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REVIEW

P Wave Dispersion: A Valuable Non-Invasive Marker of Vulnerability to Atrial Arrhythmias

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ABSTRACT

The prolongation of intraatrial and interatrial conduction time and the non-homogeneous propagation of sinus impulses are well known electrophysiologic characteristics in patients with atrial arrhythmias and especially paroxysmal atrial fibrillation (AF). Previous studies have demonstrated that individuals with clinical history of paroxysmal AF show a significantly increased P wave duration in 12-lead surface electrocardiograms (ECG) and signal-averaged ECG recordings. The inhomogeneous and discontinuous atrial conduction in patients with atrial arrhythmias has been studied, during the last years, with a new ECG index, P wave dispersion. P wave dispersion is defined as the difference between the longest and the shortest P wave duration recorded from multiple different surface ECG leads. Extensive clinical evaluation of P wave dispersion has been performed in the assessment of the risk for AF in patients without apparent heart disease, in hypertensive patients, in patients with coronary artery disease, in patients undergoing coronary artery bypass surgery, in patients with congenital heart diseases, as well as in other groups of patients suffering from various cardiac or non-cardiac diseases. P wave dispersion has proven to be a sensitive and specific ECG predictor of AF in the various clinical settings. However, the methodology used for the calculation of P wave dispersion has not been standardized so far and more efforts to improve the reliability and reproducibility of P wave dispersion measurements are needed. In conclusion, P wave dispersion constitutes a significant contribution to the field of non-invasive electrocardiology and seems to be quite promising in the field of AF prediction.

KEY WORDS: *P wave duration, P wave dispersion, atrial fibrillation, atrial conduction*

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INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. One of the mechanisms implicated in its pathogenesis is the presence of multiple, randomly reentrant wavelets that propagate, become extinct, or fractionate within the atrial tissue. The correlation between the presence of atrial conduction abnormalities and the induction of paroxysmal AF has been well documented [1]. Although markedly prolonged intra- and interatrial conduction time can be recognized by prolongation of the surface P wave duration, the question arises as to whether non-homogeneous atrial conduction could be identified by variation in P wave duration between differently oriented surface ECG leads. Regional delays in atrial depolarization might produce a heterogeneous P wave duration because surface P waves in different locations could

be affected to a different extent by regional changes in atrial activation times. In support of this local hypothesis, a previous study has postulated that the electrical activity in the surface ECG closely correlates with the conduction in specific parts of the atria [2]. The local hypothesis explaining the interlead variation in P waves duration, that is the so-called P wave dispersion, competes with the global hypothesis explaining the variation in surface ECG measurements with different projections of a common P-wave vector. Whether the interlead variation in P waves duration (P wave dispersion) could be attributed to an underlying heterogeneity of atrial conduction (a local effect), or to a variable projection of a single depolarization vector onto different ECG leads (a projection phenomenon) and/or to imprecision of measurement when the P wave amplitude is low and the P wave onset and offset are difficult to define, is not justified from the available, up to now, body of evidence. The present review aims to inform clinicians about the already gained experience from the use of P wave dispersion. Numerous studies from many centers have contributed to elucidate the rationale and clinical applicability of this new ECG index (Table 1).

Table 1. Predictive Role of P Wave Dispersion in Patients Vulnerable to Atrial Fibrillation

