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Evaluation of P wave Dispersion and Tissue Doppler Imaging for Predicting Paroxysmal Atrial Fibrillation in Patients with Hypertension

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ABSTRACT

Background: There are no previous studies dealing with paroxysmal atrial fibrillation (AF) and hypertension using electrocardiogram and tissue doppler imaging (TDI). The aim of this study was to investigate and identify the predictive indicators for paroxysmal AF in hypertensive patients using P wave dispersion (Pd) and TDI.

Methods: Patients with hypertension were enrolled. Patients with paroxysmal AF were classified as the PAF group, and patients without a history of paroxysmal AF were classified as the NAF group. The clinical data, P wave indicators and TDI indicators were collected and compared between the two groups.

Results: A total of 120 patients were enrolled into the study with 40 cases in the PAF group and 80 cases in the NAF group. Compared with NAF group, Pd, maximum P wave duration (Pmax), left ventricular end-diastolic dimension (LVEDd) and left atrial dimension (LAD) were significantly longer ($P < .05$) in the PAF group. PAL, PAI, PAR, LR, LI and IR were significantly longer ($P < .05$) in the PAF group than in the NAF group. As for ROC analysis, Pd and PAL had the greatest area under the curve. The best diagnostic value of Pd and PAL was 40ms and 78ms, respectively. The combination of Pd ≥40ms with Pmax ≥ 110ms showed higher specificity and positive predictive value but decreased sensitivity and negative predictive value for paroxysmal AF.

Conclusions: The PAF group had significantly longer atrial electromechanical time and higher Pd compared with NAF group. The combination of Pd and TDI may be helpful to predict the onset of paroxysmal AF in patients with hypertension.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia [Hijazi 2013; Andrade 2014] and accounts for one-third of hospitalizations for rhythm disorders. Atrial fibrillation is of public health importance and profoundly increases morbidity, mortality, and health-related expenditures [Khaji 2017]. Atrial fibrillation affects 33 million individuals worldwide, and increases the risk of stroke, heart failure and death, and also impairs quality of life [Chugh 2014]. The prevalence rate of AF is 0.77% in China with an increasing trend with old-age [Zhou 2004]. AF exerts a profound negative impact on the quality and quantity of life of millions [Piccini 2016].

The understanding of the etiology of AF has improved markedly, with structural and electrical remodeling of the left atrium being increasingly recognized as a process that precedes and contributes to AF vulnerability. Since elevated systemic pressures influence the size and function of the left atrium, uncontrolled hypertension is a key contributor to the generation of a substrate vulnerable to AF. Hypertension is the most common cardiovascular comorbidity among patients with AF. Hypertension leads to electrical and structural alterations to the left atrium that predisposes to AF. Epidemiologic studies have shown that hypertension is associated with a 1.8-fold increased risk of developing new-onset AF and a 1.5- fold increased risk of progression to permanent AF [de Vos 2010]. Up to now, there have been no studies showing that antihypertensive therapy can reduce AF burden. However, current studies have proven that effective treatment of hypertension may reduce the likelihood of developing AF by preventing atrial stretch from elevated ventricular filling pressures, atrial fibrosis, and extracellular collagen deposition, as well as through several other important mechanisms [Schneider 2010; Zhang 2012]. Although hypertension is not the most dangerous element among the risk factors of AF, hypertension has become the most important factor due to its high morbidity rate [Healey 2003; Huxley 2011]. It is still unclear about the exact mechanism of AF caused hypertension. Therefore, it is clinically meaningful to predict AF in patients with hypertension, and further adopt preventive measures to avoid AF.

It is recognized that there is an atrial and/or interatrial conduction delay in patients with paroxysmal AF. Takahashi et al found that preoperative Tissue Doppler Imaging (TDI)-derived atrial conduction time can predict postoperative AF in patients undergoing mitral valve surgery for mitral valve regurgitation [Takahashi 2016]. To our knowledge, there is no previous study dealing with paroxysmal AF and hypertension using electrocardiogram and TDI in patients with paroxysmal AF. The aim of this study was to investigate the predictive

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indicators for paroxysmal AF in hypertensive patients using P wave dispersion and TDI. The clinical data, P wave indicators and TDI indicators were investigated.

