Early Repolarization Increases the Occurrence of Sustained Ventricular Tachyarrhythmias and Sudden Death in the Chronic Phase of an Acute Myocardial Infarction

Running title: Naruse et al.; ER Increases VT/VF and Sudden Death in an AMI

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Abstract:

**Background** - We recently showed that the presence of early repolarization (ER) increases the risk of ventricular fibrillation occurrences in the early phase of acute myocardial infarction (AMI). This study aimed to clarify whether an association exists between ER and occurrences of ventricular tachyarrhythmias (VT/VF) or sudden death in the chronic phase of AMI.

**Methods and Results** - This study retrospectively enrolled 1,131 patients (67±12 years; 862 men) with AMIs surviving 14 days post-AMI. The primary endpoint was the occurrence of sustained VT/VF or sudden death >14 days after the AMI onset. We evaluated the presence of ER from the pre-discharge ECG (mean 10±3 days post-AMI). ER was defined as an elevation of the terminal portion of the QRS complex of >0.1 mV in inferior or lateral leads. After a median follow-up of 26.2 months, 26 patients had an episode of VT/VF or sudden death. A multivariable Cox regression analysis revealed the presence of ER (hazard ratio [HR] 5.37; 95% confidence interval [CI] 2.27–12.69; p<0.001), Killip class on admission of >1 (HR 2.75; 95%CI 1.24–6.07; p=0.013), and a left ventricular ejection fraction of <35% (HR 11.83; 95%CI 5.16–27.13; p<0.001) were significantly associated with event occurrences. As features of the ER pattern, ER in the inferior leads, high-amplitude ER, a notched morphology, and ER without ST-segment elevation were associated with an increased risk of event occurrences.

**Conclusions** - ER observed at a mean of 10 days post-AMI may be a marker for a subsequent risk of VT/VF or sudden death.

**Keywords:** arrhythmia, sudden cardiac death, early repolarization, acute myocardial infarction
Early repolarization (ER) has historically been regarded as an innocuous finding in healthy young people.\textsuperscript{1,2} While considered benign, the potential role of ER in arrhythmogenicity has been suggested in experimental studies.\textsuperscript{3} Recently, several case reports have called our attention to the association of idiopathic ventricular fibrillation (VF) with J-point elevation.\textsuperscript{4-8} In addition, recent evidence has linked ER to idiopathic VF in patients with no structural heart disease\textsuperscript{9-13} and to life threatening ventricular tachyarrhythmias (VT/VF) associated with chronic coronary artery disease.\textsuperscript{14}

We recently showed that the presence of ER increases the risk of VF occurrences in the early phase of an acute myocardial infarction (AMI).\textsuperscript{15} However, it is unknown whether there is an association between ER and VF occurrences in the chronic phase of an AMI. Accordingly, the purpose of this study was to clarify this point.

**Methods**

**Study Population**

Between April 2006 and February 2012, 1,306 consecutive Japanese patients with an AMI who underwent percutaneous coronary intervention at the University of Tsukuba Hospital, Tsukuba Medical Center Hospital, and Ibaraki Prefectural Central Hospital were included in the present retrospective study. Patients were eligible if they were 18 years or older and presented within 24 hours of the onset of symptoms associated with an AMI. Sixty-five patients died within 14 days after the AMI onset. All 8 patients who experienced sustained VT/VF between 2 and 14 days after the AMI onset died within 14 days after the AMI onset. Sixty patients had experienced a prior AMI, 3 had a Brugada ECG pattern,\textsuperscript{16} and 47 were lost to follow-up. After excluding these patients, the remaining 1,131 patients (862 men and 269 women; mean age, 67±12 years) were finally included in this study (Figure 1). We included patients with a
prolonged QRS complex duration of more than 120 ms, which is well known as a risk marker for cardiac events, however it is not possible to measure the ER in such cases.

The primary endpoint of this study was the occurrence of sustained VT/VF or sudden death more than 14 days after the onset of the AMI. Patients were classified on the basis of the occurrence of sustained VT/VF or sudden death, and the clinical data were analyzed in both the event occurrence and no event occurrence study groups. Data collection covered the age, sex, cardiovascular risk factors, culprit artery, number of diseased coronary arteries, Killip class on admission, medications before discharge, VT/VF occurrence within 48 hours after the onset of the AMI, left ventricular ejection fraction, and infarct size (based on the peak creatine kinase rise). Hypertension, hypercholesterolemia, and diabetes mellitus were scored on the basis of the previous diagnosis and initiation of therapy. Ethical approval was obtained from the institutional review board of each participating hospital, and all patients gave their written informed consent before participation.

