P-wave dispersion and maximum duration are independently associated with insulin resistance in metabolic syndrome

La dispersion et la durée maximum de l’onde P sont indépendamment associées à la résistance à l’insuline dans le syndrome métabolique

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Abstract

Background. – Metabolic syndrome (MS) is an important risk factor for atrial fibrillation. P-wave indices, including P-wave dispersion (PWD) and P-wave duration, can be used as non-invasive markers of heterogeneous atrial conduction. The aim of our study was to evaluate the relationship between P-wave indices and insulin resistance in patients with MS. Methods. – Seventy-four patients with MS (44 men, 30 women) and 81 patients without MS (48 men, 33 women) were enrolled in the study. A diagnosis of MS was made as defined by the Adult Treatment Panel III of the National Cholesterol Education Program. Insulin resistance was estimated using the homeostasis model assessment (HOMA) index. P-wave maximum duration (Pmax) and P-wave minimum duration (Pmin) were calculated on a 12-lead electrocardiogram, and the difference between the Pmax and the Pmin was defined as PWD.

Results. – Patients with MS had a longer PWD and a higher Pmax compared with patients without MS (PWD, 35.65 ± 4.36 vs. 26.27 ± 4.04, P < 0.001; Pmax, 117.12 ± 10.77 vs. 105.98 ± 9.02, P < 0.001), whereas no difference was found between Pmin values from MS patients and controls (81.47 ± 9.54 vs. 79.70 ± 8.76, P = 0.231). Stepwise multivariate analysis revealed only the HOMA index to be an independent predictor of PWD (β = 3.115, P < 0.001) and Pmax (β = 7.175, P < 0.001).

Conclusion. – This study suggests that patients with MS have a prolonged PWD and Pmax. The increase in these parameters may be an indicator for identification of patients at an increased risk for atrial fibrillation.

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Keywords: Metabolic syndrome; P-wave dispersion; Insulin resistance; Atrial conduction

Résumé

Contexte. – Le syndrome métabolique (SM) est un facteur de risque important pour la fibrillation auriculaire. Les indices des ondes P, à savoir leurs dispersion et durée, peuvent être utilisés comme marqueurs non invasifs de la conduction auriculaire hétérogène. Le but de notre étude était d’évaluer la relation entre les indices des ondes P et la résistance à l’insuline chez les patients atteints de SM. Méthodes. – Soixante-quatre patients atteints de SM (44 hommes, 30 femmes) et 81 patients non atteints (48 hommes, 33 femmes), ont été inclus dans l’étude. Le diagnostic de MS était défini par le Adult Treatment Panel III du National Cholesterol Education Program. La résistance à l’insuline était estimée au moyen du modèle d’évaluation de l’homéostasie (HOMA). La durée maximale de l’onde P (Pmax) ainsi que sa durée minimale (Pmin) ont été calculées sur un électrocardiogramme à 12 dérivation, et la différence entre la Pmax et la Pmin a été définie comme dispersion de l’onde P (DOP). Résultats. – Les patients atteints de SM ont une vitesse de dispersion de l’onde P supérieure et une Pmax plus élevée par rapport aux patients sans SM (DOP, 35.65 ± 4.36 vs 26.27 ± 4.04, P < 0.001; Pmax, 117.12 ± 10.77 vs 105.98 ± 9.02, P < 0.001), alors qu’aucune différence n’a été observée entre les valeurs Pmin de patients atteints de SM et les témoins (81.47 ± 9.54 vs 8,76 ± 79.70, p = 0.231). L’analyse multivariée pas à pas a révélé que l’indice HOMA était un facteur prédictif indépendant de la DOP (β = 3.115, p < 0.001) et de la Pmax (β = 7.175, p < 0.001).

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1. Introduction

Metabolic syndrome (MS), defined as the clustering of several cardiovascular risk factors in an individual including abdominal obesity, dyslipidemia, elevated blood pressure, and glucose intolerance, is associated with a 2-fold increase in cardiovascular events and a 1.5-fold increase in all-cause mortality [1]. Recent studies have shown that MS can increase the risk for the development of atrial fibrillation (AF) [2,3], the most common cardiac arrhythmia. It has been suggested that insulin resistance (IR), a common pathologic condition observed in MS, can trigger atrial remodeling [4,5].