PATIENTS AND METHODS

Patients

The study was approved by the Ethics Committee of the Affiliated Hospital of Taishan Medical University and was conducted in accordance with the Helsinki declaration. Consecutive patients with hypertension were enrolled in the study. The diagnosis of hypertension was on the basis of a systolic blood pressure (SBP) of 140 mmHg or more or a diastolic blood pressure (DBP) of 90 mmHg or more, measured on at least 2 different occasions according to the WHO-ISH (World Health Organization–International Society of Hypertension) guidelines (WHO 2004). Patients were admitted to the hospital between July 2013 and September 2014. Diagnostic criteria for sinus rhythm were obvious P wave (<0.12s) in the preoperative electrocardiogram, amplitude of P wave in the limb leads <0.25 mV, amplitude of P wave in the precordial leads <0.15mV, upright on II and III avF lead, inversed on avR lead, Pr of 0.12-0.20s, and normal QRS and ST-T. Diagnostic criteria for AF were the absence of P waves, with disorganized electrical activity in their place, and irregular R-R intervals. Diagnostic criteria for paroxysmal AF were AF duration ≤7 days that convert to sinus rhythm [Association 2007].

The inclusion criteria were patients who met the diagnostic criteria for hypertension: systolic pressure ≥140 mmHg, diastolic pressure ≥90 mmHg, paroxysmal AF confirmed by ECG, and more than two attacks of paroxysmal AF within the last 6 months. The exclusion criteria were: valvular heart disease, ischemic heart disease, corpulmonale, congenital heart disease, hyperthyroidism, secondary hypertension, electrolyte disorder and arrhythmia.

Clinical blood pressure in this study was measured three times by the traditional method with a mercury sphygmomanometer after the patient had rested for 30 minutes, and the mean values were obtained. Medical history of hypertension was recorded.

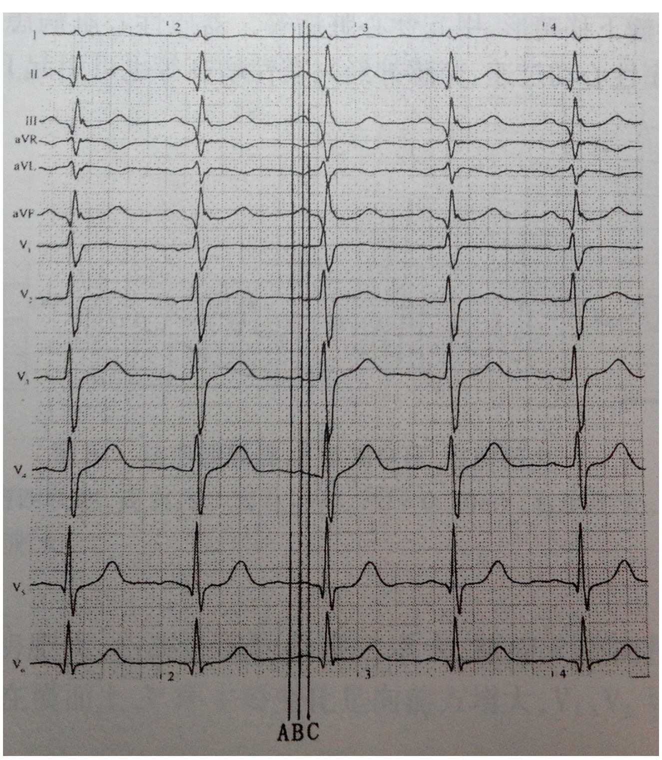

Figure 1. The measurement of P wave dispersion. Line A was the onset of P wave; Line B was the minimum P wave duration (Pmin); Line C was the maximum P wave duration (Pmax). The distance between B and C was calculated and defined as P wave dispersion (Pd). In this case, Pd was 40ms.

Table 1. Baseline Characteristics Between the Two Groups

	PAF (n = 40)	NAF (n = 80)	*P*
Age	68.70 ± 10.48	66.15 ± 10.48	.212
Sex (M/F)	20/20	38/42	.796
Smoking (Y/N)	12/28	23/57	.887
Alcohol drinking (Y/N)	6/34	15/65	.610
Systolic arterial pressure (mmHg)	154.50 ± 30.46	156.36 ± 24.20	.717
Diastolic arterial pressure (mmHg)	96.15 ± 18.36	92.69 ± 12.79	.231
GOH (1/2/3)	26/7/7	53/16/11	.842
Uric acid (umol/L)	318.35 ± 115.27	310.79 ± 90.59	.699
Creatinine (umol/L)	71.41 ± 32.75	66.79 ± 21.40	.362
FBG (mmol/L)	5.93 ± 2.33	6.07 ± 2.46	.768
Total cholesterol (mmol/L)	4.92 ± 0.81	4.96 ± 1.51	.874
Triglyceride (mmol/L)	1.28 ± 0.69	1.42 ± 0.89	.379
LDL (mmol/L)	2.48 ± 0.64	2.77 ± 0.88	.072
HDL (mmol/L)	1.29 ± 0.31	1.28 ± 0.31	.945

