Incidence and Prognostic Value of Early Repolarization Pattern in the 12-Lead Electrocardiogram

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Background—Early repolarization pattern is a common ECG finding characterized by J-point elevation and QRS notching or slurring in the inferior and/or lateral leads, yet little is known about its incidence and long-term prognosis in Asian populations.

Methods and Results—We reviewed all the ECG records of the 5976 atomic-bomb survivors who were examined at least once during our biennial health examination in Nagasaki, Japan, between July 1958 and December 2004. We defined early repolarization pattern as ≥0.1-mV elevation of the J point or ST segment, with notching or slurring in at least 2 inferior and/or lateral leads. We assessed unexpected, cardiac, and all-cause death risk by Cox analysis. We identified 1429 early repolarization pattern cases (779 incident cases) during follow-up, yielding a positive rate of 23.9% and an incidence rate of 715 per 100 000 person-years. Early repolarization pattern had an elevated risk of unexpected death (hazard ratio, 1.83; 95% confidence interval, 1.12 to 2.97; P=0.02) and a decreased risk of cardiac (hazard ratio, 0.75; 95% confidence interval, 0.60 to 0.93; P<0.01) and all-cause (hazard ratio, 0.85; 95% confidence interval, 0.78 to 0.93; P<0.01) death. In addition, both slurring and notching were related to higher risk of unexpected death (hazard ratio, 2.09; 95% confidence interval, 1.06 to 4.12; P=0.03), as was early repolarization pattern manifestation in both inferior and lateral leads (hazard ratio, 2.50; 95% confidence interval, 1.29 to 4.83; P<0.01).

Conclusions—Early repolarization pattern is associated with an elevated risk of unexpected death and a decreased risk of cardiac and all-cause death. Specific early repolarization pattern morphologies and location are associated with an adverse prognosis. (Circulation. 2011;123:00-00.)

Key Words: death, sudden ■ epidemiology ■ electrocardiography ■ mortality

Sudden cardiac death is a major health issue, and accounts for 300 000 to 400 000 deaths per year in the United States.1,2 Coronary artery disease, cardiomyopathy, left ventricular hypertrophy, valvular disease, congenital heart disease, and primary electrophysiological abnormalities are the major causes of sudden cardiac death.1,2 Approximately 5% of sudden cardiac deaths caused by ventricular tachyarrhythmias occur in the absence of structural heart or coronary artery disease and are attributable to primary electrophysiological abnormalities. Some cases with ventricular tachyarrhythmias show a characteristic 12-lead ECG pattern such as a long-QT interval (long-QT syndrome) and a coved-type ST-segment elevation in the right precordial leads (V1, V2, and V3; Brugada syndrome).3,4

Clinical Perspective on p ●●●
Early repolarization pattern (ERP) is characterized by an elevation of the QRS-ST junction (J point) and QRS notching or slurring (J wave) in multiple leads, especially in the inferior and/or left precordial leads, and is found in a relatively large proportion (1% to 13%) in previous reports.5,6 Although conventionally considered benign,5 it is potentially arrhythmogenic,6 and in 2 clinical case-control studies, patients with a history of idiopathic ventricular fibrillation (VF) showed an increased prevalence of ERP.7,8 It has recently been reported that ERP in the inferior leads is associated with increased risk of cardiac death in Western populations.10 Not much is known, however, about the incidence and long-term prognosis of ERP in Asian populations. Thus, we prospectively examined the incidence and prognostic value of ERP in terms of unexpected death, cardiac death, and all-cause death in Nagasaki Adult Health Study (AHS) subjects.

Methods

General Procedures
Since July 1, 1958, 7564 atomic-bomb survivors (3374 men) in Nagasaki, Japan, have been invited to participate in biennial health examinations as part of a follow-up program conducted by the Radiation Effects Research Foundation (RERF). Detailed descrip-

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tions of the program have been published elsewhere.\textsuperscript{11,12} Each examination includes a standard 12-lead ECG obtained by the regular procedure. We extracted 5976 subjects (2612 men) who had been examined at least once between July 1, 1958, and December 31, 2004, and did not have intraventricular conduction disturbances and pacemaker implantation at the first examination and reviewed all the ECG records (12.2 ± 7.5 ECG records per subject) obtained during the follow-up period. The mean length of follow-up for ECG recordings was 23.6 ± 14.7 years. The date of the first examination is different for each individual. During the first 2 years from July 1, 1958, to June 30, 1960, 2912 subjects underwent examination; the remaining 3064 subjects underwent their first examination after that period. We treated subjects who already had ERP at their first examination regardless of the date of examination as prevalent cases and subjects who first showed ERP after their second examination as incident cases. We used the current dosimetry System DS02 to estimate the bone marrow atomic-bomb radiation doses of individual subjects.\textsuperscript{13} The Research Protocol Review and Human Investigation Committees of RERF approved the protocol (RP A 14–08).

