Presence of early repolarization on admission electrocardiography is associated with long-term mortality and MACE in patients with STEMI undergoing primary percutaneous intervention

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Abstract

Background: Early repolarization (ER) is associated with increased risk of sudden cardiac death and ventricular fibrillation (VF) in patients with/without structural heart disease. In this trial we examined the short- and long-term prognostic value of ER on admission electrocardiogram (ECG) in patients with ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI).

Method: Consecutive 521 patients with acute STEMI who underwent primary PCI were enrolled prospectively. Twelve-lead ECGs obtained during the initial diagnosis were scanned and stored digitally. The leads showing the typical ST segment elevation due to the acute infarction were excluded and the remaining ECG leads were included in the analysis for the presence of ER.

Results: The study group included 61 STEMI patients (55 male; mean age 57.6 ± 12.6 years) with ER and 460 STEMI patients (378 male; mean age 57.1 ± 12.5 years) without ER on ECG. In the ER group, 14 patients (22.9%) had notching, 10 patients (16.4%) had slurring, and 37 patients (60.7%) had only J-point elevation. When analyzing regional leads, ER was observed mostly in inferior leads (n = 40, 65.6%). During the hospitalization period, ventricular tachycardia or VF occurred more frequently in the ER group (19.6% vs. 10.9%; p = 0.04), and 6 patients (6.9%) from the ER group and 14 patients (3%) from the control group died (p = 0.01). During a follow-up period of 21.1 ± 10.2 months, mortality was significantly higher in the ER group (12.7% vs. 4.2%; p = 0.01). When total mortality rates were considered, highest mortality was observed in patients with notching pattern (5/14 subjects; 35.7%) when compared to patients with slurring (3/10 subjects; 30%), patients with only J-point elevation patterns (5/37 subjects; 13.5%) and the control group (33/460 subjects; 7.1%). Presence of notching and slurring pattern on admission ECG was found as independent predictors of long-term mortality; whereas presence of only J-point elevation was not.

Conclusion: Presence of ER pattern in admission ECG in patients with STEMI is associated with both in-hospital and long-term mortality.

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Introduction

Early repolarization (ER) which is characterized by an elevation of the junction between the end of the QRS complex and the beginning of the ST segment (J point) from baseline on standard 12-lead electrocardiography (ECG) has been considered a benign finding for a long time. However, population-based studies established the correlation of this relatively common ECG finding with primary ventricular fibrillation (VF) and sudden cardiac death (SCD) even in subjects without prior diagnosis of structural heart diseases [1–7]. Little is known about the prognostic significance of this electrocardiographic pattern in patients with structural heart disease. In chronic coronary artery disease (CAD), it has been observed that patients exhibiting ER pattern on ECG have an increased risk of ventricular tachyarrhythmias [8]. Acute ST segment elevation myocardial infarction (STEMI) is associated with high incidence of
ventricular arrhythmias and it has been the most frequent cause of sudden cardiac death in the adult population [9]. However, the prognostic importance of ER in acute myocardial infarction is confined to a few case–control studies with limited number of patients and short-term follow up [10–13]. The correlation of ER diagnosed on admission ECG in patients with STEMI treated with primary percutaneous coronary intervention (PCI) and long-term adverse cardiovascular events has not been established in the literature before. In this trial, we examined the short- and long-term prognostic value of this ECG finding in this patient population.

Materials and methods

Patient population

Our study was conducted between January 2009 and February 2012 in Siyami Ersek Thoracic and Cardiovascular Surgery Hospital, a tertiary reference center. We prospectively enrolled 521 consecutive patients with acute STEMI who underwent primary PCI. Patients with diagnosis of non-STEMI, with prior diagnosis of CAD, heart failure (including arrhythmogenic right ventricular dysplasia), any type of channelopathies associated with arrhythmias (such as Brugada syndrome), chronic liver/kidney disease, chronic inflammatory disease, malignancy, or endocrine disease (excluding diabetes mellitus) were excluded from the study. In addition, patients with atrial fibrillation or flutter, paced rhythms, ventricular pre-excitation, intraventricular conduction disturbances, or pathological Q-waves were also excluded from further analysis. Informed consent of patients was obtained before the study. The study was authorized by the institutional ethics committee.