M, male; F, female; GOH, grade of hypertension; FBG, Fasting blood-glucose; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 2. Comparison of the Ultrasound Cardiogram Indexes Between the Two Groups

	PAF (n=40)	NAF (n=80)	*P*
Pmax (ms)	125.5±26.7	108.3±23.8	.001
Pmin (ms)	81.3±18.5	80.2±21.5	.820
Pd (ms)	45.3±16.9	27.5±19.3	<.001
AO (mm)	32.6±3.1	31.6±3.1	.081
LVPWd (mm)	10.3±0.9	10.1±1.1	.391
IVSd (mm)	10.6±1.1	10.6±2.5	.990
LVEDd (mm)	49.8±5.9	46.9±5.0	.005
LAD (mm)	42.2±5.1	38.7±7.1	.005

PAF, paroxysmal atrial fibrillation; Pmax, maximum P wave duration; Pmin, minimum P wave duration; Pd, P wave dispersion; AO root, aortic root; LVPWd, Left ventricular posterior wall dimension at end diastolic; IVSd, interventricular septum dimension at end diastolic; LVEDd, Left ventricular end-diastolic dimension; LAD, left atrial dimension.

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Methods for Electrocardiogram

After the patient had rested in bed for 5 min, 12-lead synchronized ECG (F8322, Yasuo ltd. Co, Japan) was performed during sinus rhythm. The sweep speed was 50mm/s and voltage was 2mV/cm. At least five cardiac recycles were recorded, and the mean value was used. As for the dynamic ECG, 3M disposable electrode patches were pasted after cleaning the skin and the patient kept still. At least five cardiac cycles during the rest time were chosen for analysis. It was measured manually, and the average data were used.

For measurement of the P wave dispersion (Figure), line A was the onset of P wave, line B was the minimum P wave duration (Pmin), and line C was the maximum P wave duration (Pmax). The distance between B and C was defined as P wave dispersion (Pd) [Dilaveris 1998]. Pd was measured manually in more than three heart beats, and the average data were used. The criteria were Pmax ≥ 110ms and Pd ≥ 40ms. The measurement was performed by an experienced doctor who was blind to the groups.

Methods for TDI Indicators Measurements

TDI images were reviewed by an experienced cardiovascular specialist with more than 10-years experience in echocardiography. Left ventricular posterior wall dimension at end diastolic (LVPWd), interventricular septum dimension at end diastolic (IVSd), Left ventricular end-diastolic dimension (LVEDd), early diastolic peak flow velocity (E), late diastolic peak flow velocity (A), the diameter of aortic root (AO) according to a previous report [Pieruzzi 2015]. In addition, the transverse diameter of the left ventricle, longitudinal diameter of the left ventricle, anteroposterior diameter of the left ventricle, and the left ventricle area were also measured. The time interval between the onset of P wave and the onset of A wave of tissue velocity imaging (TVI) was measured as P-A time [Rein 2003], corresponding to the atrial electromechanical time. The time interval between the onset of P wave and the onset of A wave of TDI in mitral annulus of the left ventricle lateral wall (PAL), the time interval between the onset of P wave and the onset of A wave of TDI in mitral annulus of the interventricular septum (PAI), and the time interval between the onset of P wave and the onset of A wave of TVI in tricuspid annulus of the right ventricle (PAR) were measured according to a previous report [Rein 2000]. LR was calculated as the difference between the time intervals (PAL) and time intervals (PAR); LI was calculated the difference between the time intervals (PAL) and time intervals (PAI). IR was calculated as the difference between the time intervals (PAI) and time intervals (PAR).