**Definition and Confirmation of Early Repolarization Pattern and Brugada-Type Electrocardiogram**

Using criteria similar to those of Haïssaguerre and colleagues,\textsuperscript{7} we defined ERP cases as having (1) an elevation of the QRS-ST junction (J point) in notching formation (positive J deflection inscribed on the S wave) or of the ST segment in slurring formation (smooth transition from QRS complex to the ST segment) in at least 2 leads and (2) an amplitude of QRS-ST junction (J point) or ST-segment elevation ≥0.1 mV above the baseline as QRS notching or slurring in the inferior leads (II, III, aVF), lateral leads (I, aVL, V\textsubscript{4} through V\textsubscript{6}), or both\textsuperscript{2} (Figure 1) at least once during follow-up. In slurring formation, because the transition from QRS complex to ST segment is smooth or the J point may be hidden in the QRS complex, we used ≥0.1 mV of the ST-segment elevation to indicate high-takeoff QRS-ST junction as the criterion. We classified the time course of the J-point abnormality into 1 of 2 categories: a persistent course showing permanent abnormalities or an intermittent course showing transient disappearance of the J wave itself or normalization of the magnitude of the J point during follow-up (Figure 2). During follow-up, we classified cases by positive-ERP lead location (inferior, lateral, or both) and by J-wave morphology (notching, slurring, or both). We defined the onset of ERP as the date of its first appearance during follow-up and used the age at the onset of ERP in calculating the incidence. One cardiologist (D.H.) reviewed the 12-lead ECGs of all subjects without knowledge of the clinical diagnosis or death certificate information. A second cardiologist (K. Matsuo) blindly reviewed all the ECG records of 200 subjects (50 with ERP and 150 without ERP) who were randomly selected from the 5976 subjects. The concordance rate was 86.0% for ERP diagnosis. Next, he blindly reviewed all the ECG records obtained during follow-up for 194 subjects (94 subjects with only slurring in either inferior or lateral lead and 100 subjects with only notching in either inferior or lateral lead) among the 1429 subjects diagnosed as having ERP by the first cardiologist. The concordance rate was 83.8% for lead location and 81.3% for morphology.

In the diagnostic criteria of Brugada syndrome by consensus reports,\textsuperscript{14,15} type 1 characterized by ≥0.2-mV coved-type ST segment elevation is essential, whereas types 2 and 3 characterized by saddleback-type ST elevation are not.\textsuperscript{14,15} Therefore, in this study, we defined subjects with type 1 characterized by ≥0.2-mV coved-type ST-segment elevation in ≥1 right precordial leads (V\textsubscript{1} through V\textsubscript{3}) at least once during follow-up as Brugada-type ECG cases.

**Definition and Confirmation of Sudden Death, Unexplained Accidental Death, and Cardiac Death**

The RERF followed the vital status of all participants using Japan’s family registration system. We collected all of the death certificates from July 1, 1958, to December 2004 to check the cause and circumstance of death for deceased subjects and defined 3 types of death as we did in our Brugada-type ECG study: sudden death, an out-of-hospital death occurring within 1 hour of the onset of acute symptoms; unexplained accidental death, an accidental death in which VF might have been the cause of the accident; and unexpected death, a sudden death or an unexplained accidental death.\textsuperscript{16} We treated death resulting from congestive heart failure and ischemic heart disease as cardiac death.