Data sources

Demographic data and clinical history concerning age, sex, diabetes mellitus, hyperlipidemia, smoking, family history of CAD or sudden cardiac death, and previous drug use were obtained from all patients. Twelve-lead ECGs were obtained from all patients after the first medical contact for diagnosis of MI. Detailed physical examination was performed and any findings associated with heart failure were recorded. Hypertension was defined as a history of hypertension for more than 1 year, which required the initiation of antihypertensive therapy. The diagnosis of diabetes mellitus was based on previous history of diabetes mellitus treated with or without drug therapies. Individuals who reported smoking at least one cigarette per day during the year before examination were classified as smokers. Venous blood samples were collected on admission for laboratory analysis. Fasting lipid (triglycerides, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol) and glucose levels were also measured.

Definition of early repolarization

Twelve-lead ECGs obtained during the initial diagnosis were scanned and stored digitally. For ER determination only the admission ECG was used and serial ECGs were obtained only for clinical indications. Two independent investigators who were blinded to the clinical properties of the patients analyzed ECGs for the presence of ER. A third reading was performed by a third expert electrocardiologist in case of discordance. The leads showing the typical ST segment elevation due to the acute infarction were excluded and the remaining ECG leads were included in the analysis. Early repolarization was defined as elevation of the J-point (QRS–ST Junction) above 0.1 mV relative to QRS onset in two or more inferior leads (DII–DIII–aVF), limb lateral leads (DI–aVL), or left precordial leads (V4–V6) (Fig. 1). The anterior precordial leads (V1–V3) were excluded from the analysis of the ER to avoid the inclusion of patients with right ventricular dysplasia or Brugada syndrome [16].

ECGs showing ER pattern were further searched for the presence of QRS slurring or notching. Notching was defined as a positive J deflection at the end of QRS complex. Slurring was classified as terminal slower waveform transitioning from QRS J-point to the ST

![Fig. 1. ECG of a patient with anterior ST segment myocardial infarction showing early repolarization pattern in leads DII, DIII, and aVF with horizontal/downsloping ST segments (arrows).](image-url)
segment with upright concavity. To minimize the baseline wandering effect, J-point amplitude was measured at the J point (QRS–ST junction) and relative to QRS onset. The amplitude of slurring was measured at the inflection point of the QRS complex relative to QRS onset. Amplitude of notching was measured at the peak of the positive deflection relative to QRS onset. Amplitude was calculated as a pooled mean among all types of ER [1,6,10–12]. ST-segment patterns after the J point were also classified as horizontal/descending or concave/rapidly ascending due to established criteria by Tikkanen et al. [17]. QT duration was measured for all patients and corrected QT was calculated.

**Angiographic data**

All patients received chewable aspirin (300 mg, unless contraindicated) and clopidogrel (600 mg, loading dose) before a coronary angiography. In all cases, percutaneous femoral approach and nonionic, low-osmolality contrast media were used. The infarct-related artery was graded according to the thrombolysis in myocardial infarction (TIMI) classification [10]. Heparin (10,000 U) was administered after coronary anatomy was defined. Coronary artery stenosis of more than 50% was considered clinically significant. Multivessel disease was defined by a stenosis of more than 50% in more than one major epicardial coronary artery. Primary coronary interventions, including balloon angioplasty and/or stent implantation, were performed only for infarct-related artery according to lesion anatomy. For each procedure, interventional success at the acute phase was defined as an obstruction and stenosis of the infarct-related artery having been reduced to less than 50% stenosis with TIMI of 2 or 3 flows after primary PCI. After stent placement, clopidogrel was used for more than 1 year and aspirin was used indefinitely. Left ventricular ejection fraction assessment was performed by echocardiography during the index hospitalization.

**Definition of short-term and long-term events**

Acute stent thrombosis was defined as an abrupt onset of cardiac symptoms along with an elevation in levels of biomarkers or electrocardiographic evidence of myocardial injury after stent deployment in the first 24 h. This was accompanied by angiographic evidence of a flow-limiting thrombus near a previously placed stent. Reinfarction was described as a 2-fold increase of serum creatine kinase (CK)–MB enzyme levels and ST segment re-elevation. Target lesion revascularization (TLR) was defined as vascularization of the stented segment or within 5-mm margins proximal or distal to the stent by either repeat PCI or coronary artery bypass grafting.