Table 3. The Comparison of the TDI Indicators Between the Two Groups

	PAF (n=40)	NAF (n=80)	*P*
PAL(mm)	93.70±10.69	76.60±14.07	<.001
PAI(mm)	70.78±11.56	58.08±14.91	<.001
PAR(mm)	54.05±10.83	43.79±12.24	<.001
LR(mm)	39.65±10.55	32.81±7.03	<.001
LI (mm)	22.93±9.59	18.53±5.16	.009
IR (mm)	18.58±8.00	14.29±9.29	.010

PAL, the time interval between the onset of P wave and the onset of A wave of TDI in mitral annulus of left ventricle lateral wall; PAI, the time interval between the onset of P wave and the onset of A wave of TVI in mitral annulus of interventricular septum; PAR, the time interval between the onset of P wave and the onset of A wave of TVI in tricuspid annulus of right ventricle; LR, the differences between the time intervals (PAL and time intervals (PAR); LI, the differences between the time intervals (PAL) and time intervals (PAI); IR, the differences between the time intervals (PAI) and time intervals (PAR).

Statistical Analysis

All data were analyzed using SPSS 19.0 (SPSS Inc, Chicago, USA). Qualitative data were presented as number or percentage. Quantitative data were presented as means ± standard deviation (SD). The Kolmogorov–Smirnov test was used to test the normality of the distribution of the continuous variables. Comparison of the two groups for normally distributed data was performed with independent t-test. Logistic analysis and receiver operating characteristic (ROC) curve analysis were performed to evaluate the possible predictive parameters. $P < .05$ was considered statistically significant.

RESULTS

A total of 120 consecutive patients met the inclusion criteria and were enrolled into the study, with 40 cases in the PAF group and 80 cases in the NAF group. The baseline characteristics of the participants in the groups are described in Table 1. There were no significant differences regarding the age, sex, smoking, alcohol drinking, systolic arterial pressure, diastolic arterial pressure, grade of hypertension, uric acid, creatinine, fasting blood-glucose, total cholesterol, triglyceride, low-density lipoprotein, and high-density lipoprotein in two groups (all $P > .05$).

Compared with NAF group, Pd, Pmax, LVIDd and left atrial dimension (LAD) were significantly longer ($P < .05$) in PAF group. There were no statistical differences ($P > .05$) regarding AO, LVWP and IVST between the two groups (Table 2). PAL, PAI, PAR, LR, LI and IR were significantly longer ($P < .05$) in PAF group than in NAF group (Table 3). Multivariate analysis showed that Pd and PAL were significant influencing factors (Table 4).

With AF as state variable and Pmax, Pd, LVDd, LAD, PAL, PAI, PAR, LR, LI and IR as test variables, a ROC curve was made and the area under and the curve was calculated. The results showed that Pd and PAL had the greatest area under the curve. The best diagnostic values of Pd and PAL

Table 4. Multivariate Analysis Logistic Regression Analysis of Ultrasound Cardiogram and TDI Indexes Between the Two Groups

Parameters	Significance	Exp (B)	95.0% CI for Exp (B)	
			Lower	Upper
Pd	0.007	1.138	1.036	1.249
PAL	<0.001	1.147	1.081	1.217

Pd, P wave dispersion; PAL, the time interval between the onset of P wave and the onset of A wave of TDI in mitral annulus of left ventricle lateral wall.

Table 5. The Diagnostic Value of Pd > 40ms, PAL > 78ms and Their Combination

	AUC	*P*	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Kappa value	*P*
Pd	0.791	<.001	82.5%	73.75%	61.11%	89.39%	0.517	<.001
PAL	0.810	<.001	97.44%	66.25%	58.46%	98.15%	0.530	<.001
Pd + PAL	NS	NS	77.50%	91.25%	81.58%	89.02%	0.696	<.001

Kappa values and *P* values were calculated on the basis of Pd > 40ms and PAL> 78ms; Pd, P wave dispersion; PAL, the time interval between the onset of P wave and the onset of A wave of TDI in mitral annulus of left ventricle lateral wall; AUC, area under the curve; NS, not applicable

were 40ms (sensitivity: 0.825, specificity: 0.738, Youden index: 0.563) and 78ms (sensitivity: 0.950, specificity: 0.663, Youden index: 0.613) respectively. The Kappa values are shown in Table 5.

DISCUSSION

The present study showed that there were statistical differences regarding P wave indicators and TDI indicators between the PAF group and the NAF group. TDI was valuable for predicting paroxysmal AF.