Study	Patients (No.)	Heart Disease	Electrocardiograph		Cutoff Value (ms)	Sens. (%)	Spec. (%)
			Type	Leads			
Dilaveris P. Am Heart J 1998	100	No	Thermal	12	40	83	85
Kloter Weber U. Eur Heart J 1998	107	Post-CABG	Thermal	12	-	-	-
Gialafos J. A.N.E. 1999	125	No	Digital	12	40	81	80
Dilaveris P. PACE 1999	110	CAD	Digital	12	-	-	-
Chang CM. Int J Cardiol 1999	120	Post-CABG	Thermal	12	-		
Yamada T. Eur Heart J 1999	112	HD	Signal-averaged	16	-	-	-
Kubara I.J Cardiovasc Electrophysiol 1999	63	HD	Signal-averaged	16	-	-	-
Dilaveris P. PACE 1999	60	HD	Digital	12	-	-	-
Dilaveris P. J Hypertens 1999	110	Hypertension	Digital	12	-	-	-
Dilaveris P. PACE 2000	88	HD	Digital	12	-	-	-
Tukek T. Am J Cardiol 2000	54	HD	Thermal	12	-	-	-
Ciaroni S. Am Heart J 2000	97	Hypertension	Thermal	12	40	74	81
Aytemir K. PACE 2000	160	No	Thermal	12	36	77	82
Gilligan D. PACE 2000	48	HD	Thermal		-	-	-
Andrikopoulos G. PACE 2000	110	No	Thermal/Digitized		40	83	85
Fan K. Circulation 2000	132	Post-CABG	Thermal		-	-	-
Rosiak M. A.N.E. 2002	130	AMI	Thermal	12	25		
Dogan A. J Electrocardiol 2003	96	HD	Thermal	12	47	82	83
Kose S. Clin Cardiol 2003	22	HCM	Thermal	12	46	76	82
Dogan A. Am J Cardiol 2004	64	HD	Thermal	12	46	89	96
Hallioglu O. A.N.E. 2004	25	CTF	Digital	12	35	83	89
Ozdemir O. Int J Cardiol 2004	27	HCM	Thermal	12	52.5	96	91
Wong T. Circulation 2004	33	Post-Fontan	Thermal/Digitized	12	66	79	79
Perzanowski C. J Electrocardiol 2005	81	HD	Thermal	12	80	27	88
Boriani G. Int J Cardiol 2005	37	HD	Digital	12	25		
Aras D. Int J Cardiol 2005	193	Hyperthyroidism	Thermal	12	37.5	90	85
Amasyali B. A.N.E. 2006	72	Post-ablation AVNRT	Digital	12	35.5	90	85

AMI = acute myocardial infarction; AVNRT = atrioventricular nodal reentrant tachycardia; CABG = coronary artery bypass surgery; CAD = coronary artery disease; CTF = corrected tetralogy of Fallot; HCM = hypertrophic cardiomyopathy; HD = organic heart disease; Sens. = sensitivity; Spec. = specificity.

CLINICAL USE OF P WAVE DISPERSION

In a first attempt to correlate the asynchronous atrial conduction with an isoelectric interval derived from surface ECG, Buxton and Josephson [3] introduced the isoelectric interval, which was derived by subtracting the longest P wave duration in the standard limb lead from the total P wave duration, measured from the earliest onset to the latest end of the P wave in any of the simultaneously recorded leads I, II, and III. This isoelectric interval was found to be significantly higher in patients with AF history than in controls, although it was not proven to be a sensitive or specific ECG predictor of AF [3]. In another study [4], it was postulated that the regional differences in the atrial activation found in patients with AF history could be reflected in the temporal variation across the leads of the filtered orthogonal ECG.

In later studies, a standard 12-lead ECG was generally used to obtain the quantity of the largest information concerning the interlead variation in the P wave duration. In many of the original studies, P wave duration and P wave dispersion were calculated from 12-lead ECGs recorded on standard paper printed ECGs. P wave dispersion was defined as the difference between the shortest and the longest P wave duration in any of the 12 ECG leads [5]. In the same study, P wave dispersion was found to be significantly higher in 60 patients with paroxysmal lone AF (49±15ms) than in 40 healthy controls (28 ±7ms, $p < 0.0001$) [5]. P wave dispersion was proven to be a sensitive and specific ECG marker for the best separation between patients with history of paroxysmal lone AF and healthy subjects [5]. A cutoff value of 40msec 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 [5]. Moreover, during a 12-month follow-up period, the relative risk of a AF recurrence was 2.37 for a P wave dispersion value ≥40 ms [5]. In another publication [6], P wave dispersion was shown to be a sensitive and specific ECG predictor of paroxysmal lone AF. In the same study, P wave dispersion showed a significant correlation with maximum P wave duration ($r = 0.702$, $p < 0.001$) and a weak, although significant, association with age ($r = 0.270$, $p < 0.001$) [6]. In another study, P wave dispersion was shown to be a significant predictor of frequent symptomatic AF paroxysms but only in the univariate analysis [7]. In the same study, P wave dispersion was found to be significantly correlated positively with maximum P wave duration ($p < 0.001$) and negatively with minimum P wave duration ($p = 0.06$). It is obvious that, when beyond P wave dispersion both maximum and minimum P wave duration are incorporated as covariates in multivariate regression models, P wave dispersion may not remain an independent predictor of AF in the multivariate analysis [7,8]. The predictive roles of P wave dispersion after cardioversion of AF [9-14], as well as its difference in accordance to the classification of AF episodes [15-17], have been verified in several different studies.