**Statistical Analysis**

We calculated the 46.5-year (July 1, 1958, to December 31, 2004) incidence on the basis of the age of incident cases at ERP appearance by a person-year method, stratified according to age. We used Cox regression analysis to assess the long-term prognosis of ERP and Brugada-type ECG cases after controlling for age and sex. We compared ERP and Brugada-type ECG cases with control subjects who had neither ERP nor Brugada-type ECG with respect to unexpected death, cardiac death, and death resulting from all causes. We also assessed unexpected death risk according to lead location and J-wave morphology in ERP cases. Survival time is the time from the date of the first examination for controls and prevalent ERP and Brugada-type ECG cases and the date of the first appearance for incident ERP and Brugada-type ECG cases to the date of death or December 31, 2004, whichever came first. All analyses were conducted with SAS for UNIX (SAS Institute, Cary, NC).\textsuperscript{17} We expressed the data as mean±SD and considered \( P<0.05 \) to be statistically significant.
Results

Incidence of Early Repolarization Pattern

We identified 1429 ERP cases (815 men) among 5976 AHS subjects during the whole study period (July 1, 1958, to December 31, 2004); 650 cases (413 men) were classified as prevalent cases and 779 cases (402 men) were classified as incident cases (mean ± SD age at first appearance of ERP, 47.2 ± 15.4 years), yielding a follow-up positive rate of 23.9% (1429 of 5976) and an incidence of 715 per 100 000 person-years (Table 1). Incidence was highest in the second decade of life for men and women and was almost identical between the sexes, whereas the male preponderance became obvious thereafter, leading to twice as high an overall incidence for men (Table 1). Radiation dose was not associated with ERP in both prevalent and incident cases (P = 0.89, data not shown).

We identified 30 Brugada-type ECG cases (see Table 2). Brugada-type ECGs showed a J-point elevation in the anterior precordial leads. Among them, 6 cases had both ERP and Brugada-type ECG (Figure 3).

Lead Location and Morphology of the J Wave

Table 3 shows the morphology and lead location of the J wave observed during the follow-up period. Almost all of the

Table 1. Number of Subjects at the First Examination for Each Individual and Incidence From July 1958 to December 2004

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Subjects, n</th>
<th>Person-Years*</th>
<th>Incident ERP Cases, n</th>
<th>Incidence, n/100 000 Person- y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>19</td>
<td>160</td>
<td>155</td>
<td>287</td>
<td>358</td>
</tr>
<tr>
<td>20–29</td>
<td>432</td>
<td>551</td>
<td>1798</td>
<td>2532</td>
</tr>
<tr>
<td>30–39</td>
<td>609</td>
<td>1250</td>
<td>5434</td>
<td>10 024</td>
</tr>
<tr>
<td>40–49</td>
<td>492</td>
<td>598</td>
<td>7009</td>
<td>14 811</td>
</tr>
<tr>
<td>50–59</td>
<td>533</td>
<td>478</td>
<td>9199</td>
<td>16 573</td>
</tr>
<tr>
<td>60–69</td>
<td>296</td>
<td>236</td>
<td>8718</td>
<td>14 724</td>
</tr>
<tr>
<td>70–79</td>
<td>80</td>
<td>78</td>
<td>4810</td>
<td>8858</td>
</tr>
<tr>
<td>≥80</td>
<td>10</td>
<td>18</td>
<td>1292</td>
<td>2587</td>
</tr>
<tr>
<td>Total</td>
<td>2612</td>
<td>3364</td>
<td>38 547</td>
<td>70 467</td>
</tr>
</tbody>
</table>

ERP indicates early repolarization pattern.

*Aggregate numbers of years contributed to each age category from 1958 to 2004 by all subjects remaining at risk for ERP.
ERP cases (98.3%) showed intermittent manifestations, and both characteristics changed over time (Figure 2).

Mortality From Unexpected Death, Cardiac Death, and All-Cause Death

Table 2 shows the breakdown of the 5976 subjects into ECG category and their cause of death. The 27 ERP cases with or without Brugada-type ECG (19 men; age at death, 68.6±19.1 years; age range, 20.7 to 96.1 years), 4 Brugada-type ECG cases without ERP (3 men; age at death, 59.5±12.4 years; age range, 42.3 to 71.7 years), and 45 controls (23 men; age at death, 65.6±16.3 years; age range, 24.2 to 95.8 years) had unexpected death. Age at unexpected death was not different among the 3 groups. The time interval between the first ECG appearance of ERP and unexpected death based on 16 incident ERP cases was 21.7±13.8 years (range, 2.5 to 42.3 years). In Cox proportional hazards analysis, ERP predicted unexpected death (HR, 1.83; 95% CI, 1.12 to 2.97; P=0.02) and had a favorable effect on cardiac (HR, 0.75; 95% CI, 0.60 to 0.93; P<0.01) and all-cause (HR, 0.85; 95% CI, 0.78 to 0.93; P<0.01) death (Table 4). We saw no unexpected deaths for patients with ERP with Brugada-type ECG and so could not calculate that HR for unexpected death.

