Association of Early Repolarization and Sudden Cardiac Death During an Acute Coronary Event

Jani T. Tikkanen, BM; Viktor Wichmann, BM; M. Juhani Junntila, MD; Meri Rainio, MD; Eeva Hookana, MSc; Olli-Pekka Lippi, BM; Marja-Leena Kortelainen, MD; Olli Anttonen, MD; Heikki V. Huikuri, MD

**Background**—Electrocardiographic early repolarization (ER) pattern has been previously associated with arrhythmic mortality and with an increased risk of ventricular fibrillation. We hypothesized that there is an association between ER and sudden cardiac death (SCD) during an acute coronary event.

**Methods and Results**—The present study included 432 consecutive victims of SCD because of acute coronary event and 532 survivors of such an event, in whom 12-lead ECGs recorded before and unrelated to the event could be evaluated. SCDs were verified by medicolegal autopsy to be because of acute coronary event. ER was defined as an elevation of the QRS-ST junction in at least 2 inferior or lateral leads, manifested as QRS notching or slurring. The prevalence of ER pattern ≥0.1 mV was more common in cases (62/432; 14.4%) than controls (42/532; 7.9%) (P=0.001). The victims of SCD were younger, were more commonly men and smokers, had lower body mass index, had elevated heart rate, had prolonged QRS complex, and had lower prevalence of history of prior cardiovascular disease than controls. After adjustments for baseline differences, the odds ratio for J waves without ST-segment elevation in the SCD group was 2.15 (95% CI, 1.20–3.85; P=0.01).

**Conclusions**—Higher prevalence of ER in a standard 12-lead ECG in victims of SCD than in survivors of an acute coronary event suggests that the presence of ER increases the vulnerability to fatal arrhythmia during acute myocardial ischemia and provides a plausible mechanistic link between this ECG pattern and higher arrhythmic mortality of middle-aged/elderly subjects. (*Circ Arrhythm Electrophysiol. 2012;5:714-718.*)

**Key Words:** sudden death ■ electrocardiography ■ epidemiology ■ heart attack (myocardial infarction) ■ early repolarization

Interlateral early repolarization (ER) pattern is characterized by an elevation of the QRS-ST junction (J point), manifested as QRS notching or slurring (J wave) in multiple inferior or lateral leads, with or without ST-segment elevation. It is prevalent in 1% to 13% of the population depending on age, race, and sex differences. Although conventionally considered benign, the pattern is potentially arrhythmogenic because it has been associated with an increased risk of idiopathic ventricular fibrillation in clinical case-control studies.¹⁻³ Thereafter, it has been reported that ER pattern, especially in the inferior leads⁴⁻⁵ and with specific ST-segment variant,⁶ is associated with increased arrhythmic mortality rate in general population. The underlying causes and mechanism for these associations have remained unanswered.

**Clinical Perspective on p 718**

In our previous observational study of middle-aged subjects, we found that the risk of arrhythmic deaths started to increase >10 years after the baseline ECG recordings in middle-aged subjects with the ER pattern.⁴ Thus, this ECG pattern did not seem to increase the risk for an immediate fatal event but could perhaps increase the vulnerability to fatal arrhythmia during some other modifying factor, such as an acute coronary event, which is the most prevalent cause of cardiac events in middle-aged/elderly subjects. Recently, it was also speculated by others that patients with J waves would be at increased risk of ischemic ventricular fibrillation in the event of myocardial infarction.⁷ However, there have been no data to support these hypotheses.

We performed a case-control study by comparing the prevalence of ER patterns between the victims of sudden cardiac death (SCD) caused by an acute coronary event and survivors of such an event from the Finnish study of genotype and phenotype profiles of SCD (Finnish genetic study of arrhythmic events; FinGesture).