Follow-up information was obtained through review of hospital records and telephone contact with the patient or the patient’s relatives. All subsequent hospital admissions (for angina, recurrent infarction, additional intervention) during follow-ups were recorded. “Definite” late stent thrombosis was defined as ischemic clinical events with angiographically proven stent thrombosis, TLRs not related to thrombosis-related events were assumed to be “restenosis-related.” Major adverse cardiac events (MACE) were defined as cardiovascular mortality, reinfarction and TLR (percutaneous or surgical).

**Statistical analysis**

All data were presented as mean ± SD for parametric variables and as percentages for categorical variables unless stated otherwise. Continuous variables were checked for the normal distribution assumption using the Kolmogorov–Smirnov statistics. Differences between patients and control subjects were evaluated using the 2-sample t test and Mann–Whitney U test as appropriate. Categorical variables were tested by Pearson’s χ² test and Fisher’s Exact Test. For clinical outcomes, Kaplan–Meier estimates and curves were generated, and comparisons were made using log-rank test. Forward stepwise multivariate logistic regression models were created to identify the independent predictors of in-hospital and long-term adverse events. Variables with a p-value <0.10 in univariate analysis were included in the multivariate model. All statistical studies were carried out using Statistical Package for Social Sciences software (SPSS 16.0 for Windows, SPSS Inc., Chicago, IL, USA) and a p-value <0.05 was considered statistically significant.

**Results**

A total number of 521 patients with STEMI who were treated with primary PCI were included in our study. Sixty-one patients (55 male; mean age 57.6 ± 12.6) whose ECGs were compatible with ER were compared to 460 patients (378 male; mean age 57.1 ± 12.5) without ER on ECG. Demographic, clinical properties, and ECG findings of the study participants are depicted in Table 1. The two groups were age-gender matched and the frequencies of cardiovascular risk factors were similar between the groups. In the ER group, 14 patients (22.9%) had notching, 10 patients (16.4%) had slurring, and 37 patients (60.7%) had only J-point elevation. When analyzing regional leads, ER was observed mostly in inferior leads (n = 40, 65.6%) and then left precordial leads (n = 10, 16.4%), and lateral leads (n = 11, 18%). In ER patients, ST segments were horizontal/downsloping type in 41 (67.2%) and upsloping type in 20 (32.8%) subjects. In patients with ER, mean amplitude of J-point elevation was 1.07 ± 0.25 mm and there were 5 patients with J-point elevation amplitude of ≥2 mm. Laboratory variables including creatinine, peak–CK-MB, and cholesterol parameters were also comparable between the two groups. Angiographic findings including presence of multivessel disease and post-PCI TIMI 3 flow restoration rates and left ventricular ejection fraction were not different between the groups.

In-hospital and long-term clinical outcomes are listed in Table 2. Sustained ventricular tachycardia or VF occurred more frequently in the ER group (19.6% vs. 10.9%; p = 0.04). Six patients (6.9%) from the ER group and 14 patients (3%) from the control group died during the hospitalization period which was significantly higher (p = 0.01). Whereas, recurrent MI, TLR, and MACE rates were similar between the two groups (p = 0.92; p = 0.65, and p = 0.16, respectively). In subgroup analysis, the incidence of in-hospital ventricular tachyarrhythmias was significantly higher in the notch subgroup (6/14 subjects; 42.8%) compared to slurring (1/10 subjects; 10%) and only J-point elevation (5/37 subjects; 13.5%) subgroups (p = 0.04). The incidence of in-hospital mortality was 21.4% (3/14 subjects) among patients with notching pattern and 8.1% (3/37 subjects) among patients with only J-point elevation. No patient with slurring pattern died during the hospitalization period (p = 0.20). The incidence of in-hospital ventricular tachyarrhythmias and mortality did not differ significantly in horizontal/downsloping and upsloping ST segment subgroups (p = 0.52, and p = 0.18, respectively).