Brugada-type ECG cases had the highest HR for unexpected death (HR, 27.15; 95% CI, 9.35 to 78.85; P<0.01), whereas in contrast to ERP cases, it had no favorable effects on cardiac and all-cause death (Table 4). Radiation dose was not associated with unexpected death (P=0.45; data not shown).

Discussion

As far as we know, this 5-decade study is the first Asian population-based study of the incidence and prognosis of ERP. We learned that ERP was a common ECG finding, with a follow-up positive rate of 23.9% and an incidence of 715 in 100 000 person-years, and was associated with a higher risk of unexpected death and a lower risk of cardiac and all-cause death. Although the subjects were atomic-bomb survivors, radiation dose was not associated with ERP or unexpected death, so the results should be generalizable.

Incidence of Early Repolarization Pattern

The prevalence of ERP has been reported to be 1% to 13%. However, because ERP (defined by the modified criteria of

Table 2. Cause of Mortality in Subjects With Early Repolarization Pattern, Brugada-Type ECG, and Neither Early Repolarization Pattern nor Brugada-Type ECG

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Subjects, n</th>
<th>All</th>
<th>Unexpected</th>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERP (with Brugada-type ECG)</td>
<td>1429 (6)</td>
<td>628 (4)</td>
<td>27 (0)</td>
<td>100 (0)</td>
</tr>
<tr>
<td>Brugada-type ECG without ERP</td>
<td>24</td>
<td>14</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Neither ERP nor Brugada-type ECG</td>
<td>4523</td>
<td>2262</td>
<td>45</td>
<td>434</td>
</tr>
<tr>
<td>Total</td>
<td>5976</td>
<td>2904</td>
<td>76</td>
<td>535</td>
</tr>
</tbody>
</table>

ERP indicates early repolarization pattern.

Table 3. Lead Location and Morphology of the J Wave During Follow-Up Among Subjects With Early Repolarization Pattern

<table>
<thead>
<tr>
<th>Lead location</th>
<th>Notching</th>
<th>Slurring</th>
<th>Notching and Slurring</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior</td>
<td>337</td>
<td>44</td>
<td>41</td>
<td>422</td>
</tr>
<tr>
<td>Lateral</td>
<td>335</td>
<td>54</td>
<td>172</td>
<td>561</td>
</tr>
<tr>
<td>Inferior and lateral</td>
<td>141</td>
<td>50</td>
<td>255</td>
<td>446</td>
</tr>
<tr>
<td>Total</td>
<td>813</td>
<td>148</td>
<td>468</td>
<td>1429</td>
</tr>
</tbody>
</table>

Figure 3. A case with both early repolarization pattern and Brugada-type ECG in chest leads V1 through V6. Coved-type ST elevation with 0.2 mV at the J point was seen in V1 and V2, and early repolarization pattern with notching morphology 0.1 mV at the J point was seen in V5 through V6. Coved-type ST elevation of Brugada-type ECG (V1 and V2) and notching morphology of early repolarization pattern (V5 through V6) at the last recorded beat are highlighted by circles.
Haïssaguerre and colleagues appeared intermittently, we based our calculation on both prevalent and incident cases and found that 23.9% manifested ERP at least once during follow-up, indicating that ERP was not a rare ECG finding. In past studies, only the prevalence, not incidence, of ERP has been reported because longitudinal studies covering the period before the diagnosis of ERP were lacking. We report the incidence of ERP for the first time here and reveal that the incidence of ERP was highest in the second decade of life in men and women and decreased thereafter (Table 1). It is possible that the difference in the age distribution of the subjects in the target cohort and the intermittent appearance of ERP may have affected the reported prevalence of ERP. It is also possible that if we used criteria other than the modified criteria of Haïssaguerre and colleagues, we would have found different incidence values.

The incidence of ERP that we observed (Table 1) was times as high as the incidence reported for Brugada-type ECG, whereas the male/female incidence ratio for ERP (1.95) was about one-fifth that of Brugada-type ECG, but the incidence of both ERP and Brugada-type ECG is high at a relatively young age. Because our cohort of atomic-bomb survivors did not include subjects who were years of age on July 1, 1958, and the appearance of ERP was intermittent, it is necessary to follow up a large number of the population who are years of age to arrive at a more precise value.

