Original Article

Effects of Early Repolarization on Electrocardiography and Long-Term Cardiovascular Outcomes: A 15-Year Population-Based Cohort Study

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Abstract

Background: *We aimed to investigate the association between persistent early repolarization (ER) in healthy individuals and long-term cardiovascular events and mortality rates in a large cohort study.*

Methods: *Demographic characteristics, medical records, 12-lead electrocardiograms (ECGs), and laboratory data were retrieved and analyzed from the Isfahan Cohort Study. The participants were followed up biannually via telephone interviews and 1 live structured interview in between until 2017. Individuals who had ER in all their ECGs were considered persistent ER cases. Study outcomes were cardiovascular events (unstable angina, myocardial infarction, stroke, and sudden cardiac death), cardiovascular-related mortality, and all-cause mortality. The independent t test, the χ^2 test, the Mann-Whitney U test, and the Cox regression models were used for statistical analyses.*

Results: *The study population consisted of 2696 subjects (50.5% female). Persistent ER was found in 203 subjects (7.5%), with a higher frequency in men (6.7% vs 0.8%; P<0.001). Cardiovascular events, cardiovascular-related mortality, and all-cause mortality occurred in 478 (17.7%), 101 (3.7%), and 241 (8.9%) individuals, respectively. After controlling for known cardiovascular risk factors, we found an association between ER and cardiovascular events (adjusted hazard ratio [95% confidence interval] =2.36 [1.19–4.68], P=0.014), cardiovascular-related mortality (4.97 [1.95–12.60], P=0.001), and all-cause mortality (2.50 [1.11–5.58], P=0.022) in women. No significant association was found between ER and any study outcomes in men.*

Conclusion: *ER is common in young men with no apparent long-term cardiovascular risks. In women, ER is relatively rare, but it could be associated with long-term cardiovascular risks.*

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Introduction

Early repolarization (ER) is an idiopathic phenomenon characterized by the elevation of the J-point (the junction between the QRS complex and the ST segment) from the baseline in the electrocardiogram (ECG).[1] Wasserburger defined it in 1961 as an elevation of the J-point with a downwardly concave ST segment and a symmetrical T wave, mainly seen in the lateral ECG leads.[2] The definition of ER was further specified by other investigators as an elevation of the J-point by at least 1 mm (0.1 mV) from the baseline in 2 adjacent ECG leads, accompanied by a slurred or notched appearance of the QRS complex. An ST-segment elevation was not necessary for this definition.[3] ER is not rare and may be found in up to 13% of the general population.[4] It is more frequent among young males with high-level physical activities (eg, athletes)[5, 6] and in the black race.[6-8] Although ER has historically been considered a benign phenomenon, some recent studies have found an association between ER and adverse cardiovascular events.[1] Accordingly, the pathophysiology, risk factors, and prognosis of this so-called "innocent finding" are still under investigation.[9,10]

Several studies have found an association between ER and ventricular fibrillation (VF),[3, 5] sudden cardiac death (SCD),[3] cardiac mortality,[11,12] and all-cause mortality.[12] Moreover, ER is associated with increased risks of VF recurrence after defibrillation therapy,[3] fatal VF in patients with coronary artery disease,[13] and mortality in patients with nonischemic cardiomyopathy.[14]

The mechanisms underlying these associations are not clear yet.[5-10] ER seems to be a sign of heterogeneity in the transmural myocardial repolarization.[8-12] It is a key point for the arrhythmogenic potential of ER.[9-16] Consistency between the location of ER and the origin of ectopic activity, initiating VF on the ECG, supports the arrhythmogenic characteristic of ER.[4]

Limited data are available on the association between ER and adverse cardiovascular events. Few population-based longitudinal cohorts have been done in this regard, and the results have been inconsistent in some cases. Therefore, there is still a lack of clinically useful risk-stratifying data. ER can rarely be a primary cause of arrhythmic cardiac disorders, and clinicians may not be concerned when they observe ER in an asymptomatic and otherwise healthy person.[1] Nonetheless, ER may become significant when seen in the context of existing cardiovascular diseases (CVDs) or when accompanied by other cardiovascular risk factors.[4] Given the lack of data, we aimed to investigate the prevalence of ER and its association with long-term cardiovascular outcomes in a large community-based cohort study in the Iranian population.