Electrical conduction delays in the atrium and ventricle is likely to cause AF [Buxton 1981]. The characteristics of the P wave may be useful for predicting AF. The present study showed that Pd, Pmax, IVLDd and LAD were significantly longer ($P < .05$) in PAF group than those in NAF group. Pmax could be considered as a predictor for paroxysmal AF. As for Pmin, there was no statistical difference in two groups, which was consistent with a previous report by Ciaroni et al [Ciaroni 2000]. Dilaveris et al proposed that Pd was a specific and sensitive predictor for AF and can be used to evaluate the electrical conduction heterogeneity in the atrium, which can obviously increase the accuracy of Pmax as a predictor for AF. The present study showed that Pd is a sensitive predictor for paroxysmal AF after multivariate logistic regression analysis. Ciaroni et al [Ciaroni 2000] and Guo et al [Guo 1999] reported that Pd could be used as an independent predictor for AF, while was contrary to previous claims by Dilaveris et al [Dilaveris 2000].

The different results among the above reports might be due to the different measurement methods that were used. Manual measurement was adopted in the present study, which was consistent with the previous report by Ciaroni et al. Taking manual measurements will inevitably cause measurement errors because of the start point and endpoint determination. To minimize the error caused by manual measurement, P wave width was measured in five consecutive cardiac cycles by the same physician, with the average values used for final analysis. In addition, a 12-lead synchronous resting ECG was recorded, and the width of P wave was also measured. Thus, this reduced the measurement errors and ensured the objectivity of P wave. Errors may occur when only II-lead and V1- lead P waves are used to determine Pmax, Pmin and Pd [Yuan 2003].

Drugs can also exert an influence on the results, such as calcium antagonist, angiotensin converting enzyme inhibitors (ACEI) and blockers of beta receptors [Li 2001].

The possible mechanism may be that the activation of the renin-angiotensin-aldosterone system in hypertensive patients could prompt and maintain the AF. Ciaroni et al [Ciaroni 2000] found that systolic blood pressure and age are important independent risk factors for AF in patients with hypertension. However, our study did not show the correlation of the above factors. This might be attributed to the limited samples.

As we know, atrial myocardial wall is thin with poor tension and thus vulnerable to geometric configuration changes under the influence of various pathological factors and mechanical forces. The atrial expansion and aggravated fibrosis in patients with primary hypertension can lead to diffuse atrial electrical activity and slow conduction velocity, which then increases the atrial electrophysiological anisotropy, eventually resulting in the occurrence of AF. The focal fibrosis of the atrial myocardium aggravates the heterogeneity of atrial electrical activity which increases the difference in atrial autorhythmicity and excitability among different parts of the atrium. Therefore, a larger difference in P wave duration among different leads will be shown on 12-lead resting ECG [Tong 2013].

Andrikopoulos et al [Andrikopoulos 2000] suggested that the dispersion degree of the P wave has positive predictive value for AF. However, there are still controversial results regarding the patients with primary hypertension and concomitant paroxysmal AF [Ciaroni 2000; Ozer 2000]. Guo et al [Guo 2007] reported that Pd ≥ 40ms and Pmax ≥ 110ms were reliable predictors for AF. In this study, our findings showed that Pd ≥ 40ms showed higher predictive value for paroxysmal AF in patients with hypertension which is in accordance with the previous study [Wang 2005]. In addition, we also found that Pd ≥ 40ms, Pmax ≥ 110ms and the combinations of these two indexes were reliable predictors for paroxysmal AF. The combination of Pd ≥ 40ms with Pmax ≥ 110ms showed higher specificity and positive predictive value but decreased sensitivity and negative predictive value for paroxysmal AF.

TDI is useful in early detection of myocardial dysfunction in several diseases and can give accurate information about the functions of the ventricle in hypertensive patients [Mori 2007; Tenekecioglu 2010]. TDI is sensitive and reliable when determining left ventricular hypertrophy. However, the limitation of pulse repetition frequency may produce frequency distortion. To avoid the above distortion, low frequency probe, reducing sampling depth, moving the zero line, changing the angle between the direction of acoustic beam and blood flow, and increasing pulse repetition frequency were adopted in this study.

CONCLUSIONS

The present study suggested that PAF group showed significantly longer atrial electromechanical time and higher

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Pd compared with NAF group. The combination of Pd and TDI may be helpful to predict the onset of paroxysmal AF in patients with hypertension.

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