### Table 4. Age- and Sex-Adjusted Hazard Ratio for Each Group (Cox Analysis)

<table>
<thead>
<tr>
<th>Subjects, n</th>
<th>Unexpected Deaths, n</th>
<th>HR (95% CI)</th>
<th>Unexpected Death</th>
<th>Cardiac Death</th>
<th>All-Cause Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control*</td>
<td>4523</td>
<td>45</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>ERP</td>
<td>1429</td>
<td>27</td>
<td>1.83 (1.12–2.97)</td>
<td>0.75 (0.60–0.93)</td>
<td>0.85 (0.78–0.93)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lead location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>422</td>
<td>8</td>
<td>1.91 (0.88–4.14)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral</td>
<td>561</td>
<td>7</td>
<td>1.37 (0.61–3.04)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>446</td>
<td>12</td>
<td>2.50 (1.29–4.83)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Morphology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notching</td>
<td>813</td>
<td>11</td>
<td>1.36 (0.70–2.65)</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slurring</td>
<td>148</td>
<td>5</td>
<td>1.60 (0.61–4.24)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>468</td>
<td>11</td>
<td>2.09 (1.06–4.12)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Brugada-type ECG</td>
<td>24</td>
<td>4</td>
<td>27.15 (9.35–78.85)</td>
<td>0.47 (0.07–3.35)</td>
<td>1.09 (0.65–1.85)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5976</td>
<td>76</td>
<td>27.15 (9.35–78.85)</td>
<td>0.47 (0.07–3.35)</td>
<td>1.09 (0.65–1.85)</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval; and ERP, early repolarization pattern.

*Subjects with neither ERP nor Brugada-type ECG.

### Prognostic Value of Early Repolarization Pattern

Sinner et al recently reported in a prospective cohort study that ERP was associated with a to 4-fold increased risk of cardiac mortality, which was determined through the use of death certificates. They did not mention the association between ERP and unexpected death because cardiac death was assumed in the ninth version of the International Classification of Diseases codes 390 to 429 and 798. On the other hand, Haïssaguerre et al reported that ERP in the inferior or lateral leads was more frequent among patients with idiopathic VF than among control subjects. Rosso et al reported a similar association between ERP and idiopathic VF. Those studies were cross-sectional; here, in a prospective cohort study, ERP predicted unexpected death. How ERP did that, however, is unclear. It has been reported that 11% of Brugada syndrome patients show ERP in the inferior-lateral leads and that drug challenge tests provoke a coved pattern in the inferior-lateral leads in 4.6% of Brugada syndrome patients. Those observations suggest that ERP and Brugada syndrome overlap in phenotype and electrophysiological similarities. The presence of a prominent I<sub>Na</sub>-mediated action potential notch (spike and dome) in the epicardium, but not the endocardium, generates a transmural voltage gradient during the early phase of repolarization, which manifests J-wave and J-point elevation in the surface ECG in both ERP and Brugada syndrome. Heterogeneous loss of the action potential dome produces phase 2 reentry, leading to polymorphic ventricular tachycardia/VF. It is possible that ERP has a vulnerability to arrhythmias that is due to transmural heterogeneity of ventricular repolarization and that ERP is affected by such factors as testosterone and drugs through ion channel activity.

A J-wave manifestation in both inferior and lateral leads was associated with a higher risk of unexpected death. A J-wave manifestation in many leads suggested that electric instability caused by heterogeneity of repolarization was
occurred in broad regions of the ventricles. Merchant et al. reported that notching in lateral leads is significantly more prevalent among ERP patients with idiopathic VF, but they did not assess morphological changes over time. In our study, we defined slurring, notching, and slurring and notching, taking morphological changes into account during follow-up, and found that manifestation in both slurring and notching has an important implication for risk stratification.

