Additional Value of Early Repolarization Pattern in Prediction of Obstructive Coronary Artery Disease as Assessed by Coronary Angiography
Wei-Yi Mei, *MD, Li-Juan Liu, *MD, Qing Xu, *MD, Dong-Dan Zheng, MD and Yun-Jiu Cheng, MD

Summary
Recent reports show that an early repolarization pattern (ERP) is associated with a higher incidence of sudden cardiac death in patients with obstructive coronary artery disease (CAD). Sporadic case studies have pointed out that ERP might be related to obstructive CAD.

In consecutive patients who had undergone coronary angiography, we investigated the relationship between ERP and obstructive CAD by evaluating its association with coronary artery stenosis.

The study population consisted of 3785 patients (59.9% men; mean age 63.1 years) with or without obstructive CAD. Adjusting for major cardiovascular risk factors, ERP was significantly associated with obstructive CAD (adjusted odds ratio (OR): 2.24 [95% CI 1.70-2.95]) with an incremental predictive value (ROC AUC 0.76 versus 0.71, \(P = 0.02\); NRI 55.3%, \(P < 0.001\); IDI = 0.05, \(P = 0.008\)), specifically in subjects with low risk and intermediate risk. ERP also significantly improved the predictive value for multi-vessel disease (AUC: 0.77 versus 0.72, \(P = 0.02\) for two-vessel disease; 0.79 versus 0.73, \(P = 0.04\) for three-vessel disease). ERP was consistently associated with stenoses of 3 main coronary arteries.

ERP is associated with significant increased risk for obstructive CAD. Further studies are warranted to confirm our results and to elucidate the specific pathogenic mechanisms.

Key words: Ischemic heart disease, J-point elevation, Risk factors

A n early repolarization pattern (ERP) is defined as a J-point elevation from the baseline (0.1 mV) and or a notching or slurring morphology of the QRS complex in at least 2 contiguous leads on a standard 12-lead electrocardiogram (ECG). ERP has commonly been regarded as a benign finding because it is mostly observed in young, healthy individuals or athletes without structural heart disease. However, recent large cohort studies and meta-analysis demonstrated an association between ERP and fatal arrhythmias or sudden cardiac death in patients without structural heart disease. In addition, other observational studies reported that ERP was related to ventricular fibrillation and sudden cardiac death in patients with obstructive coronary artery disease (CAD).

Obstructive CAD is the leading cause of mortality and morbidity worldwide. Several risk prediction methods have been developed to estimate the probability of a CAD event based on traditional risk factors, such as the Framingham risk score and QRISK. This calls for the need to improve its risk prediction accuracy. Recently, several case reports have described an augmentation of J point by myocardial ischemia and our previous prospective cohort study also reported positive risk of ERP associated with CHD mortality. This raises the possibility that ERP might be associated with obstructive CAD. In this study, we aimed to evaluate the association of ERP with obstructive CAD detected via coronary angiography and whether the inclusion of ERP could improve the prediction accuracy of obstructive CAD.

Methods

Study population: We retrospectively enrolled Chinese individuals who underwent coronary angiography and 12-lead resting ECG at the First Affiliated Hospital of Sun Yat-Sen University in Guangzhou, China from March

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was also tested. Obstructive CAD was also classified based on a modified model of the coronary tree with 15 segments. The stenotic lesions were evaluated and described as the percentage of lumen diameter reduction. Significant or obstructive CAD was primarily defined as stenosis ≥ 50% in any major epicardial coronary artery, although the other typical definition of obstructive CAD using the alternative cut-off of a stenosis diameter of ≥ 70% was also tested. Obstructive CAD was also classified into single-vessel or multi-vessel (two- and three-vessel) disease. Angiograms were graded by visual inspection by the cath-lab physician performing the diagnostic procedure, who was blinded to all non-invasive data specific to the study.

Electrocardiographic analysis: All 12-lead resting ECGs performed prior to coronary angiography were reviewed for analysis. Briefly, an ERP is present if all of the following criteria are met: (1) an end-QRS notch or slur on the final 50% of the downslope of a prominent R-wave; (2) J-point ≥ 0.1 mV in two or more contiguous leads of the 12-lead ECG, excluding leads V1-V3; and (3) QRS duration < 120 ms. In the present study, we also analyzed the amplitude of J-point elevation (0.10-0.2 mV or ≥ 0.2 mV), J wave distribution (inferior and/or lateral leads), J wave morphology (notching or slurring), and ST-segment patterns after J point (rapidly ascending or horizontal/descending). All ECG records were read and analyzed in random order by 3 independent cardiologists who were blinded to the patients’ medical conditions.