P-wave indices such as P-wave dispersion (PWD) and P-wave maximum duration (Pmax) serve as intermediate phenotypes reflecting alterations in atrial electrophysiology and morphology [6]. A prolonged PWD and an increase in Pmax are associated with an increased risk for AF [7,8]. Recently, a cross-sectional study of 14,433 subjects reported that P-wave indices are significantly associated with MS [9]. Accordingly, the goal of the present study was to investigate the associations among MS, IR and indices of P-wave duration and dispersion.

2. Methods

2.1. Study population

We selected 74 consecutive hospitalized patients with MS and 81 control subjects without MS who visited our hospital from October 2011 to December 2012 to participate in the study. MS was diagnosed according to the Adult Treatment Panel (ATP) III criteria of the National Cholesterol Education Program [10]. Metabolic scores were calculated as the number of abnormal items in the ATP III criteria, with a score of 0 representing absence of any abnormal metabolic components and 5 representing an individual with all five abnormal metabolic components. Cases with a history of myocardial infarction or angina pectoris, AF, previous implantation of a pacemaker, or overt renal insufficiency (creatinine > 2.5 mg/dL) were not included in the study. In addition, patients were excluded if they had left ventricular ejection fraction (LVEF) < 50%, pre-excitation syndrome, atrioventricular conduction abnormalities, abnormal thyroid function or serum electrolytes, more severe pulmonary hypertension (defined as systolic pulmonary arterial pressure higher than 60 mmHg), chronic lung disease, existence of congenital heart disease on echocardiography, known prior cardiac surgery, or valvular heart disease. In addition, patients using antihypertensive drugs thought to improve atrial electrical remodeling, such as beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, were excluded from the study.

The study protocol was approved by the Ethics Committee of Fujian Medical University and conformed to the principles outlined in the Declaration of Helsinki. Signed informed consent was obtained from all participants.

2.2. Lab data acquisition

Fasting blood glucose, insulin, total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and N-terminal pro-brain natriuretic peptide (NT-proBNP) values were measured from venous blood collected from the subjects after fasting for eight hours. Plasma insulin concentrations were analyzed using chemiluminescent immunoassays on a Beckman Coulter Unicell DXI 800 immunoassay analyzer (Beckman Coulter Inc., CA, USA). Insulin resistance was calculated by the homeostasis model assessment insulin resistance (HOMA-IR) method: HOMA index = fasting glucose (mmol/L) × fasting insulin (μU/mL)/22.5.

2.3. Electrocardiographic analysis

The 12-lead electrocardiogram (ECG) was recorded for each subject at a paper speed of 50 mm/s and 20 mm/mV. All recordings were performed in the same quiet room during spontaneous breathing, following 15 minutes of adjustment in the supine position. P-wave duration was measured manually using calipers by two investigators who were blinded to the clinical status of the patients. The onset of the P-wave was defined as the junction between the isoelectric line and the beginning of the
**Table 1**
Clinical characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>MS group (n = 74)</th>
<th>Control group (n = 81)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>44 (59.46)</td>
<td>48 (59.26)</td>
<td>0.980</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.73 ± 6.51</td>
<td>55.00 ± 7.21</td>
<td>0.807</td>
</tr>
</tbody>
</table>

- **Clinical features**
  - Smoker (%): 18 (24.32) vs. 19 (23.46)
  - Body mass index (kg/m²): 27.33 ± 2.72 vs. 23.79 ± 2.92
  - Waist circumference (cm): 90.97 ± 7.00 vs. 84.31 ± 7.79
  - Elevated BP or hypertension (%): 55 (74.32) vs. 8 (9.88)
  - Systolic blood pressure (mmHg): 137.22 ± 11.04 vs. 117.25 ± 10.20
  - Diastolic blood pressure (mmHg): 82.32 ± 6.12 vs. 69.70 ± 6.36
  - Heart rate (beat/min): 75.69 ± 11.01 vs. 76.17 ± 10.40
  - Diabetes mellitus (%): 18 (24.32) vs. 9 (11.11)