Value of P wave dispersion in hypertensive patients

P wave dispersion, adjusted P wave dispersion, that is P wave dispersion corrected according to the number of measurable leads, and the standard deviation of the P waves duration were all found to be significantly higher in 50 hypertensive patients with history of paroxysmal AF as compared to 60 hypertensive patients with no previous history of AF [18]. Each of these 3 indices was found to be significantly related to the other 2 (correlation coefficients ranging from 0.926 to 0.998) and all of them were found to be significantly associated positively with maximum P wave duration (correlation coefficients ranging from 0.585 to 0.719) and negatively with minimum P wave duration (correlation coefficients ranging from –0.289 to –0.460). In another study, P wave dispersion was also found to be significantly increased (48±14 ms) in 19 hypertensive patients developing AF during a mean follow-up of 25±3 months when compared to 78 hypertensive patients who showed no AF episodes during the follow-up period (30±8 ms, $p < 0.01$) [19]. In the multivariate analysis, P wave dispersion was an independent predictor for the onset of AF in the hypertensive population (odds ratio 2.81, $p < 0.001$), even after correction for age (odds ratio 1.63, $p < 0.001$). No significant correlation was found in the same study between P wave dispersion and the blood pressure levels, the left atrial dimension, the left ventricular mass and the velocity of the A wave or the E/A ratio of the diastolic mitral flow [19]. Another study also verified the ability of P wave dispersion to predict AF in hypertensive patients [20].

Assessment of P wave dispersion in patients undergoing open-heart surgery

In one study, it was demonstrated that P wave dispersion was significantly increased in 47 patients developing AF after coronary artery bypass surgery (49±12ms) as compared to 60 patients with no postoperative AF (41±12ms, $p = 0.0009$) [8]. P wave dispersion was found to be a significant predictor of postoperative AF but only in the univariate analysis [8]. Other studies have also postulated the predictive ability of P wave dispersion in patients undergoing by-pass surgery [21-24].

Value of P wave dispersion in coronary artery disease patients

The effects of myocardial ischaemia on P wave dispersion were evaluated in 95 patients with documented coronary artery disease and spontaneous angina pectoris [25]. P wave dispersion was found to be significantly increased during the anginal episodes irrespective of the presence of history of a previous myocardial infarction [25]. Furthermore, P wave dispersion showed higher values during the anginal episode in patients with left ventricular dysfunction, independently of the presence of a previous myocardial infarction [25]. Increased P wave dispersion values were demonstrated in patients after acute myocardial infarction [26-28], in patients with syndrome

X [29], or those receiving reperfusion therapies [30].

Estimation of P wave dispersion in patients with valvular heart diseases

The presence of increased P wave dispersion values in patients with valvular heart diseases [31-33], as well as the effects of medical treatment [33], or of balloon valvuloplasty on P wave dispersion in patients with mitral stenosis [31], have also been demonstrated.

Assessment of P wave dispersion in patients with congenital heart diseases

The predictive ability of P wave dispersion in patients with congenital heart diseases, before and after surgery was assessed in several studies [34-38]. Wong et al. [37] demonstrated that patients with atrial tachyarrhythmias late after Fontan operation have longer P-wave duration and P-wave dispersion and larger right atrial dimension than those without the arrhythmias; these abnormalities are interrelated. The authors of that study concluded that their observation represents an atrial mechano-electrical remodeling phenomenon in parallel to an increase in arrhythmia propensity in this vulnerable population.

Autonomic tone influences on P wave dispersion

An insight on the modulatory effects of the autonomic tone changes on P wave dispersion were previously given by Tukek and colleagues [39]. They showed that the Valsalva maneuver normalized the increased values of P wave duration and P wave dispersion found in patients with history of paroxysmal AF and, on the other hand, increased P wave duration and dispersion in normal subjects [39]. These findings may imply that the Valsalva maneuver decreases the heterogeneity of atrial impulse propagation due to changes in the atrial size and electrophysiology [39]. The effect of Valsalva maneuver on P wave dispersion was also assessed by Altunkeser et al [40], while the effect of exercise on this index was reported by Yigit et al. [41].

Association of P wave dispersion with echocardiographic indices

The association of P wave dispersion with left atrial size and function [42], left atrial appendage function [43], and left ventricular diastolic function [44,45] were provided by several investigators. In a recent study [46], Ozer et al. showed that interatrial electromechanical delay gets longer in mitral stenosis patients and is correlated with P wave dispersion.