Coronary angiography: All patients underwent coronary angiography for evaluation of palpitations, chest pain, pre-operative conditions, and malignant ventricular arrhythmia. Coronary arteries were visualized in left and right oblique planes with cranial and caudal angulations. The presence of coronary stenosis was anatomically assessed based on a modified model of the coronary tree with 15 segments. The stenotic lesions were evaluated and described as the percentage of lumen diameter reduction. Significant or obstructive CAD was primarily defined as stenosis ≥ 50% in any major epicardial coronary artery, although the other typical definition of obstructive CAD using the alternative cut-off of a stenosis diameter of ≥ 70% was also tested. Obstructive CAD was also classified into single-vessel or multi-vessel (two- and three-vessel) disease. Angiograms were graded by visual inspection performed by the cath-lab physician performing the diagnostic procedure, who was blinded to all non-invasive data specific to the study.

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Statistical analysis: All continuous data are presented as the mean and standard deviation (SD), and categorical data are reported as numbers and percentages in each group. Unpaired t-tests and the chi-square test were performed to compare continuous and categorical variables, respectively. Multivariate logistic regression analysis was conducted to identify the relationship between ERP and obstructive CAD, adjusted for age, sex, body mass index, hypertension, hyperlipidemia, diabetes mellitus, and smoking status. Receiver operating characteristic (ROC) curves were subsequently generated using CAD as the event. The added value of ERP for CAD diagnosis was evaluated by comparing the areas under the receiver operating characteristics curve (ROC AUC) of the multivariable logistic regression models without ERP and with ERP. For reclassification, we computed the integrative discriminative improvement (IDI) and net reclassification improvement (NRI) associated with the addition of ERP to the model. Statistical analysis was performed with SPSS version 20.0 software (SPSS Inc., Chicago, IL, USA). A P-value of < 0.05 was considered statistically significant.

Results

Baseline characteristics: After application of exclusion criteria, we present results for 3785 individuals undergoing coronary angiography, with a male proportion of 59.9% and a mean age of 63.1 years. In the study population, the overall prevalence of ERP was 21.6%, 66.9% of the patients had hypertension, 25.6% had hyperlipidemia, 32.6% had diabetes mellitus, and 34% were current smokers. Most subjects (48.0%) were low in FRS risk, while 28.5% were intermediate risk and 23.5% high risk. Table I lists the baseline characteristics of the study population. Individuals with ERP were more often male and current smokers, had a lower BMI, lower blood pressure, and lower TC, LDL-C and TG levels, and had a higher QRS angle than those without ERP. At baseline, mean age and heart rate were not significantly different between subjects with and without ERP. In addition, subjects with palpitations, chest pain, a pre-operative condition, or malignant ventricular arrhythmia were not significantly different between the two groups.

Association between early repolarization pattern and obstructive coronary artery disease: Obstructive CAD was observed in 545 (66.7%) and 1457 (49.9%) patients in the ERP and no ERP groups (P< 0.001), respectively. Compared to those without ERP, subjects with ERP were significantly associated with obstructive CAD (adjusted odds ratio (OR): 2.24 [95% CI 1.70-2.95]), adjusted for traditional cardiovascular risk factors (Table II). Similar results were achieved for men (aOR: 2.06 [95% CI 1.51-2.81]) and women (aOR: 2.33 [95% CI 1.76-3.08]) when stratified analyses were performed by gender (P = 0.56). Other factors associated with CAD included old age, diabetes mellitus, and current smoking. On ROC curve analysis, the model for obstructive CAD had a significantly higher predictive value when ERP was included (AUC: 0.76 [95% CI 0.73-0.79]) compared to when it was not (AUC: 0.71 [95% CI 0.68-0.74]; P = 0.02) (Table II; Figure). The reclassification analysis yielded both a signifi-
Table I. Baseline Subject Characteristics for Overall Sample and by ERP Status