The mean follow-up period of the participants was 21.1 ± 10.2 months. During this period, 15 MACE (27.3%) occurred in the ER group and 70 MACE (15.7%) occurred in the control group which was significantly higher (p = 0.05). The difference was mainly driven by the high mortality and TLR rates in the ER group compared to the controls (12.7% vs. 4.2%; p = 0.01 and 23.6% vs. 10.8%; p = 0.02, respectively). The frequency of recurrent MI was not statistically different between the groups (p = 0.16). In cox-regression analysis, presence of ER on ECG resulted in increased rate of mortality and MACE during the follow-up period (Log Rank p = 0.01 and 0.01, respectively) (Figs. 2 and 3).
In total, 13 out of 61 patients in the ER group (21.3%) and 33 out of 460 patients (7.2%) without ER died during the study period ($p = 0.01$). In subgroup analysis, mortality rate was highest in patients who had notching pattern on ECG (5/14 subjects; 35.7%) when compared to patients with slurring (3/10 subjects; 30%) and patients with only J-point elevation patterns (5/37 subjects; 13.5%) ($p = 0.17$). When regional distribution of the ER pattern on ECG was considered, the total mortality rate was similar between inferior lead ER (6/40 subjects; 15%) and non-inferior lead ER subgroups (7/21 subjects; 33.3%) ($p = 0.11$). The total mortality rate was similar in patients with horizontal/downsloping ST segments (9/41 subjects; 21.9%) and upsloping ST segments (4/20 subjects; 20%) ($p = 0.85$).

Table 3 lists the results of univariate and multivariate logistic regression analysis for the predictors of total mortality in the study group. In univariate analysis, age, gender, Killip class >1 on admission, door-to-balloon time, post-PCI TIMI flow <3, left ventricular ejection fraction, admission creatinine levels, peak CK-MB level, and presence of ER on ECG were associated with total mortality. In multivariate analysis, presence of ER on ECG remained an independent predictor of long-term mortality when subjects without ER served as the reference group. However, presence...
of only J-point elevation was not correlated with increased risk of mortality in univariate and multivariate analyses. When subgroups of ER are analyzed separately in univariate logistic regression analysis, presence of notching (OR: 3.55 95% CI 1.04–15.05; p = 0.08) and slurring (OR: 2.73 95% CI 0.52–14.02; p = 0.23) were not predictors of long-term mortality compared to subjects with only J-point elevation. The regional distribution of the ER pattern on the ECG did not predict mortality, neither.

Discussion

The main finding of our study was that presence of ER on admission ECG was associated with higher rates of in-hospital ventricular arrhythmias and mortality and was an independent predictor of long-term mortality beyond well-known other parameters. Presence of notching or slurring pattern was correlated with long-term mortality in multivariate analysis, however, presence of only J-point elevation was not.

Presence of ER on ECG has been associated with ventricular arrhythmias in population-based studies [1–7]. Ventricular arrhythmias are the main cause of mortality in patients with STEMI and CAD [9]. Although, presence of ER has been shown to be related with arrhythmogenicity, the prognostic importance of this ECG finding in patients with STEMI has not been well elucidated. Few trials investigated the prognostic value of ER pattern in patients with CAD and STEMI [8,10–13].

Patel et al. conducted a case–control study including 50 patients with STEMI complicated by ventricular arrhythmias within 72 h of hospitalization. They have analyzed the ECGs obtained an average of 1 year before STEMI and have found that presence of ER pattern (notching or J-point elevation) on the initial ECG was associated with ventricular arrhythmias after MI [11]. In another report, the same group found that the presence of notching pattern on ECG was associated with higher rates of ventricular tachyarrhythmias in patients with stable CAD (60 case and 60 control subjects) during a follow-up period of about 1.75 years [8].

