Review

Utility of P-Wave Dispersion in the Prediction of Atrial Fibrillation

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ABSTRACT: Prevention is important in the case of the most common sustained arrhythmia-atrial fibrillation, with the intention of obtaining both medical and economic benefits. Electrocardiographic parameters have been tested as predictors of atrial fibrillation in different settings, and indices of P-wave have been assiduously studied. Increased P-wave dispersion has been described in different illnesses and correlated with several echocardiographic and clinical parameters. Several studies have demonstrated the relationship between P-wave dispersion with the first episode or paroxysmal atrial fibrillation, as well as with the recurrence of atrial fibrillation after conversion to sinus rhythm. Despite of some critics, the current evidences entitle us to continue studying P-wave dispersion and use it for identifying patients with risk for atrial fibrillation.

KEYWORDS: Atrial fibrillation; Electrocardiography; P-wave dispersion

Introduction

The well-known idea that "it is easier to prevent than to treat" remains valid today, when scientific and technological advances constantly bring us new diagnostic and therapeutic methods. Prevention is also important in the case of the most common sustained arrhythmia-atrial fibrillation (AF), with the intention of obtaining both medical and economic benefits.

Health surveys have shown that atrial fibrillation is underdiagnosed and undertreated, and the incidence of ischemic stroke is increasing. AF is associated with higher rates of death, cardiovascular and thromboembolic events, and is leading to poor quality of life, decreased exercise capacity and aggravation of heart failure.

The most important objective in the management of patients with AF is prevention of thromboembolism. Despite recent advances in understanding the mechanisms of AF, in drug and interventional therapy, AF remains a public health problem, the cost to society is very high and thromboembolic complications related morbidity are often devastating for the individual patient.

Prediction of atrial fibrillation is an important issue because the identification of patients at increased risk could support their close monitoring, more aggressive risk factors therapy, or even anticoagulation in patients at high risk without documented atrial fibrillation [1]. Numerous clinical, electrocardiographic, echocardiographic and biological parameters have been tested as predictors of atrial fibrillation in different settings. Due to the accessibility of the standard electrocardiogram and the mechanisms of AF, it is logical that indices of P-wave have been assiduously studied.

Definition, measurement and reproducibility of P-wave dispersion

P-wave dispersion (PWD) was defined as the difference between the longest (Pmax) and the shortest (Pmin) P-wave duration measured in any of the standard ECG leads [2]. Some studies required visualizing P-wave onset and offset in a minimum of eight to nine leads as an requisite criterion, although usually a minimum of three leads have been used to determine P-wave duration [3].

The methodology used for measurement of P-wave dispersion is not standardized. Previous studies were diverse regarding the leads used, the paper speed and amplification, regarding using a paper or an electronic recording, and even using standard or signal-averaged ECG. 12-lead surface ECG during sinus rhythm is obtained from each patient in supine position following 15 minutes of rest and with room temperature and lighting kept constant (PWD and Pmax are lower in the right lateral decubitus lying position than in other positions) [4].

PWD can be measured manually (with a caliper) or by computerized methods. Manual measurement is best done with an ECG recording at 50mm/s paper speed and the voltage to 10mV/mm or better 20mV/mm. Some authors recommend using a magnifying glass. Computerized analysis requires recording the ECG in a digital form or scanning the printed ECG and then using appropriate software to measure PWD with aide of a high-resolution

computer screen [5]. The intra-observer error of measurements in some studies was as high as 20%, but it was improved by using digitized recordings [6].

The intra-observer relative errors were reduced from 16% to 7% and the inter-observer relative errors were diminished from 17% to 8%, comparing paper and digital measurements, for maximum P-wave duration measurements. Similarly, the relative errors for P-wave dispersion were reduced from 24% to 13% for intra-observer, and from 30% to 14% for inter-observer comparing paper and digital measurement acquisition [7]. The literature has varied in reproducibility metrics reported. Studies have described mean inter-observer percent error ranging from 2% [8] to 14% [7]. Coefficients of variation have ranged from 2% [9] to 5% [10]. Intra-observer reproducibility has been shown to be strong, with correlation coefficients ranging from r=0.78 [11] to r=0.97 [12].

There is no report examining correlations of P-wave indices measured in different electrocardiographic leads [13]. Currently, PWD is calculated from the absolute difference between the shortest and longest P-waves from the surface ECG. Use of adjacent leads with shared vectorial orientation may provide greater sensitivity for distinguishing the inhomogeneity of atrial activation. Future studies should analyze lead heterogeneity in findings, and report results highlighting the lead(s) from which they were derived.