<table>
<thead>
<tr>
<th>Subject characteristics</th>
<th>All Subjects (n = 3785), mean (SD) or %</th>
<th>No ERP (n = 2968), mean (SD) or %</th>
<th>ERP (n = 817), mean (SD) or %</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.1 (11.5)</td>
<td>63.1 (11.3)</td>
<td>63.0 (12.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Male (%)</td>
<td>2267 (59.9)</td>
<td>1733 (58.4)</td>
<td>534 (65.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Risk factors for vascular events (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2531 (66.9)</td>
<td>1999 (67.3)</td>
<td>532 (65.1)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>968 (25.6)</td>
<td>820 (27.6)</td>
<td>148 (18.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1235 (32.6)</td>
<td>993 (33.5)</td>
<td>242 (29.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>137.4 (24.8)</td>
<td>138.0 (25.9)</td>
<td>135.0 (19.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79.6 (15.2)</td>
<td>80.1 (15.9)</td>
<td>77.7 (12.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>1287 (34.0)</td>
<td>985 (33.2)</td>
<td>302 (37.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td></td>
<td>24.4 (4.2)</td>
<td>24.5 (4.3)</td>
<td>24.1 (4.0)</td>
</tr>
<tr>
<td>Laboratory values, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mean (SD), mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>187.9 (51.3)</td>
<td>190.6 (52.4)</td>
<td>178.2 (46.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>118.1 (40.5)</td>
<td>120.3 (40.8)</td>
<td>110.1 (38.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>40.8 (10.2)</td>
<td>40.8 (10.2)</td>
<td>40.8 (10.1)</td>
<td>0.95</td>
</tr>
<tr>
<td>Triglycerides, mean (SD), mg/dL</td>
<td></td>
<td>161.2 (152.1)</td>
<td>164.7 (159.3)</td>
<td>148.3 (121.6)</td>
</tr>
<tr>
<td>Electrocardiographic findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71.0 (14.0)</td>
<td>71.5 (13.9)</td>
<td>69.4 (14.2)</td>
<td>0.78</td>
</tr>
<tr>
<td>PR interval, ms</td>
<td>166.7 (32.1)</td>
<td>166.7 (30.2)</td>
<td>166.6 (38.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>QTc duration, ms</td>
<td>422.6 (30.1)</td>
<td>423.0 (30.1)</td>
<td>421.1 (30.2)</td>
<td>0.55</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>95.1 (15.1)</td>
<td>95.2 (14.9)</td>
<td>94.7 (15.9)</td>
<td>0.99</td>
</tr>
<tr>
<td>QRS angle, degrees</td>
<td>26.1 (38.3)</td>
<td>22.8 (39.4)</td>
<td>38.2 (31.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Left ventricular hypertrophy on electrocardiogram (%)</td>
<td>551 (14.6)</td>
<td>443 (14.9)</td>
<td>108 (13.3)</td>
<td>0.22</td>
</tr>
<tr>
<td>FRS risk groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1815 (48.0)</td>
<td>1394 (47.0)</td>
<td>421 (51.5)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>1079 (28.5)</td>
<td>791 (26.7)</td>
<td>288 (35.3)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>891 (23.5)</td>
<td>783 (26.4)</td>
<td>108 (13.2)</td>
<td></td>
</tr>
<tr>
<td>Reasons for coronary angiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>792 (20.9)</td>
<td>618 (20.8)</td>
<td>174 (21.3)</td>
<td>0.77</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2583 (68.2)</td>
<td>2027 (68.3)</td>
<td>556 (68.1)</td>
<td>0.90</td>
</tr>
<tr>
<td>Malignant ventricular arrhythmia</td>
<td>331 (8.7)</td>
<td>258 (8.7)</td>
<td>73 (8.9)</td>
<td>0.83</td>
</tr>
<tr>
<td>Pre-operative examination</td>
<td>79 (2.1)</td>
<td>65 (2.2)</td>
<td>14 (1.7)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

*Significance tests for comparisons by J wave pattern status based on two-sample t-test for continuous subject characteristics and Pearson’s χ² test for categorical subject characteristics. †SI conversion factors: To convert total, LDL, and HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; glucose to mmol/L, multiply by 0.0555.