An AMI was defined as a rise in the MB fraction of the creatine kinase above the 99th percentile of the upper reference limit together with symptoms of ischemia, ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block), and/or the development of pathologic Q waves on the ECG. An ST-elevation myocardial infarction was defined as an AMI with new ST elevation at the J-point in two continuous leads with the following cut-off points: ≥0.2 mV in men or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in the other leads. Successful percutaneous coronary intervention was defined as the attainment of a Thrombolysis in Myocardial Infarction 3 flow. We defined sudden death as that occurring within 1 hour of the onset of symptoms. The definition of sustained VT/VF was that lasting longer than 30 seconds or that requiring adequate therapy with an implantable
cardioverter-defibrillator (ICD).

**ECG Analysis**

To blind the ECG interpreters from the clinical characteristics and patient groupings, all tracings were scanned and coded. We evaluated the 12-lead ECG recorded before the AMI onset (if possible), just after the onset of the AMI and before discharge. In case the duration of the patient’s hospitalization was over 14 days, an ECG obtained around 14 days after the onset of the AMI was assessed. The mean duration from the onset of the AMI to the pre-discharge ECG recording was 10±3 days. ER was electrocardiographically defined as an elevation of the terminal portion of the QRS complex of more than 0.1mV in at least 2 contiguous inferior (II, III, and aVF) or lateral (I, aVL, and V4 to V6) leads, manifested as QRS notching or slurring (Figure 2). A notched ER was defined as an upward deflection, and slurring as a conduction delay beginning on the QRS downslope.\(^{19,20}\) The amplitude of the ER was measured from the onset of the QRS slur in the case of slurred ER or the peak of the end of the QRS notch in the case of notched J waves,\(^{20}\) and relative to the QRS onset to minimize any baseline wandering effect.\(^{14}\)

We analyzed the inferior and lateral ER independently to clarify the significance of the localization and used two predefined cutoff points (\(\geq 0.1\) mV and \(\geq 0.2\) mV) to assess the significance of the amplitude of the ER from baseline. The morphologic characteristics of the ER (notching or slurring) were also analyzed independently.\(^{19,20}\) The anterior precordial leads (V1 to V3) were excluded from the analysis of the ER to avoid the inclusion of patients with right ventricular dysplasia or Brugada syndrome.\(^{16,21}\) We also analyzed the ST-segment elevation independently to clarify the significance of the ST-segment characteristics according to the criteria proposed by Heng\(^{20}\) and Uberoi.\(^{19}\) ST-segment elevation was defined as an elevation of the ST-junction of \(\geq 0.1\) mV and upward sloping of the ST-segment. We assessed the
prevalence, localization, amplitude, morphology, and ST-segment of the ER in both patient
groups. Two trained investigators independently evaluated the baseline 12-lead ECGs for the
presence of ER with no knowledge of the other observer’s judgment or the clinical information.
A third observer was consulted in the case of disagreement. All ECGs containing an ER pattern
were double-checked, and the grading was established by consensus. The interobserver
variability was assessed in all patients. In 100 randomly selected patients, one observer
evaluated a new arbitrary judgment on a separate occasion to determine the intraobserver
variability.