In this study, ERP cases had a lower risk of cardiac and all-cause mortality. On the other hand, it has also been reported that ERP in the inferior leads is associated with an increased risk of cardiac death, (HR, 1.28; 95% CI, 1.04 to 1.59; \( P = 0.03 \)), and ERP in any localization was associated with an increased risk of all-cause death (HR, 1.87; 95% CI, 1.03 to 3.37; \( P = 0.038 \)). Thus, the association between ERP and mortality other than unexpected death is still controversial. We proposed a hypothesis that testosterone may modulate cardiac and total mortality in ERP cases. Various reports indicate that testosterone may be associated with ERP and Brugada syndrome. Early repolarization pattern showed male preponderance; the typical coved-type Brugada ECG disappears after surgical castration for prostate cancer; and male Brugada syndrome cases have significantly higher plasma testosterone levels than age-matched male controls.

It has been suggested that testosterone may increase the outward repolarizing potassium currents such as \( I_{K1} \), \( I_{Kr} \), \( I_{Ka} \), and \( I_{lo} \), inhibiting inward L-type Ca\(^{2+}\) current. Such effects help to induce an outward shift of current in the epicardium, aggravate transmural voltage gradient between epicardium and endocardium, and lead to the J-point and ST-segment elevation seen in ERP and Brugada syndrome. These reports suggest that testosterone is associated with ERP and Brugada syndrome through ion channel activity. On the other hand, several studies reported that low serum testosterone level was associated with an increased risk of cardiovascular and all-cause mortality and cardiovascular risk factors in men (abnormal lipid profiles, impaired glucose metabolism, and high blood pressure). Thus, elevated serum testosterone level may influence the prognosis of patients with ERP by increasing the risk of sudden death through a more prominent transmural voltage gradient, which leads to phase 2 reentry and ventricular tachycardia/VF, while decreasing the risk of cardiac and all-cause death, probably through protective effects. However, this hypothesis should be supported by more direct evidence of the association between testosterone and ERP.

In the present study, the HR for unexpected death was lower for ERP (1.83) than for Brugada-type ECG (27.15), and may not directly lead to the recommendation of implantable cardioverter-defibrillator treatment. However, because the number of ERP cases (1429) was much larger than the number of Brugada-type ECG cases (24), the unexpected death rate was greater for ERP cases (27 of 76, 35.5%) than for Brugada-type ECG cases (4 of 76, 5.3%), suggesting a greater public health implication for ERP and a careful evaluation of the past history of syncope and the family history of sudden death or syncope. Further epidemiological and electrophysiological studies are needed to clarify what characteristics among the large number of ERP cases are predictive of high risk.

**Study Limitations**

In this study, only 1 cardiologist reviewed all the ECG records obtained during follow-up in 5976 subjects. However, the accuracy of the diagnosis was ensured because all the ECG records (12.2±7.5 ECG records per subject) during follow-up were reviewed for each subject. A second cardiologist blindly reviewed all the ECG records obtained during follow-up in 200 subjects (50 with ERP and 150 without ERP) and 194 ERP cases, and the concordance rate was 86.0% for ERP diagnosis, 83.8% for lead location, and 81.3% for morphology.

We could not deny the effect of structural heart diseases on ERP because we did not perform echocardiography and cardiac catheterization in this epidemiological study.

We did not assess the risk of unexpected death by the nature of the manifestation of ERP (intermittent/persistent), because almost all of the ERP cases (98.3%) showed the intermittent course. Because the magnitude of the J point fluctuated over time in ERP cases, the most elevated values of J point were biased, depending on how many times the ECG was recorded. Thus, we did not assess the effects of the magnitude of J point on unexpected death. For the same reason, other ECG characteristics such as QRS duration and QTc interval were not used as covariates in Cox regression analysis.

With respect to Brugada-type ECG, we did not include 10 patients with types 2 and 3 in the Brugada-type ECG group. We cannot deny the possibility that they might have changed into type 1 if they had drug challenge tests, which could not be performed in our cohort study. We observed 3 unexpected deaths among 10 patients with types 2 and 3.

Age at unexpected death was relatively high in both ERP cases and controls. Uncertainty of the cause of sudden or unexplained accidental death without autopsy information, especially for coronary heart disease, may limit the present results, but this possible bias would be equal for ERP cases and controls.

Because the number of unexpected deaths in ERP cases by lead location and morphology subgroup and in Brugada-type ECG cases was small, such data might limit efforts to draw a definitive conclusion about effects of ERP by lead location and morphology subgroup and Brugada-type ECG on unexpected death.