Normal values of P-wave dispersion

Studies on healthy individuals reported a wide range of PWD values. Nussinovitch, in a meta-analysis from 2012 including 6,827 subjects, found highest reported values of 58.56±16.24ms, and lowest of 7±2.7ms, with the weighted mean PWD 33.46±9.65ms; weighted median was 32.2ms [14].

Magnani et al. [15] randomly selected 20 men and 20 women from 10-year age intervals between <25 years to 76-85 years from the Framingham Heart Study Original and Offspring Cohorts, excluding subjects with prevalent cardiovascular disease, hypertension, diabetes or obesity. The total included 295 subjects; eligibility in women >75 years was limited by exclusion criteria. They used a digital measurement technique with demonstrated reproducibility to determine P-wave indices. P-wave indices examined included the Pmax, P-wave mean duration, P-wave duration in lead II and PR durations, dispersion, and the standard deviation of duration. There was an increase in the values of PWD with age. In men less than 25 years old PWD was 27ms; in women less than 25 years old it was 31ms. In men between 76 up to 85 years old, PWD value was 46.7ms; in women with the same age range, the value was 40.0ms.

There are few studies carried out on children, and the number of children is few in these studies. Köse et al. [16] examined electrocardiograms from 232 healthy children (143 boys, 89 girls, aged 7 to 15 years) for determining the normal values of P-wave duration and P-wave dispersion. There was no significant gender difference in maximum P-wave duration (103±9.5ms in males vs. 102±8.4ms in females, p=0.23) or P dispersion (27.2±5.3ms vs. 26.8±6.2ms, p=0.643). Maximum P-wave duration (r=0.23, p<0.01) and P dispersion (r=0.16, p<0.01) were related to age. They concluded that age affects the P-wave duration and dispersion in healthy children, and thus, should be taken into account when maximum P-wave duration and P dispersion are considered for any purpose in healthy children.

Chávez et al [17] studied 515 children between 8 and 11 years of age. The sample was divided into normotensive, pre-hypertensive and hypertensive. Normotensive children (healthy children) were 333 of the total. The mean PWD value for them was 31.85ms.

PWD related with echocardiographic parameters

Several studies have demonstrated that the presence of structural and functional heart alterations at echocardiography in several diseases is related with PWD increased value. An increase in P-wave dispersion was associated with left atrium enlargement, left ventricular hypertrophy, valvular heart disease, congenital heart diseases, diastolic dysfunction, systolic dysfunction/heart failure.

Left atrium structural and functional characteristics measured by echocardiography are established predictors of atrial fibrillation [18].

Saravi et al [19] found that PWD in patients with paroxysmal Atrial Fibrillation (PAF) and normal Left Atrial diastolic diameter (LAD) was longer than in controls with normal left atrial (LA) size (51±9ms vs. 34±8ms, p<0.002). P-wave dispersion increased in patients with PAF (60±14ms vs. 50±7ms, p<0.001) and controls (39±9ms vs. 33±9ms, p<0.004) with increased LAD. In the PAF group, P-wave dispersion correlated with LAD (r=0.40,

p=0.001) and LA diastolic volume (r=0.62, p<0.001). On multivariate logistic regression analysis, only P-wave dispersion retained significance on development of PAF.

Ozyigit et al. [20] studied the relationship between PWD and left atrial volume index (LAVI) measured by 2D and also 3D echocardiography in seventy-three consecutive patients over the age of 65 (mean age: 75±7 years, 17 men). The mean PWD of the study patients was 42.93±11.51ms. P-wave dispersion was significantly correlated with 2D LAVI (r=0.600, p<0.001), 3D systolic LAVI (r=0.688, p<0.001) and diastolic LAVI (r=0.566, p<0.001), and this association was independent of other factors like age, sex, arterial hypertension or left ventricular mass index. A 3D systolic LAVI ≥25mL/m^2 separated patients with PWD ≥40ms with a sensitivity of 82.2%, specificity of 67.9%, positive predictive value of 80.4%, and negative predictive value of 70.4%.

