Early repolarization pattern and its day-to-day dynamic change as markers for ventricular fibrillation in patients with vasospastic angina

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Aims
An early repolarization (ER) pattern is a risk factor for ventricular fibrillation (VF) in certain diseases. However, it is unclear whether this association holds for patients with vasospastic angina (VSA). Moreover, the reported long-term follow-up of implantable cardioverter defibrillator (ICD) therapy for VSA patients is limited to 3 years. This study aimed to clarify the relation between ER and VF in patients with VSA and to investigate the long-term outcomes of ICD therapy.

Methods and results
This retrospective, observational survey evaluated 265 consecutive VSA patients, including 21 with VF. Their electrocardiogram findings and clinical course were analysed over a mean follow-up of $5.5 \pm 3.3$ years. Early repolarization was observed in 64 patients (24.2%) and was more frequent in patients with VF history than those without ($P = 0.001$). Early repolarization was independently associated with VF history. During follow-up, four patients had VF recurrences. Ventricular fibrillation recurrence was higher in patients with ER (log-rank, $P = 0.018$) or VF history (log-rank, $P < 0.001$) than those without. Among patients with ER, day-to-day variations in ER ($P = 0.003$) and notching of ER pattern ($P = 0.03$) were associated with VF history. Cases with day-to-day variation showed a higher incidence of VF recurrence during follow-up (log-rank, $P = 0.007$). During long-term follow-up, 23.5% of patients with an ICD received appropriate shock therapy.

Conclusion
The presence of ER, especially with day-to-day variation, can help predict VF recurrence in VSA patients. Implantable cardioverter defibrillator implantation is a reasonable approach for the secondary prevention of VF in high-risk VSA patients.

Keywords
Early repolarization • Ventricular fibrillation • Vasospastic angina • Sudden cardiac death • Implantable cardioverter defibrillator

Introduction
An early repolarization (ER) pattern is defined as a J-point elevation from the baseline (0.1 mV) and/or a notching or slurring morphology in the late phase of the QRS complex in ≥2 contiguous inferior and/or lateral leads on a standard 12-lead electrocardiogram (ECG). The ER pattern generally used to be regarded as a benign ECG sign, since it was mostly observed in young, healthy individuals or athletes without structural heart disease. Several recent studies, however, have indicated that an ER pattern in the inferior and lateral leads is associated with the development of ventricular fibrillation (VF) in patients with idiopathic VF. Furthermore, ER patterns in the inferior leads or multiple leads with a horizontal/descending ST segment have been associated with increased mortality in the general population. The presence of an ER pattern in patients with Brugada syndrome, acute myocardial infarction, chronic heart failure, long QT syndrome or familial sudden arrhythmic death syndrome has also been implicated as high risk for fatal ventricular arrhythmias.

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Early repolarization and VF in patients with VSA

What’s new?
- The presence of early repolarization pattern in 12-leads electrocardiogram, especially with day-to-day variation, can help predict ventricular fibrillation (VF) recurrence in VSA patients.
- Implantable cardioverter defibrillator implantation is a reasonable approach for the secondary prevention of VF in high-risk vasospastic angina (VSA) patients, because VSA patients with VF history had a high recurrence rate during the long-term follow-up.

Vasospastic angina (VSA) is a unique form of ischaemic heart disease, and patients suffering from VSA occasionally develop life-threatening ventricular arrhythmias, including VF.14–18 While an ER pattern and ST-segment variation have been suggested as markers for an increased risk of VF in patients with VSA,19 the detailed characteristics of the ER pattern and the long-term prognosis and follow-up of implantable cardioverter defibrillator (ICD) therapy have not been fully elucidated.20

The aim of the present study was to evaluate the prevalence, characteristics, and prognostic significance of an ER pattern for the development of VF during the acute and follow-up periods in patients with VSA. In addition, we evaluated the long-term follow-up of ICD implantation for secondary prevention of VF.

Methods

Study population
The subjects of this study were 265 consecutive patients with VSA who were admitted and followed at the Tokyo Metropolitan Hiroo Hospital between January 2003 and March 2014. Twenty-one patients were resuscitated from VF, which was documented by the records of automated external defibrillators or ECG monitors when the patients were admitted to our hospital due to cardiopulmonary arrest. On resuscitation, these patients were diagnosed as having VSA by emergent coronary angiography (CAG) and a drug provocation test with acetylcholine (ACh) injection. Vasospastic angina was diagnosed in the remaining 244 patients for diagnostic evaluation of chest pain. Other aetiology of VF was excluded by routine cardiac examinations, CAG, echocardiography, or cardiac magnetic resonance imaging. There were no patients with hypertrophic cardiomyopathy.