- **Transthoracic echocardiogram**
  - Left atrial diameter (mm): 33.38 ± 3.89 vs. 30.35 ± 3.41
  - LV end-diastolic diameter (mm): 45.52 ± 2.50 vs. 44.87 ± 2.18
  - LV end-systolic diameter (mm): 27.15 ± 2.74 vs. 26.30 ± 2.68
  - LV ejection fraction (%): 65.65 ± 3.60 vs. 65.79 ± 3.33
  - LV septal thickness (mm): 101.01 ± 10.90 vs. 97.02 ± 11.50
  - LV posterior wall thickness (mm): 102.55 ± 10.74 vs. 96.22 ± 12.13
  - E (cm/s): 77.30 ± 23.58 vs. 81.19 ± 19.54
  - A (cm/s): 82.09 ± 14.19 vs. 77.33 ± 14.74
  - E/A ratio: 0.94 ± 0.22 vs. 1.06 ± 0.18

**Note:** MS: metabolic syndrome; BP: blood pressure; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; NT-proBNP: N-terminal pro-brain natriuretic peptide; HOMA: homeostasis model assessment; LV: left ventricle; E: mitral early diastolic velocity; A: mitral late diastolic velocity.

P-wave deflection. The offset of the P-wave was defined as the junction between the end of the P-wave and the isoelectric line. Pmax in any of the 12-lead surface ECGs was calculated and used as a marker of prolonged atrial conduction time. The difference between Pmax and P-wave minimum (Pmin) durations was defined as the P-wave dispersion (PWD = Pmax − Pmin). Intra- and inter-observer coefficients of variation (the standard deviation of differences between two observations divided by the mean value and expressed as a percent) were found to be 3.2 and 3.7% for P-wave dispersion, and 3.1 and 3.4% for Pmax, respectively.

### 2.4. Echocardiographic study

Transthoracic echocardiography was performed using a digital imaging system equipped with a 2.5- to 3.5-MHz transducer (Vivid-7, GE healthcare, USA) for all patients. All images were digitally recorded for cardiac function assessment. Left atrium (LA) diameter was measured in the parasternal long axis view at end systole, and the left ventricle (LV) diameter in end diastole. Interventricular septum and LV posterior wall thickness in end diastole were measured from the M-mode readings. The LV ejection fraction was estimated by the use of a modified version of Simpson’s biplane method. Pulse wave mitral flow velocities were measured from the apical 4-chamber view by inserting a sample volume to mitral leaflet tips. Mitral early diastolic velocity (E), late diastolic velocity (A), and the E/A ratio were determined.

### 2.5. Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as percentages. Skewed data are presented as medians and interquartile ranges. Comparisons of categorical and continuous variables between the two groups were performed by the chi-square and an unpaired t-test, respectively. The Mann-Whitney rank-sum test was used for the analysis of skewed variables. Pearson correlation tests were used to determine the correlations between PWD and Pmax and clinical parameters. Stepwise multiple variable linear regressions were used to determine the variables for PWD and Pmax. A P value < 0.05 was considered as statistically significant.
3. Results

The clinical characteristics of the cases in the MS group and the control group are shown in Table 1. Seventy-four patients with MS (44 men, 30 women; mean age, 54.73 ± 6.51 years) and 81 patients without MS (48 men, 33 women; mean age, 55.00 ± 7.21 years) participated in our study. There were no significant differences between the two groups with regard to age, gender and number of smokers. Compared with the control group, there was a higher prevalence of hypertension and diabetes mellitus in the MS group. Additionally, body mass index, waist circumference, and systolic and diastolic blood pressures were significantly increased in the MS group. The level of fasting plasma glucose, total cholesterol, triglyceride, LDL cholesterol and NT-proBNP levels were significantly higher, while HDL cholesterol levels were significantly lower in the MS group. In addition, the insulin levels, HOMA indices and metabolic scores were increased in the MS group. Among transthoracic echocardiogram parameters, no significant differences were present between the two groups when considering LV end-diastolic diameter, LV end-systolic diameter, LV ejection fraction and left ventricular wall thicknesses and mitral late diastolic velocity (A velocity) were significantly higher, and the E/A ratio was significantly lower in the MS group compared with the control group.