Elansary et al. [21] conducted a study where they included 60 patients with non-hemorrhagic stroke. During one week of continuous intensive care unit monitoring, 30% of patients had PAF (group 1), the remaining 42 patients did not develop PAF (group 2). All patients were subjected to detailed history taking, serial ECGs for calculation of maximum and minimum P-wave duration and PWD, and transthoracic echocardiography for calculation of left atrial volume (LAV), and left atrial volume index (LAVI). It was found that PWD was significantly higher in group 1 in comparison to group 2 (54.1±7.5ms vs. 30.2±7ms, p<0.001). Also, LAV and LAVI were significantly higher in group 1 compared to group 2 (57.1±10ml vs. 40.1±12ml, p<0.001 for LAV; and 28.9±3ml/m^2 vs. 20.1±8ml/m^2, p<0.001 for LAVI). On multivariate logistic regression analysis PWD and LAVI were the most significant independent predictors of PAF.

Gunduz et al. [22] studied 133 patients: 73 with diastolic dysfunction and 60 without. The relationships between PWD and the presence, cause, severity, and echocardiographic measurements of diastolic dysfunction were investigated. P-wave dispersion was 53±9ms in patients with diastolic dysfunction and 43±9ms in the control group (p<0.01). When patients were grouped according to stage of diastolic dysfunction, P-wave dispersion was 48±7ms in stage 1, 54±8ms in stage 2, and 58±9ms in stage 3. As the severity of diastolic dysfunction increased, P-wave dispersion increased but the difference did not reach statistical significance (p>0.05). When the cause of diastolic dysfunction was considered, P-wave dispersion was 53±8ms in patients with ischemic heart disease and 52±9ms in patients with left ventricular hypertrophy (p>0.05).

Donoiu et al. [23] studied 86 patients (52 males, aged between 35-67 years). There were 47 patients with diastolic dysfunction and 39 without. By standard transthoracic echocardiography they investigated the presence and degree of diastolic dysfunction, classified as: stage 1-prolonged relaxation pattern, stage 2-pseudonormalization pattern, and stage 3-restrictive pattern. The relationships between P-wave dispersion and echocardiographic measurements of diastolic dysfunction were analyzed. P-wave dispersion was 62±12ms in patients with diastolic dysfunction and 49±10ms in those without (p<0.01). The maximum P-wave duration was 118±9ms in patients with diastolic dysfunction vs. 107±8ms in the control group (p<0.05). The minimum P-wave duration was 64±11ms vs. 63±10ms (not significant). When patients were grouped according to the stage of diastolic dysfunction, P-wave dispersion was 52±8ms in stage 1, 58±9ms in stage 2, and 64±13ms in stage 3.

İnci et al. [24] studied 26 pregnant women with preeclampsia and 24 age-matched pregnant women without preeclampsia (control group). Atrial electromechanical coupling and intra-atrial and inter-atrial electromechanical delay (EMD) were measured using tissue Doppler echocardiography. They found atrial electromechanical coupling lateral and septal durations were significantly longer in the preeclampsia group than in the control group (74.6±8.1ms vs. 62.3±5.3ms, p<0.001; and 59.7±5.3ms vs. 56.2±4.9ms, p=0.005, respectively). The duration of inter-atrial electromechanical delay and intra-atrial electromechanical delay in the pre-eclampsia group was significantly longer than in the control group (25.4±4.6ms vs. 13.2±3.9ms, p<0.001; and 10.5±1.9ms vs. 7.1±1.2ms, p<0.001, respectively). PWD was significantly higher in patients with preeclampsia (43.1±9.1ms) than in the controls (37.6±7.9ms; p=0.008). There was a significant correlation between PWD and interatrial EMD and intra-atrial EMD (r=0.46, p<0.001; and r=0.39, p<0.001, respectively).

An increased PWD associated with echocardiographic changes has also been described in other situations.

Tosu et al. [25] when studying the relationship between P-wave dispersion in hypertensive patients, mentioned PWD was found to be significantly increased in the non-dipper than in the dipper group (56.0±5.6ms vs. 49.1±5.3ms, p<0.001). Correlation analysis demonstrated presence of moderate but significant correlation between P-wave dispersion and left ventricular mass index (r=0.412, p=0.011), isovolumetric relaxation time (IVRT) (r=0.290, p=0.009), deceleration time (E/A rate) (r=0.210, p=0.052) and interventricular septum thickness (r=0.230, p=0.04). Chávez et al. [26] found significant correlation between PWD and mean blood pressure for pre-hypertensive and hypertensive children, i.e., r=0.32, p<0.01 and r=0.33, p<0.01, respectively. Significant correlation between PWD and the left atrial area (r=0.45, p<0.01) was found too. Chávez et al. [17] found a relationship between PWD and left ventricular hypertrophy in hypertensive as well as pre-hypertensive children. Huang et al. [27] found PWD is increased in association with renal outcomes in chronic kidney disease.