Naruse et al. retrospectively included 220 consecutive patients with STEMI in whom the 12-lead ECGs before MI onset could be

Table 3

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate analysis</th>
<th>OR (95% CI)</th>
<th>p</th>
<th>Multivariate analysis</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.06 (1.04–1.09)</td>
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<td></td>
<td>1.04 (1.01–1.08)</td>
<td>0.01</td>
<td></td>
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<tr>
<td>Male gender</td>
<td>0.33 (0.17–0.66)</td>
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<td></td>
<td>0.28 (0.15–0.58)</td>
<td>0.01</td>
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<tr>
<td>Smoking</td>
<td>0.80 (0.33–1.56)</td>
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<tr>
<td>Hypertension</td>
<td>1.54 (0.86–2.21)</td>
<td>0.19</td>
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<tr>
<td>Diabetes mellitus</td>
<td>1.66 (0.82–3.35)</td>
<td>0.16</td>
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<tr>
<td>Hyperlipidemia</td>
<td>1.15 (0.32–3.19)</td>
<td>0.48</td>
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<tr>
<td>Door-to-balloon time</td>
<td>1.03 (1.003–1.058)</td>
<td>0.03</td>
<td></td>
<td>1.03 (0.99–1.07)</td>
<td>0.06</td>
<td></td>
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<tr>
<td>Killip class &gt;1</td>
<td>5.12 (2.68–9.35)</td>
<td>0.01</td>
<td></td>
<td>3.58 (1.61–7.92)</td>
<td>0.01</td>
<td></td>
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<tr>
<td>Multivessel disease</td>
<td>1.58 (0.86–2.92)</td>
<td>0.14</td>
<td></td>
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<tr>
<td>Post-PCI TIMI flow &lt;3</td>
<td>6.25 (3.22–11.22)</td>
<td>0.01</td>
<td></td>
<td>3.18 (1.43–7.09)</td>
<td>0.01</td>
<td></td>
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<tr>
<td>Tirofiban infusion</td>
<td>0.75 (0.32–1.55)</td>
<td>0.17</td>
<td></td>
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<tr>
<td>Left ventricular ejection fraction</td>
<td>0.91 (0.88–0.95)</td>
<td>0.01</td>
<td></td>
<td>0.95 (0.91–0.98)</td>
<td>0.01</td>
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<tr>
<td>Glucose levels</td>
<td>1.001 (0.98–1.003)</td>
<td>0.22</td>
<td></td>
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<tr>
<td>Creatinine levels</td>
<td>4.11 (2.21–7.61)</td>
<td>0.01</td>
<td></td>
<td>2.01 (0.98–4.05)</td>
<td>0.05</td>
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<tr>
<td>Peak creatine kinase-MB</td>
<td>1.003 (1.002–1.005)</td>
<td>0.01</td>
<td></td>
<td>1.002 (1.00–1.004)</td>
<td>0.07</td>
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<tr>
<td>Presence of ER on ECG</td>
<td>3.51 (1.72–7.1)</td>
<td>0.01</td>
<td></td>
<td>5.14 (2.06–12.89)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Only J-point elevation</td>
<td>1.05 (0.66–1.67)</td>
<td>0.83</td>
<td></td>
<td>1.73 (0.53–5.71)</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Presence of notching</td>
<td>6.31 (2.02–19.8)</td>
<td>0.01</td>
<td></td>
<td>12.2 (3.17–46.8)</td>
<td>0.01</td>
<td></td>
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<tr>
<td>Presence of slurring</td>
<td>4.66 (1.16–18.9)</td>
<td>0.03</td>
<td></td>
<td>10.9 (1.85–65.6)</td>
<td>0.01</td>
<td></td>
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<tr>
<td>J-Point elevation ≥2 mm</td>
<td>6.9 (1.05–45.8)</td>
<td>0.05</td>
<td></td>
<td>9.14 (0.38–126.9)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>ER in inferior leads</td>
<td>0.36 (0.12–1.25)</td>
<td>0.11</td>
<td></td>
<td>0.44 (0.15–2.64)</td>
<td>0.36</td>
<td></td>
</tr>
</tbody>
</table>

PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; ER, early repolarization; ECG, electrocardiogram.

*a* Model adjusted for age, gender, door-balloon time, Killip class >1, post-PCI TIMI flow <3, left ventricular ejection fraction, creatinine levels, peak creatine kinase-MB was used in multivariate analysis.

*b* Patients without ER pattern on ECG served as the reference.