Electrocardiographic analysis
All 12-lead resting ECGs recorded during hospital admission and on each visit to the outpatient clinic after discharge were reviewed for analysis. An ER pattern was defined as an elevation of the QRS–ST junction (J point) by ≥0.1 mV above the baseline, and/or either notching or slurring morphology of the terminal portion of QRS at ≥2 inferior (II, III, and aVF) and/or lateral (I, aVL, and V4–V6) leads.1 Forty-six patients showed an ER pattern at least on one occasion either during admission or during the follow-up in the outpatient clinic. Day-to-day variation was judged positive if an ER pattern was present on one day but disappeared on another day during the admission and the follow-up period (Figures 1 and 2). In the present study, we also analysed ST-segment patterns after J point either with ‘concave/rapidly ascending’ (ST-segment elevation of ≥0.1 mV within 100 ms after J point followed by gradually up-sloping morphology merging to T wave) or ‘horizontal/descending’ (ST-segment elevation ≥0.1 mV within 100 ms after J point followed by flat or down-slope ST segment until the onset of T wave). We confirmed ER patterns on ECG during CAG without any stenosis ‘before the ACh provocation test’. All ECG records were read and analysed in random order by three independent cardiologists who were blinded to the patients’ medical conditions.

Diagnosis of vasospastic angina
Vasospastic angina was defined as ≥90% narrowing of the epicardial coronary arteries on angiography performed during the ACh or ergonovine provocation test for vasospasms, as well as the concomitant appearance of characteristic chest pain and/or ST-segment deviation on ECG.18 The ACh provocation test or ergonovine provocation test for VSA was performed in accordance with the guidelines.21

Management
Seventeen of the 21 patients resuscitated from VF received ICD implantation. One patient died of malignant lymphoma before ICD implantation and three patients refused the implantation. All patients with VF history were treated with a calcium channel blocker immediately after diagnosis. Vasospastic angina patients without VF history were treated with medication, such as a calcium channel blocker, nitrate, or nicorandil. Additional treatment was added depending on associated disease condition of individual patients.

Statistics
Continuous variables are presented as mean ± standard deviation and categorical variables as number and percentage in each group. Comparisons of continuous variables between case and control subjects were made using Student’s t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Dichotomous variables were compared between cases and controls using the χ² contingency test and Fisher’s exact probability test. All reported P-values are two-sided, with a P-value of <0.05 being considered to indicate statistical significance. The multivariate model for VF history among all VSA patients included sex and ER pattern. Kaplan–Meier survival curves were compared by log-rank test. The statistical analyses were performed using the Statistical Package for Social Studies (SPSS), version 19.0 (IBM, Armonk, NY, USA).

Results
Twenty-one patients developed VF as a manifestation of VSA-related complications on admission (VF history), while the remaining 244 patients had no VF events. In all, 11.2 ± 9.0 ECGs were obtained for each patient. Using the ACh provocation test, all VSA patients with VF history were diagnosed as VSA, in which there were no patients with developed VF during ACh provocation test. On the other hand, among VSA patients without VF history there were 230 VSA patients diagnosed using the ACh provocation test and 35 were diagnosed using ergonovine provocation test. The characteristics of the groups with and without VF history are shown in Table 1. The ER pattern was observed in 13 of 21 patients (61.9%) in the group with VF history and 51 of 244 cases (20.9%) in the group without; the incidence with ER was higher in the former than in the latter group (P = 0.001). The male sex was predominant in the group with VF history compared with those without (90.5 vs. 63.1%, P = 0.006). An ICD was implanted in 17 of 21 patients with
VF history and none in those without. There were no significant differences between the two groups in other baseline parameters, including ECG findings. Multivariate analysis revealed that ER pattern and male sex were independently associated with VF history (ER pattern: odds ratio (OR) 5.8, 95% confidence interval (CI) 2.2–15.0, \( P = 0.001 \); male sex: OR 5.1, 95% CI 1.1–22.9, \( P = 0.033 \); Table 2).