Methods

The present study is a secondary analysis of the Isfahan Cohort Study (ICS). The ICS is a population-based, ongoing longitudinal study started in 2001 in 3 Iran cities, discussed in detail previously.[15] The inclusion criteria for this study were CVD-free subjects with regular rate-corrected QT intervals at baseline (QTc<460 ms for women and ≤450 ms for men)[16] and subjects who completed the follow-up evaluation assessments in 2007 and 2013. Patients with transient ER, any arrhythmia (including atrial fibrillation), missing data in any of the follow-up evaluations, or the Brugada syndrome in ECG, as well as residents of Arak Province, were excluded from this study. Also excluded were individuals without standard ECGs at baseline and those with considerable missing data. The institutional review board approved the Isfahan University of Medical Sciences' study, and informed consent had already been obtained from subjects in the ICS.

Procedures performed at the baseline examination in the ICS study were described before.[17] Briefly, besides standard 12-lead ECGs at rest, the subjects completed a questionnaire regarding their demographic data and medical history. Additionally, physical and biochemical examinations were done, including measuring blood pressure (systolic and diastolic blood pressures), weight, height, blood glucose, and lipid profile. The presence of diabetes mellitus (DM) and hypertension was evaluated based on the laboratory findings and physical examinations, respectively, or if the participant was under any medication. The presence of dyslipidemia was based on the laboratory findings.

All standard resting 12-lead ECGs were recorded at a paper speed of 50 mm/s and stored for further analyses. All ECGs were retrospectively interpreted for the presence of ER by 2 blinded expert cardiologists of our center. ER was defined by an elevation in the J-point for at least 1 mm (0.1 mV) from the baseline in 2 adjacent inferior or lateral ECG leads, accompanied by a slurred (a smooth transition from QRS to the ST segment) or notched (a positive J deflection inscribed on the S wave) appearance of the QRS complex.[3] The diagnosis of ER was based on unanimous opinions by our cardiologists.

The follow-up procedures of the ICS were described and published before.[17] The participants were followed up biannually via telephone interviews and 1 live structured interview in between until 2017. All baseline assessments

(including ECG, anthropometric variables, blood glucose, and lipid profile) were repeated during the study in 2007 and 2013. Individuals with ER in all their follow-up ECGs were considered persistent ER cases (ER^+), and patients without ER in all their ECGs were assigned to the ER^- group. During the telephone interviews, questions were asked regarding cardiovascular/neurological symptoms, hospitalization, and death. In that case, the following confirmation steps were performed to reach the reported events: checking with the registry database of myocardial infarction (MI) and stroke, investigating original medical/hospital records, and reviewing all relevant documents with 2 separate panels of specialists (cardiologists and neurologists). These panels made the final decision on all the study outcomes, including MI, unstable angina pectoris, stroke, and SCD. Then, cardiovascular-related mortality and all-cause mortality were determined.

The statistical analyses were performed using the IBM SPSS software version 20.0 (Illinois, USA). The data are presented as the mean with the standard deviation (SD) or numbers (percentages). Quantitative (parametric) and qualitative data were compared between the ER^+ and ER^- cases using the independent *t* test and the χ^2 test, respectively. The Mann–Whitney *U* test was conducted to compare nonparametric data. Cox regression models (proportional hazard) were conducted to control demographic characteristics and other cardiovascular risk factors. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported. All the reported P values are 2-sided, with values below 0.05 considered statistically significant.

Results

The sample size consisted of 3035 CVD-free subjects (after the exclusion of the Arak Province participants). Totally, 339 patients were excluded: 90 subjects for the presence of arrhythmia during the study period and 249 for not having a complete survey of all follow-up assessments. Females comprised 50.5% of the remaining patients. They were aged 50.51±11.43 years at the beginning of the study. Persistent ER was found in 203 subjects (7.5%). The persistent ER frequency was significantly higher in men (6.7% vs 0.8%; P<0.001).