*c* These analyses included only the subjects with ER (n = 61) and the remainder of the subgroup served as the reference.
evaluated. The patients were classified on the basis of VF occurrence within 48 h after MI onset. In multivariate analysis presence of ER on ECG was found to be a predictor for VF. As features of the ER pattern, a J-point elevation in the inferior leads, greater magnitude of the J-point elevation and notching pattern were found to be predictors of VF [10].

Rudic et al. investigated 30 patients who developed VF in the early hours of STEMI and compared their ECGs obtained on the 5th day of MI with control subjects who had STEMI but no ventricular arrhythmias. Similar to our results they have found that ER and notching pattern was more common in the VF group and they did not find a statistical difference between regional leads regarding in-hospital events [12].

However, most of these studies investigated only in-hospital events and selected cases developing ventricular arrhythmias after MI. In this prospective study, we included consecutive patients and in a blinded manner investigated the correlation between admission ECG properties with in-hospital and long-term (mean time 21.1 ± 10.2 months) cardiovascular events. Our results confirm the previously established correlation of ER with in-hospital events and extend this finding to the long-term events after STEMI.

Consistent with the literature, in our study, ER pattern was mostly observed in the inferior leads. However, correlation with long-term mortality was not different among the regional leads which show ER pattern. In univariate analysis J point elevation more than 2 mm was associated with long-term mortality but not in multivariate analysis. Moreover, the number of subjects with J-point elevation >2 mm was low. In-hospital mortality was higher in patients with ER and in concordance with previous reports was highest among patients with notching or slurring pattern on the ECG. However, in subgroup analysis, presence of notching or slurring pattern was not correlated with long-term mortality compared to subjects with only J-point elevation. A larger sample size could have led to a significant difference in subgroup analysis of ER subjects.

Different from other studies conducted on STEMI patients, we have only evaluated admission ECGs of patients. In Naruse et al.'s study they have found that patients who had ER in the baseline 12-lead ECG recording before the STEMI, ER was still observed in the admission 12-lead ECG in 56% of patients [10]. No patients who had no ER in the baseline 12-lead ECG before the STEMI patients developed any ER in the 12-lead ECG on admission. We did not analyze previous ECG recordings thus we might have underestimated the true incidence of ER in patients with STEMI. Tikkanen et al. analyzed ER from 432 victims of SCD because of acute coronary syndrome and compared 532 survivors of acute coronary syndrome, in whom 12-lead ECGs recorded before and unrelated to the event could be evaluated [13]. Early repolarization pattern was found to be associated with SCD during an acute coronary syndrome. Similar to our findings they observed that slurring pattern was associated with mortality.

It has been postulated that ER on ECG is a sign of the transmural electrical heterogeneity between depolarized endocardium and repolarized epicardium. This heterogeneity may result in dispersion of repolarization, formation of re-entry circuits, and arrhythmias [11,17–19]. Predisposing factors such as myocardial ischemia may induce ventricular arrhythmias and subjects with repolarization abnormalities may be affected worse in this situation [1–13].

Tikkanen et al. have analyzed the survival curves of patients with ER pattern on ECG and they have found that survival curves diverge at six decade and they concluded ER itself does not seem to cause ventricular rhythm disturbances, it may increase the vulnerability to fatal arrhythmias in the setting of myocardial infarction [1,12,20].

In conclusion, presence of ER pattern (especially notching and slurring patterns) on admission ECG in patients with STEMI is associated with both in-hospital and long-term mortality. ER which can be easily detected on admission ECGs of patients with STEMI may identify patients at high risk for short- and long-term mortality. In particular, much attention should be paid to the patients with ER. Further prospective larger scale trials are needed to explore and confirm this finding.

**Limitations of our study**

There are several limitations to our study. This is a small-sized study covering both short- and long-term results. In most patients, ECGs before STEMI were not available and we could not assess the presence of ER before STEMI. This may have resulted in underestimation of the true prevalence of ER in our cohort. On the other hand, because the definition of ER using the existing criteria of J-point elevation, notching, or slurring, it is also possible that we overestimated the true incidence of ER [8]. Even though, we found that long-term TLR rate was higher in patients with ER, our findings do not imply a causal relation between ECG findings and higher incidence of TLR.

**References**


