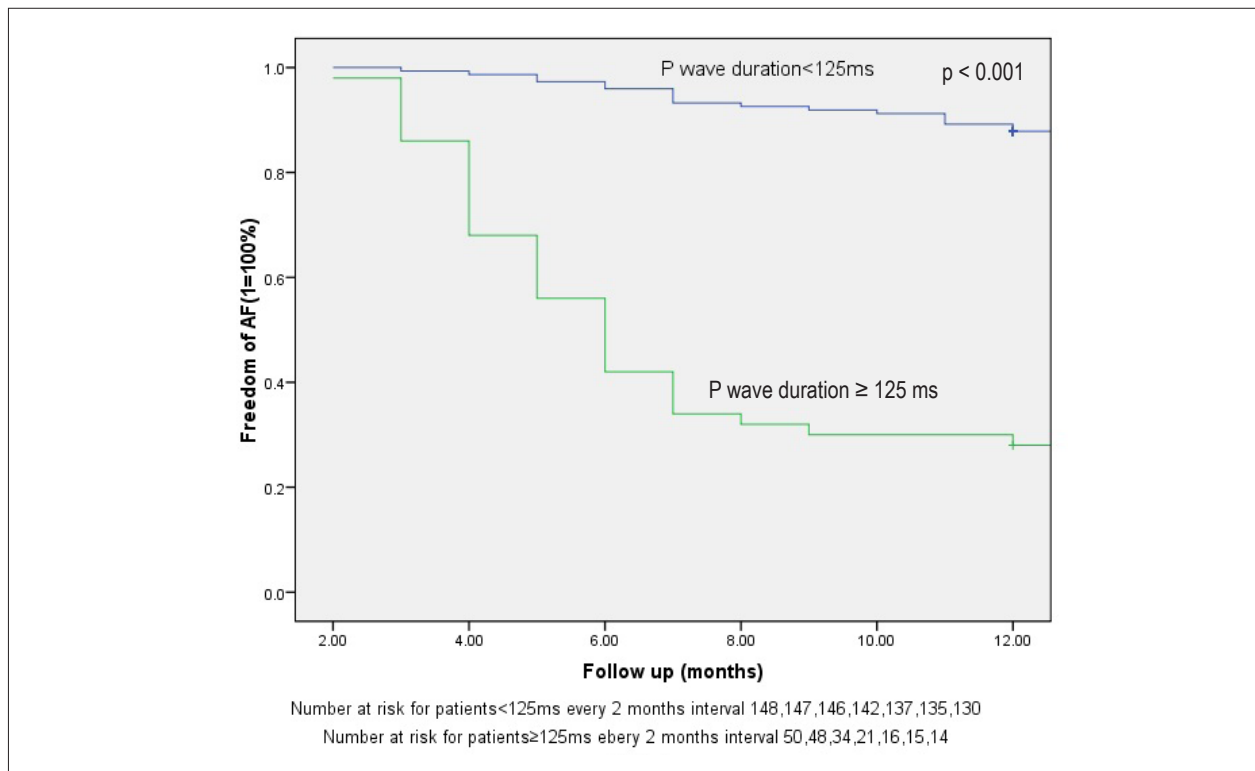**Figure 5 -** *ROC curve for different P-wave dispersion cut off points.*