**Methods**

**Study Population**

Detailed methods of the FinGesture study have been reported earlier,⁸⁻¹⁰ and only a brief description follows. The FinGesture study...
has gathered data on 2732 consecutive victims of out-of-hospital sudden unexpected death from a defined geographical area (Oulu University Hospital District in Northern Finland), and all of these deaths have been autopsy-verified to be because of an acute coronary event, as previously described in detail. 1–10 The SCD victims consisted of those with a witnessed sudden death within 6 hours of onset of the forewarning symptoms. For unwitnessed SCDS, the time definition was extended to within 24 hours of when a victim was last seen alive and in a normal state of health. Those with any other cause than SCD (accidental or suicidal intoxications) during an acute coronary event were excluded, as well as those with signs of severe heart failure (history of hospitalization because of congestive heart failure or acute pulmonary edema at autopsy). The control group consisted of 1565 survivors of an acute coronary event from the same time period and the same geographical area from which SCD victims were gathered. Diagnosis of an acute coronary event was confirmed by using the current guidelines, as described in detail elsewhere. 11–12 Forty-two percent of these control patients had ST-segment elevation acute myocardial infarction, and 58% had non-ST-elevation acute myocardial infarction. The infarction was anterior in 45% of patients, inferior in 41%, and some other location in 14% of the patients.

For the present study, subjects were included from these 2 cohorts, if a prior standard 12-lead ECG unrelated to the event (SCD or acute coronary event) had been recorded and was available for interpretation. The underlying causes for ECG recordings included numerous in-hospital situations varying from routine preoperative ECG to standard recording at admission to the emergency unit. Consequently, the study population consisted of 432 victims of SCD and 532 controls.

Demographic and clinical characteristics, as well as medication data, were collected retrospectively from electronic medical records, medicolegal autopsy records, or standardized questionnaires answered by the victims' closest relatives, as described earlier. 13 Thus, this information represents the known medical history of the subjects, before the acute index coronary event. Medication data could not be reliably obtained from 209 subjects (22%).

ECG Interpretation

The most recent ECG was used for analysis if several ECGs were available. These standard 12-lead ECGs, recorded at a paper speed of 50 mm/s and a calibration of 1 mV per 10 mm, were analyzed by 3 independent investigators blinded to outcome status and clinical data, and consensus readings were performed for variable status, if necessary. The presence of ER pattern was analyzed using the same criteria, as described previously. 11–14 J-point elevation ≥0.1 mV in at least 2 inferior or lateral leads manifested as terminal QRS notching or slurring (J waves), with or without ST-segment elevation. Furthermore, ER patterns were categorized according to the type and dominant ST variant, also as previously described. 11 QT interval was corrected for heart rate by a Bazzett formula.

Statistical Analysis

Two-sided t test and \( \chi^2 \) analyses were used for comparisons between study groups. Logistic regression analysis was used to assess the significance of predictors of SCD between groups after adjustments for age, sex, smoking, body mass index, prior myocardial infarction, history of coronary artery disease, and medication ( \( \beta \)-blocker, statin, angiotensin II receptor antagonist, and nitroglycerin in model 2). The Hosmer and Lemeshow test was used to assess the goodness of fit of the logistic regression models. All analyses were performed with the Statistical Package for Social Studies version 16.0 (SPSS Inc, Chicago, IL). All \( P \) values are 2-sided, and \( P<0.05 \) was considered statistically significant.

Results

Demographics and Clinical Variables

The victims of SCD (n=432) were more often men, were significantly younger, had lower body mass index, and were more commonly smokers than survivors of acute coronary events (Table 1). Furthermore, the victims of SCD had lower prevalence of medical admissions because of prior myocardial infarction (23% versus 51%; \( P<0.001 \)) or diagnosed coronary artery disease (44% versus 76%; \( P<0.001 \)), as well as lower usage of cardiovascular medication (Table 1).

Electrocardiography

Table 2 presents the differences in ECG variables between the groups. The victims of SCD had significantly longer QRS duration (91 versus 88 ms; \( P=0.01 \)), higher heart rate (73 versus 70 beats per minute; \( P=0.002 \)), and shorter PQ interval (166 versus 171 ms; \( P=0.03 \)). The presence of atrial fibrillation or pathological Q waves did not differ between the groups. In addition, there were no statistically significant differences observed in QTc interval or Sokolow-Lyon index between these groups (Table 2).