Statistical Analysis
Continuous variables are expressed as the means ± standard deviation or median (interquartile
range [IQR]). Comparisons between 2 groups were tested by an unpaired t-test or
Mann-Whitney U-test according to the data distribution with or without normality. All
categorical variables are presented as the number and percent in each group and were compared
by a chi-square analysis or Fisher’s exact test. An overall chi-square test for a 2 x n table was
constructed when comparisons involved >2 groups. A comparison of the probability of the
freedom from the occurrence of VT/VF or sudden death between those with and without ER was
performed using a Kaplan-Meier survival analysis with a log rank test. “Time 0” for the
survival analyses was the date of the AMI onset. A univariable analysis of the patient
characteristics was compared between the event occurrence group and no event occurrence group,
and a forward stepwise multivariable Cox proportional regression analysis was performed to
detect any independent significant predictors by adjusting for multiple variables (reported as the
hazard ratio [HR] with a 95% confidence interval [CI]). Variables, including multivariable Cox
proportional hazard models, were those that achieved statistical significance (p<0.05) or that
were close to significance (p<0.1) in the univariable analysis. Significant and independent predictors for the occurrence of VT/VF or sudden death detected by the Cox proportional hazard regression model were assessed using the Harrell’s c index. The intraobserver and interobserver variability was investigated by Kappa statistics. A p value of <0.05 was considered statistically significant. All analyses were performed with a PASW Version 17.0 statistics software package (SPSS, Chicago, IL).

Results

Demographic and Clinical Characteristics of All the AMI Patients

Among the 1,131 patients, 26 (2.3%) experienced an episode of VT/VF or sudden death during a median follow-up period of 26.2 (IQR 14.2–43.5) months. Non-resuscitated sudden death occurred in 16 patients, VF in 7, and VT in the remaining 3. Among the 16 patients who experienced sudden death, VF was documented in 4 patients. There was no statistically significant difference in the age, cardiovascular risk factors, number of diseased coronary arteries, peak creatine kinase level, medications other than statins, or prevalence of ST-elevation myocardial infarction, a successful PCI, or prolonged QRS duration between the 2 groups. However, the prevalence of a male sex (p=0.016), left anterior descending culprit artery (p=0.044), VT/VF occurrence within 48 hours after the onset of the AMI (p=0.007), and an ICD implantation (p=0.013) were higher and that of statin administration was lower (p=0.014) in patients with event occurrences than in those without (Table 1). Furthermore, the patients with event occurrences had a lower ejection fraction (p<0.001), greater prevalence of an ejection fraction of <35% (p<0.001), and higher Killip class (p=0.009) than those without (Table 1).

ER was present in 99 of 1,131 patients on the 12-lead ECG obtained before discharge and was more common in patients with event occurrences than in those without (p=0.001, Table 1).
The prevalence of ER assessed before discharge did not differ between the patients with an ST-elevation myocardial infarction and those with a non-ST-elevation myocardial infarction (9% vs. 8%; p=0.76). Kaplan-Meier curves showed that the presence of ER on the 12-lead ECG obtained before discharge was associated with an increased occurrence of VT/VF or sudden death (p<0.001 by log rank test, Figure 3). The median duration from the AMI onset to the VT/VF or sudden death occurrence was 7.3 months (IQR 2.3–35.6) in the 26 patients with an event occurrence, and shorter in those with ER than in those without ER (1.7 months [IQR 0.9–7.0] vs. 14 months [IQR 4.1–41.4]; p=0.023).

In the sub-group analysis of the patients with a left ventricular ejection fraction of less than 35%, concomitant ER was also associated with an increased risk of VT/VF or a sudden death occurrence (p=0.021 Figure 4A).

There were no significant differences in the baseline characteristics between those enrolled in our study and those who were eligible but were lost to follow-up.

Detailed Characteristics of ER for Predicting an Event Occurrence

Distribution

Among the 99 patients who had ER on the 12-lead ECG obtained before discharge, the J-point elevation was in the inferior leads in 68 (69%) patients, in the lateral leads in 23 (23%), and in the inferior and lateral leads in the remaining 8 (8%) (Table 1). The patients with an event occurrence were more likely to have ER in the inferior leads than those without an event occurrence (27% vs. 6%; p=0.001, Table 1), whereas the prevalence of ER in the lateral leads or both leads did not differ significantly between the 2 groups (Table 1).

Magnitude and morphology

An amplitude of the ER of more than 0.2 mV was found in the inferior or lateral leads in 29 (3%)
patients and was more prevalent in the patients with event occurrences than in those without (12% vs. 2%; p=0.027, Table 1).

The prevalence of a notched ER differed significantly between the patients with and without event occurrences (23% vs. 6%; p=0.004, Table 1). In contrast, the incidence of slurring did not differ significantly between the 2 groups (p=0.1, Table 1). Kaplan-Meier curves showed that the prevalence of the occurrence of VT/VF or sudden death significantly differed among the patients with a notched ER, slurred ER, and without ER (p=0.001 by log rank test, Figure 4B).