Figure 6 - *Kaplan–Meier event-free analysis for patients with P-wave duration ≥ 125 ms compared with patients with P wave duration < 125 ms.*
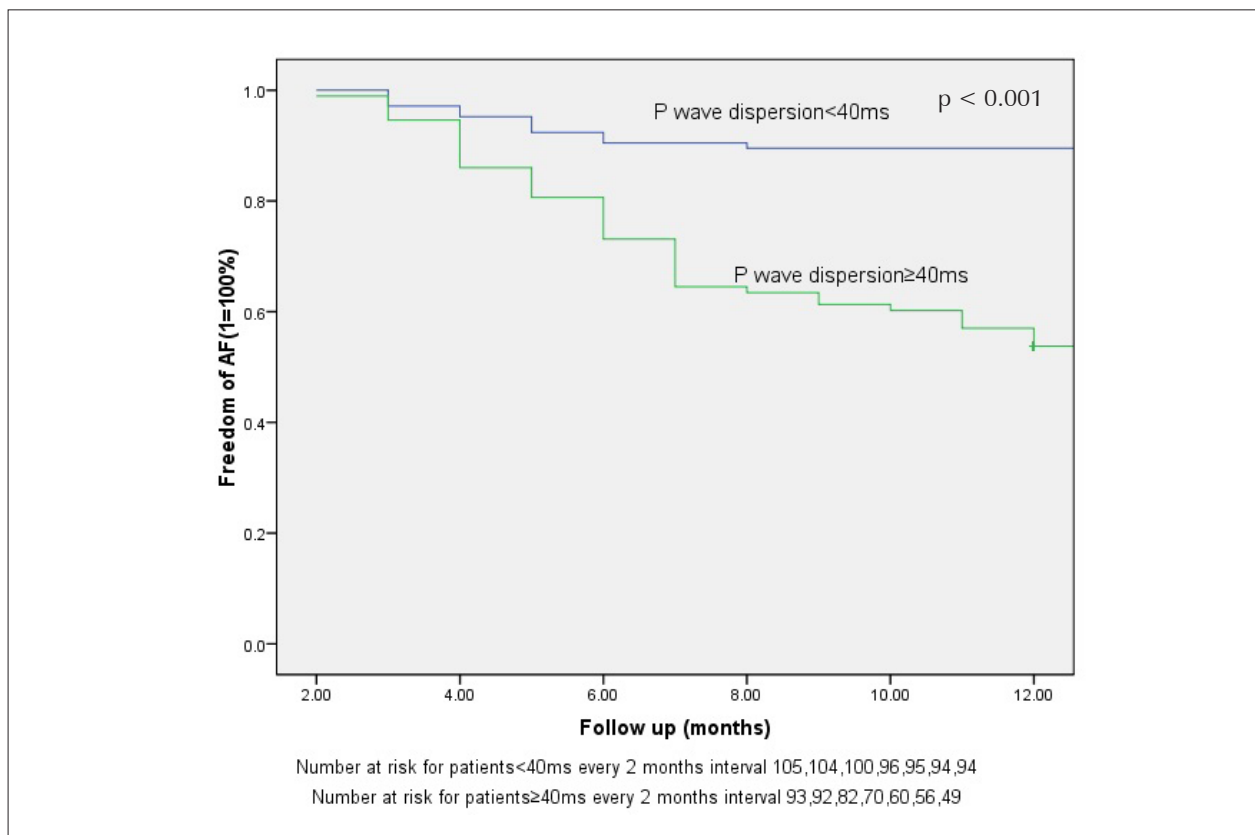

Figure 7 - *Kaplan–Meier event-free analysis for patients with P-wave dispersion ≥ 40 ms compared with patients with P wave dispersion < 40 ms.*

P wave dispersion is still under study and it remains unknown whether it is determined only by heterogeneity of atrial conduction or by other factors as well[18,19]. In our study, we found that P-wave duration ≥ 125 ms and P -wave dispersion ≥ 40 ms are associated with higher rate of AF recurrence post PVI in patients with paroxysmal AF.

Large P terminal force in lead V1 along with prolonged P-wave duration predicts left atrial abnormality, particularly in patients with underlying cardiovascular diseases (sensitivity, 82%; specificity, 40%; positive predictive value, 70%; and negative predictive value, 55%) and its presence indicates the need for further evaluation[20]. Moreover, P-wave terminal force in lead V1 has been independently associated with ischemic stroke after adjustment for other stroke risk factors (odds ratio, 2.32; 95% confidence interval, 1.29-4.18)[21].

The higher prevalence of PTFV1 ≤ -0.04 mm/second in patients with prolonged P-wave duration and wider P-wave dispersion, as noted in our study, probably reflects the associated delayed impulse conduction through already abnormal and enlarged left atria.

Clinical Implication

Our findings indicate that P-wave duration, P-wave dispersion along with P wave terminal force in V1 may be useful markers of AF recurrence post PVI, probably reflecting the extent of the atrial disease and remodeling.

Study Limitation

Pre-ablation antiarrhythmic drug therapy was not discontinued before radiofrequency catheter ablation; drugs such as amiodarone and flecainide may have influenced the recurrence. AF duration data were derived from the patient's history and ECG recordings; thus, the existence of asymptomatic AF cannot be excluded and the duration of AF might not be accurate. The asymptomatic episodes of AF may also confound the results of AF recurrence during the follow-up. The sample size is relatively small and results of the present study should be confirmed by larger prospective trials.

Conclusion

P wave duration ≥ 125 ms, P wave dispersion ≥ 40 ms, as well as a P wave terminal force in V1 ≤ -0.04 mm/sec are good clinical predictors of the already known deleterious sequelae, mainly atrial fibrillation recurrence, post PVI in patients with paroxysmal atrial fibrillation; however, they were not independent from left atrial size and age.

Author contributions

Conception and design of the research: Salah A, Zhou S. Acquisition of data: Salah A, Zhou S, Liu Q, Yang H. Analysis and interpretation of the data: Salah A, Zhou S, Liu Q, Yang H. Statistical analysis: Salah A, Zhou S, Yang H. Writing of the manuscript: Salah A, Yang H. Critical revision of the manuscript for intellectual content: Salah A, Zhou S, Liu Q, Yang H. Supervision / as the major investigator: Salah A, Zhou S. Performing pulmonary vein isolation in EP catheter Lab.: Salah A, Liu Q.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

This study is not associated with any post-graduation program.

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