ER Pattern

ECGs of 2 patients presenting with an ER pattern are shown in the Figure. In total, ER pattern was observed in 104 (10.8%) subjects. It was significantly more common in victims of SCD than survivors of an acute coronary event (14.4% versus 7.9%; \( P=0.001 \)). Those with an ER pattern had lower prevalence of diagnosed diabetes mellitus (15.8% versus 27.7%; \( P=0.01 \)) and diagnosed coronary artery disease (50.0% versus 61.5%; \( P=0.04 \)) than those without the pattern. Subjects with an ER pattern also had significantly lower heart rate (68 versus 72 beats per minute; \( P=0.02 \)) and higher Sokolow-Lyon index (30 versus 26 mm; \( P<0.001 \)) than those without the pattern.

ER pattern in inferior leads was more common in victims of SCD than survivors (6.7% versus 3.6%; \( P=0.03 \)). Furthermore, a specific ER pattern with horizontal or descending ST segment was associated with SCD (10.2% versus 5.3%; \( P=0.004 \)), whereas ER with ascending ST segment was
not (3.0% versus 2.3%; P=0.46). Also, terminal QRS slurring was more common in SCD victims than survivors (8.1% versus 4.1%; P=0.01). The location and phenotype-specific distributions are shown in Table 2.

In a secondary analysis with a subset of patients without documented coronary artery disease (n=309), the results remained essentially the same because ER was more common in victims of SCD than survivors (16.9% versus 7.2%; P=0.04).

**ER and the Risk of SCD During an Acute Coronary Event**

Table 3 presents the odds ratios (ORs) of SCD during acute coronary event in different variables. Unadjusted predictors of SCD during an acute coronary event were male sex (OR, 2.08; 95% CI, 1.55–2.80), elevated heart rate (OR, 1.90; 95% CI, 1.46–2.47), and ER pattern (OR, 1.85; 95% CI, 1.23–2.80). Specifically, ER pattern with horizontal/descending ST segment predicted the occurrence of SCD (OR, 2.04; 95% CI, 1.25–3.34). After multivariate adjustments, elevated heart rate and ER pattern with horizontal/descending ST segment remained as independent predictors of SCD (Table 3).

**Discussion**

The present study reports a significant and independent association between ECG ER pattern, documented in a random ECG recording before and remote to the event, and risk of SCD at the time of an ischemic event in a general population sample. Before and after multivariate adjustments, ER pattern was associated with a 2-fold risk of SCD during acute coronary event. In addition, victims of SCD had ECG evidence of elevated heart rate. There were also other demographic and clinical differences between the cases and controls, such as higher prevalence of male sex, smoking, and lower prevalence of prior cardiovascular disease among the SCD victims. Association between the SCD and ER was independent of these differences, suggesting a causal relationship between ER and SCD at the time of an ischemic event.

The prevalence of inferolateral ER has varied in previous studies. It was 5.4% in a general sample of Finnish middle-aged subjects and 13.1% in a similar German study. Subsequent studies of 2 random general population samples, Finnish Health 2000 population and the Framingham population,
Early Repolarization During Acute Coronary Events