The clinical courses of all 265 patients with VSA were followed at our outpatient clinic for a mean of 5.5 ± 3.3 years. There were four VF recurrences during the follow-up in 21 patients with VF history but none in 244 patients without. Figure 1 shows the series of ECG tracings from a representative case with VF recurrence during the follow-up period. All patients with VF recurrence were continuing the medication at the time of VF event and were treated appropriately with ICD shock, after which adjunctive medical therapy was adjusted. As expected, during the follow-up period, VF recurrence was higher in patients with VF history than those without (log-rank, \( P < 0.001 \)).

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study, however, did not find that ST-segment morphology was associated with VF history other than day-to-day variation of ER pattern or notching of ER pattern. While the previous reports compared the ER (+) and ER (−) patterns in VSA patients, the present study focused on VSA patients with and without a VF history, as well as VF recurrence during the long-term follow-up period. The results of our study suggest that ER may be a potential predictor of VF and its recurrence in patients with VSA.

The precise mechanism underlying ER, however, has not been clarified, and various contributing factors related to the depolarization and repolarization sequence have been suggested. The ER pattern appears to be produced by a transmural voltage gradient between the epicardium and endocardium during the early phase of ventricular repolarization. The voltage gradient could be caused by the notch of the epicardial action potential resulting from a prominent transient outward current (Ito), as opposed to the lack of a prominent notch in the endocardial action when there is less development of Ito. The trigger and substrate for the development of Phase 2 re-entry and ventricular tachycardia/VF may eventually emerge from the transmural dispersion of the action potential repolarization. In addition, fundamental mechanisms underlying ST-segment elevation and initiation of VF in the early phases of acute myocardial ischaemia are considered to be similar to those in the inherited ER syndromes. Several clinical studies have reported the association between ER and acute myocardial infarction and have proposed mechanisms that might be clues to speculate the mechanism of the association between VSA and VF. Naruse et al. noted that ER appeared when the distribution Ito was more prominent or when Ito showed greater predominance, in which circumstances VF might tend to be caused when acute myocardial infarction occurs. Rosso et al. found that patients with the ER pattern had a certain degree of increased dispersion of repolarization, predisposing them at higher risk for VF, but in the presence of additional pro-arrhythmic factors or triggers, such as myocardial ischaemia. In the present study, we could not confirm the precise mechanism underlying ER, but among patients with VSA, the cause of ER was thought to be different from that of a spastic ischaemic event like a representative case (Figure 2). Therefore, ER might present an underlying substrate responsible for the development of fatal ventricular arrhythmias among patients with VSA, as Rudic et al. also speculated in an association between acute myocardial infarction and ER.

Figure 2 A series of 12-lead ECG tracings and a coronary angiogram during ACh provocation test in a representative case of VF survivor. Note that day-to-day variation was observed on ECGs between shortly after VF episode (A) and after discharge (B). The distributions of ER before ACh provocation test (C; I, V4–V6) and the leads demonstrating ST elevation during the provocation test were discordant (D; II, III, and aVF). (A) Electrocardiogram recording 15 h after the first VF episode. Early repolarization patterns in inferolateral leads were apparent. (B) Electrocardiogram after discharge from the hospital. Early repolarization patterns disappeared. (C) Electrocardiogram before ACh 50 µg intracorony injection to right coronary artery (RCA). Early repolarization patterns were documented in lateral leads. (D) Electrocardiogram after ACh 50 µg intracorony injection to RCA. ST segment at inferior leads elevated with chest pain. (E) Coronary angiogram after ACh 50 µg injection revealed RCA stenosis.
Day-to-day variation of the early repolarization pattern in vasospastic angina patients

One of the characteristic findings in the present study was a frequent association of day-to-day variation of ER in patients with a VF history, who had a close association with VF recurrence during long-term follow-up. Oh et al.19 have not reported any different effects of ER on the incidences of VF history and VF recurrence during long-term follow-up other than ST morphology. On the contrary, we could detect differences in day-to-day variation of ER or a notching of ER pattern between VSA patients with VF history and those without. Moreover, among VSA patients with ER, Kaplan–Meier analysis showed patients with day-to-day variation of ER had worse prognosis than those without, but cases with a notching ER pattern did not show any significance.