**ST-segment**

The prevalence of ER without ST-segment elevation significantly differed between the patients with and without event occurrences (31% vs. 6%; p<0.001, Table 1). Conversely, the incidence of ER with ST-segment elevation did not differ significantly between the 2 groups (p=1.0, Table 1).

**Correlation between the location of the ER and the territory of the culprit artery**

The location of the ER matched with the territory of the culprit artery in 26 (2%) patients. There was no significant difference in the prevalence of matching between the ER and culprit artery between the patients with and without event occurrences (Table 1).

**Predictors of VF Occurrences in the Chronic Phase of an AMI**

A multivariable Cox proportional regression analysis revealed that a left ventricular ejection fraction of <35 % (HR 11.83; 95% CI 5.16–27.13; p<0.001), the presence of ER on the 12-lead ECG obtained before discharge (HR 5.37; 95% CI 2.27–12.69, p<0.001), and a Killip class on admission of >I (HR 2.75; 95% CI 1.24–6.07, p=0.013) were independent predictors of the occurrence of VT/VF or sudden death during the follow-up period (Table 2). The Harrell’s c
index of the Cox proportional hazard regression model including the ejection fraction <35%, high Killip class, and presence of ER was 0.693 (95% CI 0.666–0.720, p<0.001) for the occurrence of VT/VF or sudden death.

**Time course of ER**

Among the 99 patients with ER on the ECG obtained at pre-discharge, ER was observed also on the ECG recorded just after the onset of the AMI in only 37 (37%) patients. In contrast, in the remaining 62 (63%) patients, it could not be definitely confirmed on the ECG recorded just after the onset of the AMI because of the ST elevation or reciprocal ST depression caused by the AMI itself (Figure 5). ER assessed by the ECG recorded just after the onset of the AMI was not associated with an event occurrence (p=0.3 by the log-rank test).

Among the 234 patients in whom we could assess the ECG obtained before the onset of the AMI, the presence or absence of ER in the ECG obtained before the AMI onset and before discharge matched in the majority of the patients; 22 (67%) of 33 patients had ER in the ECG obtained both prior to the AMI onset and at pre-discharge and 195 (97%) of 201 patients did not have ER in the ECG obtained neither prior to the AMI onset nor at pre-discharge. On the other hand, the ER disappeared in 11 (33%) of 33 patients who had ER in the ECG obtained before the AMI onset due to the ST-T change caused by the AMI itself. ER was acquired in 6 (3%) of 201 patients who did not have ER prior to the AMI onset (Figure 6).

**Reproducibility of the judgment of ER**

The intraobserver variability for ascertaining the presence of ER on the ECG was κ=0.90 (p<0.001), and the interobserver variability was κ=0.89 (p<0.001).
Discussion

Main Findings

To the best of our knowledge, the results of this study showed for the first time the following findings: 1) approximately 10% of the AMI patients studied had ER on the ECG recorded at pre-discharge; 2) about one third of the patients who developed VT/VF or sudden death in the chronic phase of an AMI had ER; 3) not only severe left ventricular dysfunction and high Killip class on admission but also ER were independent predictors of the occurrence of VT/VF or sudden death; 4) as features of an ER pattern, ER in the inferior leads, high-amplitude ER, a notched morphology, and ER without ST-segment elevation were significantly associated with an event occurrence; and 5) the ER pattern was not well recognized in the ECG obtained shortly after the onset of the AMI in 64% of the patients who had ER at pre-discharge. In addition to a VF occurrence in the acute phase of an AMI,15 ER was significantly associated with an increased risk of a VT/VF occurrence or sudden death in the chronic phase of the AMI.

Proposed Mechanism of VT/VF in Patients with ER

In this study, in addition to severe left ventricular dysfunction and a high Killip class on admission, which have been reported as risk factors for the occurrence of VT/VF or sudden death during the chronic phase of an AMI,22 to the best of our knowledge, we found for the first time that the presence of ER was a new risk factor for an event occurrence even after an adjustment for multiple variables.