Table II. Association and Incremental Predictive Value of ERP with Obstructive CAD

<table>
<thead>
<tr>
<th></th>
<th>CAD &lt; 50%</th>
<th>CAD ≥ 50%</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
<th>ROC AUC (basic model)</th>
<th>ROC AUC (ERP added)</th>
<th>ROC AUC P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERP (−)</td>
<td>1511</td>
<td>1457</td>
<td>1</td>
<td>1</td>
<td>0.71 (0.68-0.74)</td>
<td>0.76 (0.73-0.79)</td>
<td>0.02</td>
</tr>
<tr>
<td>ERP (+)</td>
<td>272</td>
<td>545</td>
<td>2.08 (1.77-2.44)</td>
<td>2.24 (1.70-2.95)</td>
<td>0.71 (0.68-0.74)</td>
<td>0.76 (0.73-0.79)</td>
<td></td>
</tr>
<tr>
<td>FRS low risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERP (−)</td>
<td>825</td>
<td>569</td>
<td>2.75 (2.19-3.45)</td>
<td>2.88 (2.31-3.59)</td>
<td>0.72 (0.69-0.75)</td>
<td>0.78 (0.75-0.81)</td>
<td>0.006</td>
</tr>
<tr>
<td>ERP (+)</td>
<td>141</td>
<td>280</td>
<td>2.17 (1.63-2.87)</td>
<td>2.26 (1.51-3.38)</td>
<td>0.70 (0.67-0.73)</td>
<td>0.75 (0.72-0.78)</td>
<td>0.02</td>
</tr>
<tr>
<td>FRS intermediate risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERP (−)</td>
<td>405</td>
<td>386</td>
<td>1.07 (0.70-1.64)</td>
<td>1.09 (0.73-1.63)</td>
<td>0.68 (0.63-0.73)</td>
<td>0.69 (0.64-0.74)</td>
<td>0.78</td>
</tr>
<tr>
<td>ERP (+)</td>
<td>94</td>
<td>194</td>
<td>2.17 (1.63-2.87)</td>
<td>2.26 (1.51-3.38)</td>
<td>0.70 (0.67-0.73)</td>
<td>0.75 (0.72-0.78)</td>
<td></td>
</tr>
<tr>
<td>FRS high risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERP (−)</td>
<td>281</td>
<td>502</td>
<td>1.07 (0.70-1.64)</td>
<td>1.09 (0.73-1.63)</td>
<td>0.68 (0.63-0.73)</td>
<td>0.69 (0.64-0.74)</td>
<td></td>
</tr>
<tr>
<td>ERP (+)</td>
<td>37</td>
<td>71</td>
<td>1.07 (0.70-1.64)</td>
<td>1.09 (0.73-1.63)</td>
<td>0.68 (0.63-0.73)</td>
<td>0.69 (0.64-0.74)</td>
<td></td>
</tr>
</tbody>
</table>

*Multivariate logistic regression analysis adjusted for age, sex, body mass index, hypertension, hyperlipidemia, diabetes mellitus and smoking status. ERP indicates early repolarization; CAD, coronary artery disease; FRS, Framingham risk score; OR, odds ratio; and ROC AUC, area under the receiver operating characteristics curve.
cant continuous NRI as 55.3% (95% CI 27.7-82.9%; \( P < 0.001 \)) and a statistically significant IDI (IDI = 0.05, 95% CI 0.03-0.07; \( P = 0.008 \)). Sensitivity analysis by adding ischemic electrocardiogram changes (indicated by ST segment depression) to the traditional risk factors only slightly increased the predictive value of CAD (AUC: 0.74 [95% CI 0.71-0.77]). However, further addition of ERP could still improve the predictive values (AUC: 0.78 [95% CI 0.75-0.81]; NRI: 42.7% [95% CI 22.3%-63.1%]; IDI: 0.03 [95% CI 0.01%-0.05%]).

The study population was then divided into subjects at low (< 10%), intermediate (10-20%), and high (> 20%) FRS. ERP was tested for incremental predictive value for CAD, separately in each FRS category. ERP was significantly associated with CAD in both the low and intermediate FRS categories (aOR: 2.88 [95% CI 2.31-3.59] for low risk group; 2.26 [95% CI 1.51-3.38] for intermediate risk group), but not in the high FRS category. The risk estimate seemed to be higher in subjects with low risk as compared with subjects with intermediate and high risk. In addition, the incremental predictive value of ERP was also only significant in the low risk and intermediate risk groups (AUC: 0.78 versus 0.72, \( P = 0.006 \) for low risk group; 0.75 versus 0.70, \( P = 0.02 \) for high risk group) (Table II).