P-wave measurements are given in Table 2. Although PWD and Pmax were significantly higher in MS patients (PWD, 35.65 ± 4.36 vs. 26.27 ± 4.04, P < 0.001; Pmax, 117.12 ± 10.77 vs. 105.98 ± 9.02, P < 0.001), no difference was determined between Pmin of MS cases and controls (81.47 ± 9.54 vs. 79.70 ± 8.76, P = 0.231).

In univariate analyses with Pearson’s correlations, PWD was associated with waist circumference, fasting glucose level, insulin level, HOMA index, metabolic score and E/A ratio, while Pmax was associated with body mass index, waist circumference, insulin level, HOMA index and NT-proBNP level. However, stepwise multivariate analysis revealed only the HOMA index to be an independent predictor of PWD and Pmax (Tables 3 and 4).

4. Discussion

In this study, we investigated the associations among P-wave parameters, insulin resistance and MS. Our main findings are as follows:

- Pmax and PWD were increased in patients with MS compared with the control subjects without MS;
- PWD was independently associated with insulin resistance, but not other factors such as waist circumference, body mass index, blood pressure, LA size and left ventricular diastolic function.

There are several studies confirming the roles of P-wave duration and dispersion as non-invasive markers associated with AF. P-wave durations and PWD are markers of intra- and intertrial conduction disorders of sinus impulses and heterogeneous and discontinuous atrial conduction [11], providing a substrate that favors reentry mechanisms [12]. P-wave durations longer than 110 ms suggest interatrial block, which is associated with the development of atrial fibrillation [13]. Prolonged Pmax and increased PWD have been suggested to represent independent predictors for AF in patients with hypertrophic cardiomyopathy, hyperthyroidism, secundum atrial septal defect, isolated coronary artery ectasia, rheumatic mitral stenosis, obstructive sleep apnea, and in those after cardioversion or after radiofrequency catheter ablation for overt pre-excitation [14].

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Table 2

<table>
<thead>
<tr>
<th>P-wave parameters of the study population.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS group (n = 74)</td>
</tr>
<tr>
<td>Control group (n = 81)</td>
</tr>
<tr>
<td>Pmax (ms) 117.12 ± 10.77</td>
</tr>
<tr>
<td>Pmin (ms) 81.47 ± 9.54</td>
</tr>
<tr>
<td>PWD (ms) 35.65 ± 4.36</td>
</tr>
<tr>
<td>Control group</td>
</tr>
<tr>
<td>Pmax (ms) 105.98 ± 9.02</td>
</tr>
<tr>
<td>Pmin (ms) 79.70 ± 8.76</td>
</tr>
<tr>
<td>PWD (ms) 26.27 ± 4.04</td>
</tr>
</tbody>
</table>

Pmax: P-wave maximum duration; Pmin: P-wave minimum duration; PWD: P-wave dispersion; MS: metabolic syndrome.

Table 3

Univariate and stepwise multivariate linear regression analyses of Pmax for clinical parameters in patients with MS.

<table>
<thead>
<tr>
<th>Pmax</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>P</td>
<td>β</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.386</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.310</td>
<td>0.007</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.496</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA index</td>
<td>0.538</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.232</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Pmax: P-wave maximum duration; MS: metabolic syndrome; HOMA: homeostasis model assessment; NT-proBNP: N-terminal pro-brain natriuretic peptide; NI: indicates not included in multivariate analysis.

Table 4

Univariate and stepwise multivariate linear regression analyses of PWD for clinical parameters in patients with MS.