**Conclusions**

In this 5-decade population-based study, we described the epidemiology and long-term prognosis of ERP. Early repolarization pattern was a common ECG finding; ERP appeared intermittently, and its location and J-wave morphology changed over time. Early repolarization pattern was associated with an elevated risk of unexpected death and a decreased risk of cardiac and all-cause death. The manifestation of both slurring and notching and the manifestation of the J wave in both inferior and lateral leads were associated with the higher risk of unexpected death. Further clinical and experimental studies are needed to define the characteristics of high-risk ERP cases so that they can be singled out for preventive measures.

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Disclosures
None.

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CLINICAL PERSPECTIVE
Recent studies have suggested a potential arrhythmogenicity and a higher risk of cardiac or all-cause death of early repolarization pattern (ERP) in Western populations. But, the incidence and prognostic value of the Brugada-type electrocardiogram, a population-based study of four decades. J Am Coll Cardiol. 2001;38:765–770.
Incidence and Prognostic Value of Early Repolarization Pattern in the 12-Lead Electrocardiogram

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조기 재분극: 혼란 심전도 소견이지만 예측되지 않은 사망과 연관이 있다

오 첸일 교수 서울대학교병원 순환기내과

Summary

배경
조기 재분극(early repolarization)은 혼란 심전도 소견으로 하부(4축부) 유도에서 특정한 사상과 QRS의 notch 또는 slurring을 보이는 것이다. 동양인에서 조기 재분극의 빈도와 장기 예후에 대해서는 아직 알려진 것이 별로 없다.

방법 및 결과
일본 나가사키에서 1958년 7월부터 2004년 12월까지 54년간 시행되는 정기검진을 받은 5,976명의 일목 생존자의 심전도를 분석하였다. 연구자들은 조기 재분극을 적어도 2개의 하부(4축부) 유도에서 J점 또는 ST절의 사상과 함께 notch 또는 slurring이 있는 경우로 정의하였고 Cox 분석으로 예측되지 않은 사망, 심장사, 총 사망을 평가하였다. 총 1,490례의 조기 재분극이 발견되어서 23.9%의 양성률을 보았다. 조기 재분극은 예측되지 않은 사망의 위험도를 증가시켰으며 (HR=1.83; 95% CI 1.27-2.97, P=0.02), 심장사 (HR=0.75; 95% CI, 0.50-0.93, P<0.01)와 총 사망 (HR=0.85; 95% CI, 0.78-0.93; P<0.01)의 위험도를 감소시켰다. 또한, slurring과 notch가 모두 있는 경우 예측되지 않은 사망의 위험과 관련이 있었으며 (HR=2.09; 95% CI, 1.06-4.12; P=0.03), 하부 및 4축 유도 모두에서 조기 재분극이 관찰되는 경우도 마찬가지였다 (HR=2.50; 95% CI, 1.29-4.83; P<0.01).

결론
조기 재분극은 예측되지 않은 사망을 증가시키고, 심장사 및 총 사망의 감소와 연관이 있다. 조기 재분극 패턴의 형태와 위치에 따라 다른 예후와 연관이 있다.
Commentary

조기 재분극의 의미가 아직은 명확하게 정립되어 있지 않지만, 조기 재분극 증후군과 Brugada 증후군 등을 포함하는 일부의 심전기 이상학적인 질환의 스펙트럼은 V 파 증후군으로 이해된다. 조기 재분극은 심전도에서 매우 흔히 관찰되는 소견이다(Figure 1). 이 연구에서도 대부분 연구참여자 중 성별은 참가자 모두 1/4에서 조기 재분극이 관찰되었다고 보고하고 있다. 돌연사의 중요성을 이해할 때 고려하는 것은 그 질환 또는 상태를 가진 경우 돌연사 발생 가능성이 얼마나 크나 큰가 하는 것과 함께 해당되는 연구 집단이 얼마나 크나 크게 하는 것이다. 매일 들어, 심근경색으로 인한 전이가 발생한 환자는 돌연사 발생 가능성이 30%에 달할 정도로 매우 높다. 하지만 전체 인구에서 해당 환자가 차지하는 비율은 매우 낮다. Brugada 증후군도 마찬가지이다. 사회적인 영역에서 가장 큰 것은 돌연사 가능성을 크고 그 변수가 혼합 심병 또는 상태일 것이다. 이런 점에서는 조기 재분극은 그 변수가 높으므로 사회, 보건

References

Figure 1. 조기 재분극의 전형적인 예. 하부유도에서는 slurring, V2~V6에서는 notch가 관찰된다.