We further assessed the association between ERP and obstructive CAD according to the severity of coronary stenosis. Interestingly, although ERP remained consistently associated with single-vessel and multi-vessel disease, adding ERP to the fully adjusted model only significantly improved the predictive value for multi-vessel disease (AUC: 0.77 versus 0.72, \( P = 0.02 \) for two-vessel disease; 0.79 versus 0.73, \( P = 0.04 \) for three-vessel disease). No significant difference could be observed between the discrimination value of ERP for the presence of single-vessel disease. When we used the >70% stenosis definition, ERP maintained its significant discrimination incremental value for obstructive CAD (AUC: 0.80 versus 0.72, \( P = 0.03 \)), but the magnitude of the AUC difference seemed to be higher than what was demonstrated with the standard prediction of at least one coronary stenosis > 50% (AUC difference: 0.08 versus 0.05, \( P = 0.03 \)) (Table III).

**Assessment of stenoses of 3 main coronary arteries according to early repolarization pattern phenotype:** Association of the 3 main coronary arteries with different ERP phenotypes is shown in Table IV. ERP was consistently associated with stenosis of the right coronary artery (aOR: 2.72 [95% CI 1.36-5.44]), left anterior descending coronary (aOR: 2.31 [95% CI 1.31-4.07]), and left circumflex coronary (aOR: 2.30 [95% CI 1.13-4.68]). Of note, compared with subjects with a J wave amplitude of 0.1-0.19 mV, those with a J wave amplitude of at least 0.2 mV experienced higher risk for stenoses of the 3 main coronary arteries. Coronary stenosis was observed in subjects with a J wave in inferior leads or lateral leads, but not in those with J waves in both inferior and lateral leads. There was no significant difference in coronary stenosis in subjects with the notching type of ERP as compared with those with the slurring type. Interestingly, ERP with a horizontal or descending ST segment, rather than ERP with a rapidly ascending ST segment, was associated with stenoses of the 3 main coronary arteries.

**Discussion**

The present study, involving 3785 individuals undergoing coronary angiography, found a 2-fold increase in the risk of obstructive CAD in subjects with ERP compared with those without ERP, even after adjustment for

*Figure.* Comparison of area under the receiver operating characteristic curve (AUC) for obstructive CAD between the full model without and with ERP. ERP indicates early repolarization pattern; and CAD, coronary artery disease.

**Table III.** Association Between ERP and Obstructive CAD According to Severity of Coronary Stenosis

<table>
<thead>
<tr>
<th></th>
<th>No ERP (n = 2464)</th>
<th>Any ERP (n = 728)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI) *</th>
<th>ROC AUC (basic model)</th>
<th>ROC AUC (ER added)</th>
<th>P-value for ROC AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-vessel disease</td>
<td>606</td>
<td>210</td>
<td>1.89 (1.27-2.81)</td>
<td>1.92 (1.29-2.86)</td>
<td>0.68 (0.63-0.73)</td>
<td>0.70 (0.65-0.75)</td>
<td>0.58</td>
</tr>
<tr>
<td>Two-vessel disease</td>
<td>410</td>
<td>182</td>
<td>2.42 (1.53-3.83)</td>
<td>2.36 (1.47-3.79)</td>
<td>0.72 (0.69-0.75)</td>
<td>0.77 (0.74-0.80)</td>
<td>0.02</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>417</td>
<td>154</td>
<td>2.01 (1.30-3.11)</td>
<td>2.13 (1.33-3.41)</td>
<td>0.73 (0.69-0.77)</td>
<td>0.79 (0.75-0.83)</td>
<td>0.04</td>
</tr>
<tr>
<td>CAD &gt; 70% disease</td>
<td>951</td>
<td>478</td>
<td>2.79 (2.36-3.31)</td>
<td>2.82 (2.44-3.26)</td>
<td>0.72 (0.67-0.77)</td>
<td>0.80 (0.75-0.85)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Multivariate logistic regression analysis adjusted for age, sex, body mass index, hypertension, hyperlipidemia, diabetes mellitus and smoking status. ERP indicates early repolarization; CAD, coronary artery disease; OR, odds ratio; and ROC AUC, area under the receiver operating characteristics curve.
several conventional risk factors. Among low-risk and intermediate-risk patients, the presence of ERP in addition to traditional risk factors predicts higher rates of obstructive CAD, especially of multi-vessel disease. J-point elevation in inferior leads or lateral leads and a horizontal or descending ST segment appeared to connote higher risk for obstructive CAD.