Transmural differences in the early phases (phases 1 and 2) of the cardiac action potential, which are created by a disproportionate amplification of the repolarizing current in the epicardial myocardium due to an increase in the outward potassium currents mediated by the I_{to}, I_{K-ATP}, and I_{K-Ach} channels, are considered to be responsible for the inscription of the ECG J wave.23 The
trigger and substrate for the development of phase 2 reentry and VT/VF may eventually emerge from the transmural dispersion of the duration of the cardiac action potentials.23 Patients who suffer from a myocardial infarction have scar tissue in the myocardium that could become a substrate for VT.24 One possible speculation is that phase 2 reentry and scar tissue play an important role in the development of sustained VT/VF as the trigger and substrate, respectively, resulting in the higher prevalence of an occurrence of VT/VF or sudden death in the chronic phase of an AMI in the patients with ER than in those without.

It is known that high amplitude J-point elevation increases the risk of VF during the acute phase of an ST-elevation myocardial infarction.25 J-point elevation at the onset of an ST-elevation myocardial infarction has been proposed to be due to the opening of the $I_{K\text{-ATP}}$ channels.26 Our findings indicated that acquired ER was observed in 6 patients. We could speculate that persistent opening of the $I_{K\text{-ATP}}$ channels plays an important role in the presence of ER during the post-AMI phase.

**Previous Studies**

Previous studies have shown the characteristics of ER in those who have suffered from VT/VF.9-15 In the present study, ER in the inferior leads, high amplitude ER, a notched morphology, and ER without ST-segment elevation were associated with an increased risk of the occurrence of VT/VF or sudden death, which was quite similar to the findings of previous studies.9-15 We could consider these ER patterns indicated a malignant form.

Patel et al.14 showed that ER was the independent predictor of life-threatening VT/VF in patients with chronic coronary artery disease. All subjects of that study underwent an ICD implantation, and the mean ejection fraction was <30%. In the present study, however, the mean ejection fraction was 54%, and the prevalence of severe left ventricular dysfunction
(ejection fraction <35%) and an ICD implantation was 5% and 3%, respectively. The present study showed for the first time that ER was associated with an increased risk of the occurrence of VT/VF or sudden death >14 days after the onset of the AMI in not only patients with severe but also those with mild to moderate left ventricular dysfunction.

**Clinical Implications**

Our study showed that the presence of ER increased the risk for the occurrence of VT/VF or sudden death in the chronic phase of an AMI in the patients who survived the first 14 days after an AMI. In particular, much attention should be paid to patients with ER in the inferior leads, high amplitude ER, a notching morphology of the ER, and ER without ST-segment elevation.

It is possible to underestimate the prevalence of ER on the ECG obtained shortly after the AMI onset because of the ST-T changes caused by the AMI itself, and in the present study, ER assessed on admission was not associated with the occurrence of VT/VF or sudden death. Therefore, the presence or absence of ER should be assessed from an ECG recorded at pre-discharge because acute ST-T elevation caused by the AMI itself sufficiently resolved about 10 days after the onset of the AMI.

**Study Limitations**

First, our study was a hypothesis generating trial, not a conclusive trial, based on the retrospective design and relatively small number of endpoints. The small sample size limited the power of the study and was reflected in the broad confidence intervals, most notably in the adjusted statistical analyses. Second, because the prevalence of an ICD implantation was only 1% in our study, we could have underestimated the occurrence of sustained VT/VF. Third, patients with an AMI are hospitalized for only 4 days in the United States. It may be difficult to obtain an ECG 10 days post-AMI at pre-discharge in Western countries. Fourth, the use of
β-blockers and statins was relatively low for the cohort given existing guidelines for post AMI management. This fact may affect the increased risk of VT/VF or sudden death occurrence. Fifth, this study might miss the significance of ER presented in the precordial leads because the anterior precordial leads were excluded from the analysis of the ER. Therefore, further prospective studies with a larger sample size, long-term follow-up, and the participation of many hospitals and many countries may be needed to resolve these limitations and to confirm and enhance our results.

**Acknowledgments:** We thank Takahito Kaji for his helpful contribution to the statistical analysis.

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**Conflict of Interest Disclosures:** None.