P wave dispersion in other cardiac or non-cardiac diseases

The role of P wave dispersion for the prediction of AF episodes was also evaluated in patients with chronic obstructive pulmonary disease [47], in patients with hypertrophic cardiomyopathy [48,49], in patients with hyperthyroidism [50,51], after radiofrequency catheter ablation of atrioventricular reentrant tachycardia [52,53] or atrioventricular nodal reentrant tachycardia [54], in patients with end-stage renal failure undergoing hemodialysis [55,56], or in patients under chemotherapy regimen [57].

P wave dispersion in normal subjects and associations with demographic characteristics

The normal values of P wave dispersion and other P wave analysis indices derived from digital 12-lead ECGs were defined in a large population of 1,353 young healthy men. All ECG indices were significantly associated with the R-R interval, and with each other [58]. Moreover, the effect of obesity [59], acute caffeine ingestion [60], or alcohol intake [61,62], on P wave dispersion in healthy subjects, as well as its seasonal changes [63], have been evaluated in several studies. Moreover, the differences in these ECG predictors of atrial rhythm disturbances between trained athletes and control subjects were demonstrated by Karakaya et al. [64].

The effects of pacing on P wave dispersion

Single-site atrial, dual-chamber, as well as septal pacing showed controversial results concerning the provoked changes in paced P wave dispersion and its power to predict AF. [65-69]. High right atrial (Bachman bundle) pacing failed to alter P wave dispersion, whereas P wave duration and P wave dispersion were not predictive of AF after pacemaker implantation, in two studies [66,68]. However, the effects of multi-site atrial pacing on P wave dispersion were more promising. Gilligan et al. showed that although P wave duration was markedly reduced by biatrial pacing in patients with and without history of AF and/or flutter, P wave dispersion was unaffected [70]. On the contrary, Fan and colleagues showed that biatrial pacing, which was more effective in the prevention of postoperative AF after coronary artery bypass surgery than single-site atrial pacing, resulted in the most significant reduction in mean P wave dispersion (42±8%) when compared with single-site (left atrial pacing 13±6%, right atrial pacing 10±9%; $p < 0.05$ for biatrial versus left or right atrial pacing) atrial pacing [71]. Furthermore, P wave dispersion was only reduced in those patients whose AF was prevented by pacing therapy [71,72].

Dispersion of the filtered P wave duration

In two studies, it was demonstrated that patients with clinical history of paroxysmal AF show a significantly increased dispersion of the signal-averaged P wave duration on the precordial body surface [73,74]. The dispersion of the filtered P wave duration was calculated as the difference between the longest and the shortest filtered P wave recorded from 16 different precordial unipolar leads, and it was found to be the most sensitive and specific ECG marker for the prediction of AF [73,74]. A significant linear relationship between the

dispersion of the filtered P wave duration and filtered P wave duration ($r = 0.71$, $p < 0.0001$) was found in one of the 2 studies [74]. In the same studies, the dispersion of the signal averaged P wave duration was used to assess the efficacy of the antiarrhythmic drugs pilsicainide and disopyramide. It was found that the dispersion of the filtered P wave decreases after the administration of a single oral dose of the antiarrhythmic drug in those patients in whom the antiarrhythmic drug is going to be effective in the suppression of AF attacks and increases in patients showing multiple recurrences of AF [73,74]. The criteria of decreased dispersion of filtered P wave duration due to a single dose administration of pilsicainide, gave a sensitivity of 88%, a specificity of 65%, a positive predictive value of 54% and a negative predictive value of 92% for the prediction of drug efficacy [73]. Moreover, assessment of P wave dispersion and P wave duration from signal-averaged ECGs was able to predict AF in patients with acute myocardial infarction in the study of Rosiak and colleagues [26].

METHODOLOGICAL CONSIDERATIONS FOR THE EVALUATION OF P WAVE DISPERSION

P wave dispersion constitutes a recent contribution to the field of noninvasive electrocardiology and seems to be quite promising in the field of AF prediction. However, the methodology used to obtain the interlead variation in the P waves duration differed between the various studies. Thermal, digital, and signal-averaging ECG systems have been used to evaluate P wave dispersion which was measured manually either on paper or on a high-resolution computer screen from 12 or 16 ECG leads.