Recent studies have confirmed smoking, hypertension, diabetes, and dyslipidemia to be risk factors for obstructive CAD. This study is the first to our knowledge to report the association between ERP and coronary stenosis diagnosed by coronary angiography. The risk magnitude appears to be at least as strong as those reported for well-established major risk factors.\(^{20,21}\) In real-world clinical settings, low-risk and intermediate-risk patients with CAD might be more easily subjected to misdiagnosis than high-risk patients. In addition, patients with multi-vessel CAD had a greater chance of developing acute myocardial infarction and sudden cardiac death than those with single-vessel CAD, and the early detection of this patient group could be of greater importance.\(^{22,23}\) Therefore, our study could have a potential interesting clinical implication, thanks to the widespread availability and low cost of ECG, to stratify patients with low or intermediate risk into those who need coronary angiography from those who do not.

In agreement with the results of previous studies, the ERP was associated with several demographic and other characteristics, such as male sex, current smoking, lower BMI, and blood pressure.\(^{24}\) In addition, TC, LDL-C, and TG were lower in subjects with ERP than in those without this abnormality. However, average resting heart rate and age were not systematically different between subjects with ERP and those without ERP. Previous studies showed that the prevalence of ERP in the general population apparently varied between 2% and 31% according to the inclusion or exclusion of ST-segment elevation.\(^{25,26}\) However, according to a consensus paper published in 2015, ST-segment elevation is not a required criterion for the diagnosis of ERP.\(^{27}\) Accordingly, our study using the agreed definition found 21.6% of subjects undergoing coronary angiography manifested end QRS notch or slurring.

The underlying mechanisms involved in the association between ERP and obstructive CAD remain unclear, but several plausible explanations have been suggested. First, myocardial ischemia might reduce inward currents (principally \(I_{\text{Na}}\) and \(I_{\text{Ca}}\)), which increases outward potassium currents mediated by the \(I_{\text{K}}\) and \(I_{\text{Na}-\text{ATP}}\) and \(I_{\text{Na}-\text{K}}\) channels, especially in the epicardium, resulting in a disproportionate amplification of the repolarizing current in the epicardial myocardium, and thus transmural differences in the early phases (phases 1 and 2) of the cardiac action potential that might be responsible for the J wave on electrocardiography.\(^{28}\) Second, another possible interpretation for this association may be that J-point elevation on the ECG represented a peri-infarction block, which usually suggests latent CAD. This hypothesis was supported by augmenta-