In Brugada syndrome, day-to-day variation of the J wave and ST–T changes in leads V1–V3 were often observed preceding VF events, which were believed to be caused by abnormal modulation of the autonomic nervous tone, increasing the patient’s vulnerability to fatal arrhythmias.24 In patients with idiopathic VF, an increased J-point amplitude was observed preceding the development of ventricular tachyarrhythmia.4,7 Abe et al.25 also found a close relationship between the high-frequency spectral component on the 24 h ambulatory ECG and the amplitude of the J point, but no such relationship was seen in control subjects with an ER pattern. Increased amplitude of J wave was not found to have any predictive value for VF history and VF recurrence in the present study. These results might be due to the fact that our observations were noted in the symptom-free periods and not at the time immediately preceding VF events. While the genesis of the ER pattern in VSA is unknown, its characteristics may have certain similarities to various conditions including fluctuation and augmentation of ER preceding VF events in patients with idiopathic VF, ER syndrome, and Brugada syndrome.23 While the present study did not clarify any possible reasons for day-to-day variation in the ER pattern, the influence of the autonomic nervous tone might play a role in addition to transient ischaemia. Further studies are warranted to clarify the exact causes of day-to-day variations in ER.

Implantable cardioverter defibrillator implications for vasospastic angina

The indication of ICD implantation for patients with VSA is still controversial. This observational study of VSA patients with ICD had

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**Table 1** Comparison of baseline characteristics between patients with and without VF history

<table>
<thead>
<tr>
<th>Variables</th>
<th>With VF history, n = 21</th>
<th>Without VF history, n = 244</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>58.7 ± 10.7</td>
<td>63.4 ± 12.1</td>
<td>0.083</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>19 (90.5)</td>
<td>154 (63.1)</td>
<td>0.006</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>3 (14.3)</td>
<td>25 (10.2)</td>
<td>0.387</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>7 (33.3)</td>
<td>131 (53.7)</td>
<td>0.073</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>11 (52.4)</td>
<td>108 (44.3)</td>
<td>0.322</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>16 (76.2)</td>
<td>144 (59.0)</td>
<td>0.123</td>
</tr>
<tr>
<td>Family history of sudden cardiac death, n (%)</td>
<td>2 (9.5)</td>
<td>17 (7.0)</td>
<td>0.457</td>
</tr>
<tr>
<td>ICD implantation, n (%)</td>
<td>17 (81.0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ER pattern, n (%)</td>
<td>13 (61.9)</td>
<td>51 (20.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>PR interval, ms</td>
<td>165 ± 17.1</td>
<td>165 ± 25.3</td>
<td>0.915</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>99.8 ± 11.3</td>
<td>102 ± 13.4</td>
<td>0.551</td>
</tr>
<tr>
<td>QTc interval, ms</td>
<td>424 ± 27.3</td>
<td>418 ± 22.9</td>
<td>0.333</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>65.6 ± 6.5</td>
<td>67.8 ± 8.0</td>
<td>0.234</td>
</tr>
<tr>
<td>Calcium channel blocker, n (%)</td>
<td>20 (95.2)</td>
<td>195 (79.9)</td>
<td>0.065</td>
</tr>
<tr>
<td>Nitrates</td>
<td>9 (42.9)</td>
<td>67 (27.5)</td>
<td>0.134</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>8 (38.1)</td>
<td>50 (20.5)</td>
<td>0.061</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>9 (42.9)</td>
<td>96 (39.3)</td>
<td>0.752</td>
</tr>
<tr>
<td>ACEI/ARB, n (%)</td>
<td>7 (33.3)</td>
<td>58 (23.8)</td>
<td>0.328</td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>2 (9.5)</td>
<td>14 (5.7)</td>
<td>0.365</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

**Table 2** Multivariate analysis of factors associated with VF history among patients with VSA

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>Confidence interval (95%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER pattern</td>
<td>5.8</td>
<td>2.26–15.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>5.1</td>
<td>1.14–22.9</td>
<td>0.033</td>
</tr>
</tbody>
</table>

**Figure 3** Kaplan–Meier survival curves for VF in VSA patients with and without ER. Patients with ER pattern had a lower cumulative survival rate after VF than those without.
the longest follow-up period (mean 5.5 ± 3.3 years) among the studies reported so far. In this study, 81.0% of the patients (17/21) who survived VF were implanted an ICD and 4 of them (4/17; 23.5%) received appropriate ICD therapy while they received medical therapy as well. According to the guidelines,26 patients who survive cardiac arrest due to VF or haemodynamically unstable sustained ventricular tachycardias are recommended for ICD implantation after exclusion of any completely reversible causes. Matsue et al.20 reported a high recurrence rate of ventricular arrhythmias in high-risk VSA patients during a 2.9-year period and found that 4 of 23 patients with resuscitated VF were treated appropriately by an ICD therapy. Hence, ICD implantation for the secondary prevention of VF may be indicated in VSA patients with VF history. Since event rates of VF in patients with the ER pattern were higher than those without (Figure 3), the patients with an ER pattern, especially showing day-to-day variation, represent a high-risk population during the follow-up period.