Table 3. Odds Ratios (ORs) of Sudden Cardiac Death During Acute Coronary Event

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>Unadjusted OR</th>
<th>Adjusted OR*</th>
<th>Multivariate Model 1†</th>
<th>Multivariate Model 2‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: male</td>
<td>687</td>
<td>2.08 (1.55–2.80)</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Prolonged QRS duration</td>
<td>61</td>
<td>1.39 (0.83–2.33)</td>
<td>1.34 (0.79–2.28)</td>
<td>1.59 (0.87–2.91)</td>
<td>1.28 (0.68–2.39)</td>
</tr>
<tr>
<td>Elevated heart rate</td>
<td>377</td>
<td>1.90 (1.46–2.47)</td>
<td>1.89 (1.45–2.46)</td>
<td>1.65 (1.22–2.23)</td>
<td>1.79 (1.17–2.72)</td>
</tr>
<tr>
<td>Prolonged QTc</td>
<td>133</td>
<td>1.36 (0.96–1.95)</td>
<td>1.28 (0.89–1.84)</td>
<td>1.27 (0.84–1.93)</td>
<td>1.17 (0.73–1.89)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>135</td>
<td>1.05 (0.73–1.52)</td>
<td>0.97 (0.67–1.41)</td>
<td>0.94 (0.58–1.51)</td>
<td>1.30 (0.76–2.21)</td>
</tr>
<tr>
<td>ERP</td>
<td>101</td>
<td>1.85 (1.23–2.80)</td>
<td>1.77 (1.15–2.70)</td>
<td>1.73 (1.06–2.83)</td>
<td>2.02 (1.04–3.91)</td>
</tr>
<tr>
<td>ERP+ascending ST segment</td>
<td>25</td>
<td>1.34 (0.61–2.98)</td>
<td>1.03 (0.46–2.32)</td>
<td>1.12 (0.44–2.85)</td>
<td>1.67 (0.50–5.49)</td>
</tr>
<tr>
<td>ERP+horizontal ST segment</td>
<td>72</td>
<td>2.04 (1.25–3.34)</td>
<td>2.13 (1.29–3.52)</td>
<td>2.15 (1.20–3.85)</td>
<td>2.29 (1.16–4.54)</td>
</tr>
</tbody>
</table>

No. indicates equal number of subjects; ERP, early repolarization pattern.

OR presented as OR (95% CI).

1 Prolonged QRS ≥120 ms; elevated heart rate >80 beats per minute; left ventricular hypertrophy Sokolow-Lyon index ≥35 mm; prolonged QTc >450 ms for men and >470 ms for women.

*Adjusted for age and sex.

†Adjusted for age, sex, smoking, prior myocardial infarction, and history of coronary artery disease.

‡Adjusted for age, sex, smoking, body mass index, prior myocardial infarction, history of coronary artery disease, β-blocker, statin, angiotensin II receptor antagonist, and nitroglycerin medication.

showed prevalence values of 3.3% and 6.1%, respectively. There was an evident age dependence of ER in these populations12 so that younger subjects had a higher prevalence of ER, and the prevalence was ≈2% to 3% in the age group of 60 years corresponding to the mean age of the participants in the present study. In the present study, the prevalence was significantly higher in both study groups. This could probably be explained by a higher prevalence of cardiac disease among the subjects in this study population and suggests that structural heart disease itself increases the presence of ER pattern. There has been less information on the prevalence of ER in patients with diagnosed structural heart disease. A previous study in patients with chronic coronary artery disease reported a prevalence of 20% for ER and showed that ER pattern increased the risk of life-threatening ventricular arrhythmias among those patients.15 In the present study, SCD victims had a lower prevalence of previously diagnosed cardiac disease, supporting the concept that ER increases the risk of SCD also among the subjects who have SCD as the first clinical manifestation of cardiac disease.

Although the presence and specific phenotypes of ER pattern are increasingly recognized as a marker of risk for SCD,1–4,6,16,17 the underlying mechanisms are still unclear.18,19 The present data provide 1 plausible mechanistic link, such as the presence of ER as a factor facilitating the occurrence of fatal arrhythmia during an acute ischemic event. This concept is further supported by our previous observational study, showing that arrhythmic death occurred at a relatively high age (>55 years of age) among those who showed the ER pattern in the middle age. In this age group, SCD has been most commonly caused by an acute coronary event in the Finnish population.13 It has also been suggested that in some victims of cardiac death, an inferior ER pattern might result from perifascicular block.20,21 a consequence of healed myocardial infarction. Perifascicular block is not caused by ER but by delayed depolarization of those segments of the myocardium that exhibit inhomogeneous scar tissue and is associated with ventricular arrhythmias and sudden death.22,23 The present data do not support this hypothesis as a predominant mechanism because the history of previous myocardial infarction was in fact lower in those with ER, and the presence of q waves was similar between the groups.