**References:**


Table 1. Demographic and Clinical Characteristics of the Patients With and Without Occurrences of Ventricular Tachyarrhythmias or Sudden Death

<table>
<thead>
<tr>
<th></th>
<th>Total (n=1,131)</th>
<th>Event occurrence (n=26)</th>
<th>No event occurrence (n=1105)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67±12</td>
<td>69±8</td>
<td>67±12</td>
<td>0.376</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>862 (76%)</td>
<td>25 (96%)</td>
<td>837 (76%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>710 (62%)</td>
<td>18 (68%)</td>
<td>692 (62%)</td>
<td>0.491</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>516 (46%)</td>
<td>11 (42%)</td>
<td>505 (46%)</td>
<td>0.731</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>388 (34%)</td>
<td>13 (50%)</td>
<td>375 (34%)</td>
<td>0.088</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>637 (56%)</td>
<td>15 (58%)</td>
<td>622 (56%)</td>
<td>0.887</td>
</tr>
<tr>
<td>Culprit artery‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA, n (%)</td>
<td>394 (35%)</td>
<td>5 (19%)</td>
<td>389 (35%)</td>
<td>0.091</td>
</tr>
<tr>
<td>LAD, n (%)</td>
<td>519 (46%)</td>
<td>17 (65%)</td>
<td>502 (46%)</td>
<td>0.044</td>
</tr>
<tr>
<td>LCx, n (%)</td>
<td>198 (18%)</td>
<td>4 (15%)</td>
<td>194 (18%)</td>
<td>1.0</td>
</tr>
<tr>
<td>LMT, n (%)</td>
<td>36 (3%)</td>
<td>0 (0%)</td>
<td>36 (3%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Number of diseased coronary arteries, n</td>
<td>1 [1–2]</td>
<td>1.5 [1.0–2.8]</td>
<td>1 [1–2]</td>
<td>0.448</td>
</tr>
<tr>
<td>Killip class on admission, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.009</td>
</tr>
<tr>
<td>I</td>
<td>909 (80%)</td>
<td>15 (58%)</td>
<td>894 (81%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>108 (10%)</td>
<td>4 (15%)</td>
<td>104 (9%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>48 (4%)</td>
<td>2 (8%)</td>
<td>46 (4%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>66 (6%)</td>
<td>5 (19%)</td>
<td>61 (6%)</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>878 (78%)</td>
<td>15 (58%)</td>
<td>863 (78%)</td>
<td>0.014</td>
</tr>
<tr>
<td>β-blocker, n (%)</td>
<td>766 (68%)</td>
<td>14 (54%)</td>
<td>752 (68%)</td>
<td>0.126</td>
</tr>
<tr>
<td>ACE-I/ARB, n (%)</td>
<td>831 (73%)</td>
<td>21 (81%)</td>
<td>810 (73%)</td>
<td>0.394</td>
</tr>
<tr>
<td>Calcium blocker, n (%)</td>
<td>228 (20%)</td>
<td>3 (12%)</td>
<td>225 (20%)</td>
<td>0.268</td>
</tr>
<tr>
<td>Acetylsalicylic acid, n (%)</td>
<td>1129 (100%)</td>
<td>26 (100%)</td>
<td>1103 (100%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Clopidogrel, n (%)</td>
<td>1109 (98%)</td>
<td>26 (100%)</td>
<td>1083 (98%)</td>
<td>1.0</td>
</tr>
<tr>
<td>VT/VF occurrence in the acute phase, n (%)</td>
<td>78 (7%)</td>
<td>6 (23%)</td>
<td>72 (7%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Peak creatine kinase levels, U/L</td>
<td>1,625 [708–2,926]</td>
<td>2,370 [1,278–3,541]</td>
<td>1,602 [701–2,916]</td>
<td>0.101</td>
</tr>
</tbody>
</table>
Values are reported as the mean ± standard deviation, median (interquartile range), or n (%). *p<0.05 and †p<0.01 vs. event occurrence. ACE-I indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CL(R)BBB, complete left (right) bundle branch block; LAD, left anterior descending artery; LCx, left circumflex artery; LMT, left main trunk; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction; and VT/VF, ventricular tachyarrhythmia. ‡there were no patients who had more than 1 culprit artery.