<table>
<thead>
<tr>
<th>PWD</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>P</td>
<td>β</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.237</td>
<td>0.042</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>0.255</td>
<td>0.029</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.512</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA index</td>
<td>0.578</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic score</td>
<td>0.286</td>
<td>0.014</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>−0.263</td>
<td>0.023</td>
</tr>
</tbody>
</table>

PWD: P-wave dispersion; MS: metabolic syndrome; HOMA: homeostasis model assessment; E/A: mitral early diastolic velocity/mitral late diastolic velocity; NI: indicates not included in multivariate analysis.
MS represents a cluster of cardiovascular and metabolic derangements (i.e., increased blood pressure, abdominal obesity, insulin resistance, and dyslipidemia), which deteriorate vascular function and cause subclinical damage in a variety of organs, more than individual traditional risk factors [15]. MS was also found to be an independent predictor of AF recurrence after catheter ablation [16,17]. AF is certainly the most prevalent arrhythmia in everyday clinical practice, and its increased prevalence parallels MS frequency. Each of the MS components is related to an increased risk for AF occurrence. The vast majority of epidemiological and observational studies conducted in general population samples have shown that subjects with MS have a greater likelihood of AF than their non-MS counterparts [18–21].

Structural and electrophysiological remodeling of the atrium are critical for AF to perpetuate. Furthermore, animal and human studies have shown that MS is associated with remodeling, including an increased LA size and decreased conduction velocity [22,23]. A recent study [24] also showed that the reduction of AF recurrence and severity in patients with MS is associated to the decrease of PWD, which may be related to the improvement in atrial fibrosis and electrical remodeling. The association between atrial remodeling and MS was confirmed by the results of this study, which shows that Pmax and PWD are increased in patients with MS. The association between atrial remodeling and MS was confirmed by the results of this study, which shows that Pmax and PWD are increased in patients with MS.

A stepwise multivariate analysis revealed that the HOMA index was the only independent predictor of this prolonged PWD and Pmax. A previous study that had reported increases in Pmax and PWD in patients with MS found that PWD was independently correlated only with the triglyceride level [25]. However, the relationship between triglyceride level and AF occurrence remains controversial.

A growing body of evidence indicates that IR is the fundamental pathophysiology responsible for metabolic syndrome [26], for which this condition was originally classified [27]. However, the exact mechanism by which IR results in prolonged PWD and Pmax is still not well understood. IR may contribute to atrial electro-structural remodeling in the following ways:

- IR causes an intra-atrial conduction abnormality by worsening diastolic function and increasing atrial size [28]. A recent study also reported that a greater HOMA index was strongly associated with echocardiographic LA size in patients with HCM [29];
- it has been shown that IR is correlated with endothelial dysfunction [30]. The impairment in the vascular endothelium of atrial tissue might be a trigger for remodeling in the atrium and cause atrial conduction abnormalities and arrhythmia;
- IR can result in the activation of many proinflammatory transcription factors [31] and induce the generation of reactive oxygen species [26,32]. Inflammation and oxidative stress have been proposed as common etiological factors in the pathogenesis of AF [33–35];
- the sympathetic nervous system is overactive in insulin-resistant states [36], which results in a significant prolongation of P-wave duration and PWD [37,38];
- finally, angiotensin II receptor expression is upregulated in IR patients [39].

The activation of the renin-angiotensin-aldosterone system (RAAS) causes atrial fibrosis, cardiomyocyte apoptosis, and elicits reactive oxygen species generation [40]. The inhibition of RAAS by candesartan has been shown to prevent shortening of the atrial effective refractive period and preserve the rate of adaptation during rapid atrial pacing in dogs [41]. This indicates RAAS may be involved in the early process of electrical remodeling in AF.

5. Study limitations

There are several limitations of the present study. First, this study was of a cross-sectional design. Therefore, patients with MS were not followed prospectively for arrhythmic episodes. Second, some precise echocardiographic parameters of LA and LV diastolic dysfunction, such as LA volume, LA ejection fraction, isovolumetric relaxation time and deceleration time of early phase of mitral valve flow, were not available. Finally, inflammation markers, such as C-reactive protein, were not measured in the study. Accordingly, the association between the P-wave indices and inflammation in MS deserves further investigation.

6. Conclusion

Our study shows that PWD and Pmax are prolonged in MS, indicating that patients with MS already have atrial electrical and structural remodeling. Additionally, insulin resistance may play a key role in the changes of atrial conduction.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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