It is evident that individuals with ER pattern may consist of an inhomogeneous group reflecting diverse clinical backgrounds and electrophysiological mechanisms. The ER pattern may indeed be caused by abnormal depolarization caused by underlying subtle structural heart disease in some cases. Accelerated repolarization is likely the cause of the pattern in patients with ER syndrome, as shown in patients with idiopathic ventricular fibrillation and ER pattern without any signs of structural heart disease. The electrophysiological mechanisms of the ER pattern are still under debate. Of some potential interest is the observation of similar ECG morphology of ER and horizontal/downdosing ST segment and the ECG pattern of early ST-segment elevation myocardial infarction. The same cell-level electrophysiological mechanisms could potentially be involved both in the ER ECG pattern and in acute ischemia,24 but further experimental studies will be needed to confirm this hypothesis.

Limitations
We recognize that retrospective case-control study protocol does not definitely confirm the causal relationship between ER pattern and risk of SCD at the time of an acute coronary event because the survival of an acute coronary event is due to several factors other than those reflected in the ECG. Further observational studies will be needed to confirm this concept. In addition, the risk of SCD during ischemia may not be the same in populations that are more diverse than the population in Finland. It should also be addressed that several demographic and clinical differences were observed between the case and control groups as a consequence to lower prevalence of medical admissions in SCD victims. However, the main observations remained essentially the same in our subanalysis in subjects without documented coronary artery disease.

Conclusions and Clinical Implications
ER pattern, observed in resting ECG prior and remote to event, is independently associated with SCD during an acute...
coronary event. This information gives some preliminary information on the question of how the physicians should inform and treat the asymptomatic subjects with the ER pattern and horizontal/downsloping ST segment, that is, J waves without ST elevation, in a randomly obtained ECG. Even more emphasis should perhaps be paid to primary prevention of the first ischemic event of these subjects.

Acknowledgments
This work was performed in the Institute of Clinical Medicine, University of Oulu, Oulu, Finland. The authors acknowledge all the help with data gathering by the Oulu University Hospital staff.

Sources of Funding
This work was supported by the Finnish Foundation for Cardiovascular Research, the Finnish Cultural Foundation, the Finnish Medical Foundation, Aarne Koskelo Foundation, Emil Aaltonen Foundation, Paavo Nurmi Foundation, the Maud Kuistila Finnish Medical Foundation, Aarne Koskelo Foundation, Emil.

Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Electrocardiographic early repolarization (ER) pattern has been previously associated with arrhythmic mortality and with an increased risk of ventricular fibrillation. In the present study, the investigators analyzed ER from 432 consecutive victims of sudden cardiac death because of acute coronary event and 532 survivors of such an event, in whom 12-lead ECGs recorded before and unrelated to the event could be evaluated. ER pattern was found to be independently associated with sudden cardiac death during an acute ischemic coronary event. This novel observation suggests that the presence of ER increases the vulnerability to fatal arrhythmia during acute myocardial ischemia and provides a plausible mechanistic link between this ECG pattern and higher arrhythmic mortality in middle-aged/elderly subjects. It also gives some preliminary information on the question of how physicians should treat asymptomatic individuals with ER; primary prevention of the first ischemic event is crucial.
Association of Early Repolarization and Sudden Cardiac Death During an Acute Coronary Event

Jani T. Tikkanen, Viktor Wichmann, M. Juhani Junntila, Meri Rainio, Eeva Hookana, Olli-Pekka Lappi, Marja-Leena Kortelainen, Olli Anttonen and Heikki V. Huikuri

_Circ Arrhythm Electrophysiol_. 2012;5:714-718; originally published online June 22, 2012; doi: 10.1161/CIRCEP.112.970863

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/5/4/714