**Study limitations**

Since the numbers of patients with VF history and VF recurrence were small in our observation, the impact of this study might be limited. Therefore, we could not conduct a multivariate analysis among VSA patients with ER. Hence, large-scale, prospective studies are warranted to more precisely evaluate the presence

### Table 3 Comparison of ER pattern characteristics in VSA patients with and without VF

<table>
<thead>
<tr>
<th>Positive ER pattern, n = 64</th>
<th>With VF history, n = 13</th>
<th>Without VF history, n = 51</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day-to-day variation, n (%)</td>
<td>5 (38.5)</td>
<td>2 (3.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>J-point amplitude &gt; 0.2 mV, n (%)</td>
<td>5 (38.5)</td>
<td>11 (21.6)</td>
<td>0.183</td>
</tr>
<tr>
<td>J-point amplitude, mm</td>
<td>1.7 ± 0.7</td>
<td>1.5 ± 0.5</td>
<td>0.539</td>
</tr>
<tr>
<td>ER pattern in inferior lead, n (%)</td>
<td>8 (61.5)</td>
<td>43 (84.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>ER pattern in lateral lead, n (%)</td>
<td>8 (61.5)</td>
<td>19 (37.6)</td>
<td>0.114</td>
</tr>
<tr>
<td>ER pattern in inferolateral lead, n (%)</td>
<td>8 (61.5)</td>
<td>19 (37.6)</td>
<td>0.114</td>
</tr>
<tr>
<td>Notching of ER pattern, n (%)</td>
<td>10 (76.9)</td>
<td>23 (45.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Slurring of ER pattern, n (%)</td>
<td>6 (46.2)</td>
<td>28 (54.9)</td>
<td>0.573</td>
</tr>
<tr>
<td>Notching and slurring of ER pattern, n (%)</td>
<td>3 (23.1)</td>
<td>6 (11.8)</td>
<td>0.261</td>
</tr>
<tr>
<td>ER pattern with ascending ST segment, n (%)</td>
<td>6 (46.2)</td>
<td>28 (54.9)</td>
<td>0.573</td>
</tr>
<tr>
<td>ER pattern with horizontal/descending ST segment, n (%)</td>
<td>7 (53.8)</td>
<td>23 (45.1)</td>
<td>0.573</td>
</tr>
</tbody>
</table>

**Figure 4** Kaplan–Meier survival curves for VF among VSA patients with and without day-to-day variation of ER. Patients with day-to-day variation of ER pattern had a lower cumulative survival rate of VF than those without.

**Figure 5** Kaplan–Meier survival curves for VF among VSA patients with and without a notching pattern of ER. There was no statistical difference between two groups.
and characteristics of ER for risk stratification of VF events in VSA patients. Angiographically unidentified microvessel spasm by ACh test or unidentified silent spasm was not entirely excluded. Hence, the influence of vasospasm on underlying mechanism of ER was not clearly excluded. This study included exclusively selected patients who had chest pain and/or cardiac arrest due to VF, but certain VSA patients might not complain typical symptoms despite having an ER pattern on their ECG. Therefore, the present study might have underestimated a true prevalence of the ER pattern in VSA patients. Patients with VF history tended to have a longer hospitalization period and more frequent visits to the outpatient clinic during the follow-up period compared with those without. Therefore, the numbers of ECG recordings were variable depending on the patient’s clinical status and VF history. This might have influenced the appearance of ER pattern and its day-to-day variation. Most patients with VF history did not undergo ECG recordings before VF attacks. Therefore, we could not determine whether ER pattern was a precursor or a consequence of VF attacks. Finally, all patients with VF history were treated with a calcium channel blocker, whereas patients without VF history were treated with variable oral medications, including calcium channel blockers, nitrates, or nicorandil. The treatment protocol for patients without VF history was not standardized because of the retrospective nature of the study. In addition, it was also not clear whether the doses of calcium channel blockers were fully titrated or not to patients with VF history.

Conclusions

The high prevalence of ER pattern in VSA patients with VF history suggests that its presence is a sign of vulnerability to fatal arrhythmias. The ER pattern, especially its day-to-day variation, may be a good predictor of VF recurrence. Implantable cardioverter-defibrillator implantation can be a reasonable approach for the secondary prevention of VF in high-risk VSA patients.

Conflict of interests: none declared.

References