During acute myocardial infarction (AMI), P-wave indices are modified due to hemodynamic changes related with heart muscle injury; Acar et al. [28] conducted a prospective study which included 33 patients with AMI successfully revascularized by percutaneous coronary intervention (PCI) who underwent cardiac rehabilitation (CR). Left ventricular ejection fraction (LVEF) was measured by biplane Simpson's method. Left atrium (LA) volume and PWD was calculated. Aortic elasticity parameters were measured. LVEF was better after CR. The systolic and diastolic blood pressures decreased after CR, these differences were statistically significant. With exercise training, LA volume decreased significantly. PWD values were significantly shorter after the CR program (PWD after CR was 44±5ms). Aortic strain and distensibility increased and aortic stiffness index was decreased significantly. Aortic stiffness and left atrial volume showed a moderate positive correlation with PWD (r=0.52, p=0.005; r=0.64, p<0.001, respectively).

Related with valvular heart diseases, Guntekin et al. [29] found that P-wave duration and PWD were significantly associated with mitral valve area and mean mitral gradient. Although correlation between PWD and left atrial size was not significant at baseline it became significant after increase in left atrial size during their follow-up. Turhan et al. [30] found progressive shortening of PWD after percutaneous mitral balloon valvuloplasty. They explained this finding by the decrease in sympathetic activity and the regression of the pathologic changes in the atrial wall which result in more homogeneous and organized conduction of sinus impulses. Erbay et al. [31] found a significant correlation between maximum P-wave duration and PWD with mean diastolic gradient of the mitral valve. They also showed that long-term beta-blocker therapy caused a significant decrease in maximum P-wave duration and PWD in patients with rheumatic mitral stenosis.

Tuluce and colleagues [32], in a study on 70 patients with hypertrophic cardiomyopathy without a history of atrial fibrillation compared with 70 controls, demonstrated that PWD was correlated with various echocardiographic indices of left atrial (LA) dimensions and function like: LA maximum, LA Volume preA (left atrial volume before atrial contraction), LA Volume minimum, LA Volume maximum, LA expansion index, LA total emptying fraction and Lateral PA' time (interval from the onset of the P-wave on surface ECG to the peak of the late diastolic wave). In this study, PWD was not related to intra-and inter-atrial dyssynchrony.

PWD in the prediction of first AF episode or/and Paroxysmal Atrial Fibrillation

Yoshizawa et al. [33] studied patients with new onset AF from their digitally stored ECG database, and the P-wave morphologies were analyzed in the most recent ECG recording of sinus rhythm preceding new onset AF within 12 months. The duration and amplitude of P-waves were analyzed in 12 leads and compared between the 2 groups with the other clinical parameters. The study population consisted of 68 patients with new-onset AF and 68 age and sex-matched controls. Multivariate analysis revealed that the P-wave amplitude in leads II and V1 (0.157±0.056mV vs. 0.115±0.057mV, p=0.032, and 0.146±0.089mV vs. 0.095±0.036mV, p=0.002) and PWD (56.9±14.8ms vs. 33.5±12.9ms, p=0.001) were significant independent factors for the prediction of new-onset AF. By using these factors, new-onset AF could be predicted with a sensitivity of 69.1% and specificity of 88.2%. The authors conclude that P-wave analysis is useful for predicting new onset AF.

In another study, PWD was shown to be a significant predictor of frequent symptomatic

AF paroxysms but only in the univariate analysis [34].

Elansary et al. [21] during one week of continuous intensive care unit monitoring, found 30% of patients had PAF and they found that PWD was significantly higher in group who developed PAF in comparison to group 2 who did not developed PAF (54.1±7.5mm vs. 30.2±7mm, p <0.001).

PWD has proven to be a sensitive and specific ECG marker for the best separation between patients with history of paroxysmal lone AF and healthy subjects. A cutoff value of 40ms proved to have a sensitivity of 83%, a specificity of 85% and a positive predictive accuracy of 89% for the identification of patients with history of paroxysmal lone AF [34].