<table>
<thead>
<tr>
<th></th>
<th>Event A</th>
<th>Event B</th>
<th>Event C</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>53 ± 11</td>
<td>42 ± 12</td>
<td>54 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;35 %, n (%)</td>
<td>54 (5%)</td>
<td>9 (35%)</td>
<td>45 (4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>STEMI, n (%)</td>
<td>924 (82%)</td>
<td>20 (77%)</td>
<td>904 (82%)</td>
<td>0.606</td>
</tr>
<tr>
<td>Successful PCI, n (%)</td>
<td>1102 (97%)</td>
<td>25 (96%)</td>
<td>1077 (97%)</td>
<td>0.495</td>
</tr>
<tr>
<td>Implantable cardioverter defibrillator, n (%)</td>
<td>8 (1%)</td>
<td>2 (8%)</td>
<td>6 (1%)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

EKG parameters obtained from the ECG before discharge

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Event A</th>
<th>Event B</th>
<th>Event C</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS complex duration &gt;120 ms, n (%)</td>
<td>46 (4%)</td>
<td>1 (4%)</td>
<td>45 (4%)</td>
<td>1.0</td>
</tr>
<tr>
<td>CRBBB, n (%)</td>
<td>36 (3%)</td>
<td>0 (0%)</td>
<td>36 (3%)</td>
<td>1.0</td>
</tr>
<tr>
<td>CLBBB, n (%)</td>
<td>10 (1%)</td>
<td>1 (4%)</td>
<td>9 (1%)</td>
<td>0.208</td>
</tr>
<tr>
<td>Early repolarization, n (%)</td>
<td>99 (9%)</td>
<td>8 (31%)</td>
<td>91 (8%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Distribution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior leads, n (%)</td>
<td>68 (6%)</td>
<td>7 (27%)</td>
<td>61 (6%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Lateral leads, n (%)</td>
<td>23 (2%)</td>
<td>0 (0%)</td>
<td>23 (2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Both leads, n (%)</td>
<td>8 (1%)</td>
<td>1 (4%)</td>
<td>7 (1%)</td>
<td>0.170</td>
</tr>
<tr>
<td>Matched to the territory of culprit artery, n (%)</td>
<td>26 (2%)</td>
<td>1 (4%)</td>
<td>25 (2%)</td>
<td>0.417</td>
</tr>
<tr>
<td>Amplitude of J-point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 0.2 mV</td>
<td>29 (3%)</td>
<td>3 (12%)</td>
<td>26 (2%)</td>
<td>0.027</td>
</tr>
<tr>
<td>Morphology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notching</td>
<td>72 (6%)</td>
<td>6 (23%)</td>
<td>66 (6%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Slurring</td>
<td>27 (2%)</td>
<td>2 (8%)</td>
<td>25 (2%)</td>
<td>0.126</td>
</tr>
<tr>
<td>ST-segment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER with ST-segment elevation</td>
<td>28 (2%)</td>
<td>0 (0%)</td>
<td>28 (3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>ER without ST-segment elevation</td>
<td>71 (6%)</td>
<td>8 (31%)</td>
<td>63 (6%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ACE-I indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CL(R)BBB, complete left (right) bundle branch block; LAD, left anterior descending artery; LCx, left circumflex artery; LMT, left main trunk; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction; and VT/VF, ventricular tachyarrhythmia. ‡there were no patients who had more than 1 culprit artery.
Table 2: Univariable and Multivariable Cox Proportional Regression Analyses of Ventricular Tachyarrhythmias or Sudden Death Occurrence

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariable Hazard Ratio (95% confidence interval)</th>
<th>p value</th>
<th>Multivariable Hazard Ratio (95% confidence interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>7.711 (1.045–56.916)</td>
<td>0.045</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending culprit artery</td>
<td>2.193 (0.977–4.922)</td>
<td>0.057</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Killip class on admission &gt; I</td>
<td>3.319 (1.523–7.232)</td>
<td>0.003</td>
<td>2.746 (1.241–6.073)</td>
<td>0.013</td>
</tr>
<tr>
<td>Statin</td>
<td>0.476 (0.217–1.047)</td>
<td>0.065</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT/VF occurrence within 48 hours after AMI onset</td>
<td>3.625 (1.453–9.041)</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt; 35%</td>
<td>11.994 (5.342–26.932)</td>
<td>&lt;0.001</td>
<td>11.829 (5.157–27.131)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Early repolarization on the ECG obtained before discharge</td>
<td>4.234 (1.837–9.760)</td>
<td>0.001</td>
<td>5.370 (2.273–12.687)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AMI indicates acute myocardial infarction; and VT/VF, ventricular tachyarrhythmia.
Figure Legends:

Figure 1: Study Design. Patients that were excluded from the analysis are indicated by arrows directed to the right.
AMI= acute myocardial infarction; PCI= percutaneous coronary intervention; Pts= patients.