Although alternative methods might exist, the data analyzed in previous studies show that, manual measurement of ECG patterns like the P wave duration and P wave dispersion should be preferably performed either with signal-averaging ECG systems or with digital ECG recordings displayed on a high resolution computer screen [75]. To optimize the P wave determination and the calculation of P wave dispersion from 12-lead surface ECGs, we use a commercially available computer-based ECG system which enables us to record all 12 ECG leads simultaneously at a sampling rate of 1200 Hz and a 12bit A/D conversion rate [75]. A sufficient sampling rate and amplitude resolution are necessary for a high-resolution ECG analysis. From each lead, the average complex is calculated by the MEANS (Modular ECG Analysis) system [76]. Individual average complexes are stored digitally and displayed on a high resolution computer screen. Each lead is separately magnified with a magnification of 160mm/s and 60mm/mV [75]. The start and the end of the P wave are marked with the cursor on a high resolution computer screen. If the baseline noise is $>10\mu V$ and/or the peak to isoelectric line-P wave amplitude $<15\mu V$, the lead is excluded from the analysis. No attempt is made to correct for missing leads and an ECG with ≤ 9 measurable leads is excluded from the analysis [75]. After the measurement of all measurable P waves is completed, P wave dispersion is calculated as the difference between the longest and the shortest P wave in any of the measured ECG leads.

In a previous study [75], P wave dispersion has shown consistent clinically relevant differences between patients with history of paroxysmal AF and healthy controls irrespective of the method used for P wave measurement. A rather poor agreement was found in the same study between the manual on screen versus on digitizing board measurements of P wave dispersion and an acceptable agreement between the different methods was shown concerning the measurement of the maximum, the mean P wave duration and the standard deviation of the P waves duration [75]. Moreover, the mean intraobserver error of measurements was found to be high, around 20%, for P wave dispersion with no differences between patients with AF history and healthy controls. Smaller intraobserver relative errors were consistently found during on screen measurement of P wave dispersion. Similarly high interobserver relative errors of P wave dispersion measurements were also demonstrated with smaller errors during on screen measurement of P wave dispersion [75].

However, other studies have demonstrated a low error of the measurement of P wave dispersion on paper printed ECGs [6,8,19,39]. We believe that, P wave dispersion measurement performed manually on paper printed ECGs obtained at a standard signal size and paper speed is of questionable accuracy and reproducibility [75,77]. To improve the precision of measurement of P wave dispersion from 12-lead ECGs recorded and stored on paper, scanning and digitizing ECG signals from paper records using an optical scanner is a feasible and accurate alternative method [78].

The dispersion of the signal-averaged P wave duration on the precordial body surface constitutes an alternative approach to the estimation of the regional differences in atrial activation and conduction. The dispersion of the filtered P wave duration has been calculated as the difference between the longest and the shortest filtered P wave recorded from 16 different precordial unipolar leads [73,74]. Acceptable intraobserver and interobserver errors of the measurement of the dispersion of filtered P wave duration were reported [73,74]. However, it remains questionable whether the number and the location of the electrodes used in those studies would be optimal for the accurate estimation of the body surface distribution of atrial electrograms.

RATIONALE AND FIELDS FOR CLINICAL USE

AF is the most frequent arrhythmia managed in current cardiology practice and is responsible for the highest number of hospital admissions due to arrhythmias. The treatment of AF is considered far from optimal and accurate methods to

determine its efficacy are still lacking. Electrocardiography constitutes an important diagnostic tool to study AF. The presence of prolonged P wave duration filtered or not, identifies patients at risk for the development of AF. However, the analysis of the interlead variation in P wave duration seems to be required in order to assess the inhomogeneity of electrical atrial activity in patients with paroxysmal AF. P wave dispersion, which is derived from standard 12-lead ECGs or more sophisticated signal-averaged mapping techniques, is supposed to reflect the homogeneity of the atrial electrical activity and seems quite promising in the field of AF prediction. The present review aimed to inform clinicians about the already gained experience from the use of this ECG index. Numerous studies from many centers have contributed to elucidate the rationale and clinical applicability of P wave dispersion. Future studies should clarify its role in predicting the risk for AF and its ability to guide antiarrhythmic therapeutic strategies. To enhance its clinical use some methodological and technical problems that still exist should be resolved such as the improvement of the reliability and reproducibility of P wave dispersion measurements. The development of automatic methods able to accurately determine the P wave duration from standard 12-lead ECGs may contribute to the widespread use of this new ECG marker.

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