### Table IV. Assessment of Stenoses of Three Main Coronary Arteries According to ERP Phenotype

<table>
<thead>
<tr>
<th></th>
<th>Any vessel</th>
<th>Right coronary artery</th>
<th>Left anterior descending coronary</th>
<th>Left circumflex coronary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Adjusted OR (95% CI) *</td>
<td>P value</td>
<td>No. of cases</td>
</tr>
<tr>
<td>No ERP ((n = 2464))</td>
<td>1457</td>
<td>2.24 (1.90-2.64)</td>
<td>0.004</td>
<td>817</td>
</tr>
<tr>
<td>Any ERP pattern ((n = 728))</td>
<td>545</td>
<td>1.79 (1.21-2.65)</td>
<td>0.03</td>
<td>311</td>
</tr>
<tr>
<td>J wave slurring ((n = 272))</td>
<td>203</td>
<td>1.97 (1.45-5.68)</td>
<td>0.007</td>
<td>133</td>
</tr>
<tr>
<td>J wave location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior leads only ((n = 374))</td>
<td>318</td>
<td>1.97 (1.28-3.03)</td>
<td>0.02</td>
<td>178</td>
</tr>
<tr>
<td>Lateral leads only ((n = 178))</td>
<td>154</td>
<td>2.17 (1.03-4.57)</td>
<td>0.04</td>
<td>91</td>
</tr>
<tr>
<td>Both inferior and lateral leads ((n = 84))</td>
<td>73</td>
<td>2.42 (0.90-6.51)</td>
<td>0.12</td>
<td>42</td>
</tr>
<tr>
<td>Configuration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notching ((n = 199))</td>
<td>175</td>
<td>2.48 (1.27-4.84)</td>
<td>0.02</td>
<td>98</td>
</tr>
<tr>
<td>Slurring ((n = 437))</td>
<td>370</td>
<td>1.93 (1.30-2.87)</td>
<td>0.01</td>
<td>213</td>
</tr>
<tr>
<td>ST segment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapidly ascending ((n = 112))</td>
<td>98</td>
<td>2.48 (0.82-7.19)</td>
<td>0.11</td>
<td>63</td>
</tr>
<tr>
<td>Horizontal or descending ((n = 524))</td>
<td>447</td>
<td>2.01 (1.38-2.93)</td>
<td>0.007</td>
<td>248</td>
</tr>
</tbody>
</table>

*Multivariate logistic regression analysis adjusted for age, sex, body mass index, hypertension, hyperlipidemia, diabetes mellitus and smoking status. ERP indicates early repolarization; and OR, odds ratio.
tion of the J wave by rapid pacing in a patient with vaso-
spastic angina.29 Third, of note, in our study, ERP in infe-
rior or lateral leads was associated with stenoses of all 3
main coronary arteries. This indicates that the arterial ter-
ritory of significant stenosis might not influence the local-
ization of ERP in ECG significantly and a different mechanism
other than ischemia or peri-infarction block might be involved. It is possible that the pathogeneses of
ERP and CAD might share common factors, such as
calcium-sensing receptors (CSR), which have been re-
ported to be involved in the development of vascular cal-
cification and atherosclerosis.21 In another way, CSR in
the endothelial layer of coronary arteries could activate
I_{Ks} and intensify outward potassium currents, which may
cause J waves on ECG. Given that ERP could increase the
risk of sudden cardiac death and that CAD was associated
with ERP, we proposed that ERP might lie on the path-
way between obstructive CAD and sudden cardiac death
for some patients.

The strengths of this study include the strict inclusion
criteria, the large number of patients analyzed, and the
fact that all subgroup analyses were prespecified a priori.
Another strength is that cases of obstructive CAD were
detected via coronary angiography, which remains the
“gold standard” for the assessment of coronary anatomy.
A further strength of this study is the application of a
newly agreed definition in the diagnosis of ERP, which
might produce repeatable measurements, and greatly re-
duce between-reader variability and misdiagnosis.

There are several limitations to our study. First, we
selected patients who had undergone coronary angiogra-
phy for various reasons, such as chest pain, pre-operative
evaluation, or malignant ventricular arrhythmia, which
could have introduced selection bias because some pa-
ients with obstructive CAD might be asymptomatic. Sec-
ond, we could not find the ECG before coronary angiogra-
phy for most patients; we thus cannot comment on
whether ERP is a permanent or transient ECG pattern, or
exclude the possibility that some subjects with ERP be-
fore admission might exhibit no ERP on ECG prior to
coronary angiography. Third, some important confounding
factors possibly associated with obstructive CAD, such as
diet, physical activity, and socioeconomic factors were not
evaluated. Fourth, this study mainly included middle-aged
and elderly subjects who underwent coronaryangiogra-
phy, and thus we cannot comment on the implication of
ERP for younger subjects, which calls for further external
validation of our model in this population group. Fifth,
we excluded a small proportion of subjects (<1%) for whom
J-point amplitude data were missing; however, this might
not influence the results significantly given the small sam-
ple size excluded. In conclusion, ERP was independently
associated with obstructive CAD in patients who under-
went coronary angiography, with incremental predictive
value to significant coronary stenosis, particularly among
subjects with low risk or intermediate risk and those with
multi-vessel disease. Further studies, including well-
designed prospective cohort studies and experimental
studies, are warranted to confirm our results and to elucidate
the specific pathogenic mechanisms.

Disclosures

Conflicts of interest: None.

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