PWD in prediction of AF recurrence after conversion

Budeus et al. [35] studied a bidirectional P-wave signal-averaged ECG among 49 patients (35 men) for predicting atrial fibrillation recurrence 24 hours after electrical cardioversion. Each patient was followed up for at least 6 months. A recurrence of atrial fibrillation was observed in 23 patients (47%) after a mean of 9.2 days (range 2-92 days). There was no difference in organic heart disease or in the use of drugs. The filtered P-wave duration was longer significantly (136.2±20.1ms vs. 119.5±19.8ms, p<0.0001) and the root mean square voltage of the last 20ms of the P-wave was lower (2.77±1.10mV vs. 4.17±1.43mV, p<0.0001) in patients with a recurrence of atrial fibrillation. A cut-off point of filtered P-wave duration ≥126ms and root mean square voltage 20 was ≤3.1mV achieved a specificity of 69%, a sensitivity of 74%, a positive predictive value of 68% and a negative predictive value of 75%.

PWD may help predict in the first minutes after electrical cardioversion of long-lasting AF. Boriani et al. [12] investigated the association of different PWD values and recurrence of AF in the short and longer term in 37 patients and reported significantly higher PWD values in patients with short-term AF recurrence (≤1 month). Furthermore, they found that PWD values >25ms were associated with a higher short-term relapse rate. But no significant relation was present in the long-term in their study. Perzanowski et al. [36] reported that a PWD value of 80ms or greater was both a univariate and independent predictor for AF recurrence after cardioversion.

Militaru and Donoiu [37], conducted a prospective study which enrolled 100 patients (55 men, mean age 68.21±9.26 years) with a history of documented atrial fibrillation in the last 12 months, and that were currently in sinus rhythm. They found the atrial fibrillation recurrence was documented in 27 patients. The comparison between two studied groups showed: left atrium dimensions were significantly greater in patients with atrial fibrillation recurrence (LA diameter: 49.45±9.14mm vs. 42.54mm±6.93mm, p=0.008; LA volume: 88.53±34.74ml 80.13±30.12ml, p=0.03; LA area 32.16±12.8cm^2 vs. 27.11±18.11cm^2, p=0.05). They did not find a correlation between P-wave duration and AF. AF recurrence was more frequent in patients with longer duration of previous atrial fibrillation episode, with increased left atrium size and left ventricular mass, and it was correlated with the filtered P-wave duration and Integral of the P-wave at signal averaged ECG.

Controversies regarding PWD

Zimmer et al., in a correspondence [38] based on a study presented at EHRA/Europace Conference in Milan 2015, questioned the reality of this parameter considering that P-wave dispersion is in fact the effect of an imprecise measurement given by the presence of an isoelectric fragment of the P-wave in some leads as a consequence of the projection of the momentary electrical vector. They studied 94 patients by measuring the P-wave duration and dispersion with paper speed of 50mm/s, enhancement 8×, and at paper speed of 200mm/s, enhancement 128-256×. The measurement with 8× amplification gave the P-wave dispersion of 45.1ms whereas measurement with 128-256× gave the result of 1.2ms. In 82% of the cases with maximum magnification the PWD was equal to zero ms. The authors suggest that the positive results of PWD in different clinical settings were in fact derived from P-wave duration only, which is a marker of left atrial enlargement, and conclude that the P-wave dispersion, as it is currently defined, is a measurement artefact.

Despite this, we continue to believe there is sufficient proof supporting the PWD importance in the clinical practice and the continuation of research. In a recent review Pérez-Riera et al. [39] list the possible scenarios when PWD could be present and consider PWD is an important and easy-to-measure parameter that indicates a greater tendency to the appearance of supraventricular arrhythmias, particularly PAF. A PWD value more than 40ms is considered increased but it has been observed both in

physiological and pathological scenarios. Increased PWD in elite athletes explains the higher incidence of AF in this population. A task force to determine definitively the PWD normal limits is mandatory. The molecular substrate involves driving changes affecting the atrial tissue with involvement of numerous sarcolemmal ion channels, gap junctions, leading to degrees of fibrosis in the extracellular tissue of the atria, insufficient blood supply, significant anisotropic myoelectric activity, thin wall thickness and consequent expansion tendency, all well-known electrophysiological alterations. The authors consider PWD essential for P-wave analysis.

Conclusion

P-wave dispersion is a valuable tool for predicting atrial fibrillation and it could support means to control several risk factors of atrial fibrillation and prevent its devastating clinical outcome.

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