Figure 2: Representative Cases of Early Repolarization. (A) Notched early repolarization (arrows) without ST-segment elevation in the inferior leads was observed in an 80-year-old man after an anterior myocardial infarction. (B) Slurred early repolarization (arrows) without ST-segment elevation in the inferior and lateral leads was recognized in a 77-year-old woman after an anterior myocardial infarction. The arrows point to the measurement point of the amplitude of the peak QRS notch and QRS slur; the hash lines at the end of the QRS indicate the ST-junction where we assessed the ST-segment elevation. onQRSs=onset of the QRS slur; pkQRSn=peak QRS notch; and STj=ST-junction.

Figure 3: Kaplan-Meier Curves. There was a significant difference in the occurrence of sustained ventricular tachyarrhythmias or sudden death between the patients with and without early repolarization (ER).

Figure 4: Kaplan-Meier Curves (A) Kaplan-Meier Curves in the patients with a left ventricular ejection fraction of less than 35%. Concomitant early repolarization was associated with an increased risk of sustained ventricular tachyarrhythmias or a sudden death occurrence in the patients with severe left ventricular dysfunction. (B) Kaplan-Meier Curve according to the
morphology of the early repolarization (ER). Notched ER increased the occurrence of sustained ventricular tachyarrhythmia or sudden death (p=0.001 between the patients with a notched ER and those without ER; p=0.1 between the patients with a slurred ER and those without ER; and p=0.9 between the patients with a notched ER and those with slurred ER).

**Figure 5:** Time Course of Early Repolarization. Changes in the early repolarization pattern between that just after the onset of an acute myocardial infarction (AMI) and that before hospital discharge.

**Figure 6:** Time Course of Early Repolarization in the 234 patients whose ECG obtained before the AMI onset could be assessed. Changes in the early repolarization (ER) pattern among that before the onset of an acute myocardial infarction (AMI), just after the onset of the AMI and that before hospital discharge.
1,306 Pts with an AMI who underwent a PCI within 24 hrs after the onset of the AMI, between 2006 and 2011 (retrospective, multicenter study)

65 Pts died <14 days after the AMI onset

60 Pts: experienced a prior MI
3 Pts: co-existing Brugada-like ECG

47 Pts were lost to follow-up

1,131 Pts comprised the study group
(A) Proportion of event-free patients over days of follow-up for ER (-) and ER (+). The log-rank test yields a p-value of 0.021.

(B) Proportion of event-free patients for ER (-), Slurred ER (+), and Notched ER (+) over days of follow-up. The log-rank test yields a p-value of 0.001.
ECG just after the onset of the AMI

Early repolarization (+) (n= 44)

Early repolarization (-) (n= 1,087)

ECG before discharge (10±3 days after the onset)

Early repolarization (+) (n= 99)

Early repolarization (-) (n= 1,032)

37

7

62

1025
Before the onset of the AMI

ER (+) (n=33)

16

17

ER (-) (n=17)

13

9

3

8

ER (-) (n=11)

Before hospital discharge

ER (+) (n=22)

ER (-) (n=11)

Acquired ER

ER (+) (n=6)

3

2

4

1

198

194

195

ER (-) (n=198)

ER (-) (n=195)

ER (-) disappeared

ER (-) (n=17)

ER (+) (n=16)
Early Repolarization Increases the Occurrence of Sustained Ventricular Tachyarrhythmias and Sudden Death in the Chronic Phase of an Acute Myocardial Infarction
Yoshihisa Naruse, Hiroshi Tada, Yosie Harimura, Mayu Ishibashi, Yuichi Noguchi, Akira Sato, Tomoya Hoshi, Yukio Sekiguchi and Kazutaka Aonuma

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