The demographic and baseline characteristics and comparisons between the ER^+ and ER^- groups are summarized in Table 1 and Table 2. Compared with ER^- men, ER^+ males were significantly younger (P=0.004), had a significantly lower frequency of hypertension (P=0.037), a lower systolic blood pressure (P=0.003), a diastolic

Table 1. Comparisons of demographic and medical characteristics between men with and without early repolarization*

Study Variables	ER^+ (n=182)	ER^- (n=1152)	P
Age at Baseline (y)	48.91±11.12	51.42±11.81	0.008
Diabetes mellitus (%)	16 (8.8)	112 (9.7)	0.691
FBS (mg/dL)	87.61±41.63	89.24±33.90	0.582
Hypertension (%)	41(22.5)	329 (28.5)	0.037
SBP (mm Hg)	118.64±17.33	123.24±20.23	0.003
DBP (mm Hg)	76.41±10.83	78.61±11.22	0.015
Dyslipidemia (%)	155 (85.2)	990 (85.9)	0.784
Total Cholesterol (mg/dL)	209.81±49.32	212.21±51.20	0.553
LDL (mg/dL)	125.63±41.92	126.04±42.53	0.901
HDL (mg/dL)	46.14±9.53	45.12±10.13	0.222
Triglyceride (mg/dL)	190.81±95.62	205.54±110.81	0.093
Smoking (%)			0.005
Current smoker	95 (52.2)	480 (41.8)	
Former smoker	87 (47.8)	669 (58.2)	
Waist circumference (cm)	91.01±10.22	95.21±10.62	< 0.001
BMI (kg/m^2)	24.72±3.45	26.10±3.87	< 0.001
Normal (19–24.9 kg/m^2)	99 (54.4)	468 (40.6)	
Overweight (25–29.9 kg/m^2)	71 (39.0)	495 (43.1)	< 0.001
Obese (≥30 kg/m^2)	12 (6.6)	189 (16.4)	
Metabolic syndrome (%)	22 (12.1)	301 (26.1)	0.004

*Data are presented as the mean ± the standard deviation (SD) or frequencies (%).
ER, Early repolarization; FBS, Fasting blood sugar; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; LDL-C, Low-density lipoprotein; HDL-C, High-density lipoprotein; BMI, Body mass index

blood pressure (P=0.022), a smaller waist circumference (P<0.001), and a lower body mass index (P<0.001). Altogether, according to Table 1, ER^+ men had metabolic syndrome less frequently than ER^- men (26.1% vs 12.1%; P<0.001). Nevertheless, ER^+ women had a significantly higher frequency of DM (P<0.001), elevated fasting blood glucose (P<0.001), more hypertension (P=0.025), a higher level of triglyceride (P=0.032), and more frequent metabolic syndrome (P=0.003) than ER^- women (Table 2).

During the follow-ups, 241 deaths (8.9%) occurred, 101 (3.7%) of them associated with cardiovascular events: SCD in 53 patients (2%), fatal MI in 21 (0.8%), and fatal stroke in 25 (0.9%). Nonfatal cardiovascular events during these years were unstable angina in 248 patients (9.2%), MI in 65 (2.4%), and stroke in 66 (2.4%). The association between ER and the study endpoints are presented in Table 3. Compared with ER^- women, ER^+ women had a significantly higher frequency of total MI (14.3% vs 2.2%; P<0.001), fatal MI (9.5% vs 0.7%; P<0.001), fatal stroke (9.5% vs 0.7%; P=0.014), SCD (9.5% vs 1.3%; P=0.002),

Table 2. Comparisons of demographic and medical characteristics between women with and without early repolarization*

Study Variables	ER^+ (n=21)	ER^- (n=1341)	P
Age (y)	54.41±13.72	49.92±11.11	0.062
Diabetes mellitus	11 (52.4)	159 (11.8)	< 0.001
FBS (mg/dL)	151.82±77.23	89.12±33.73	< 0.001
Hypertension	12 (57.1)	472 (35.2)	0.034
SBP (mm Hg)	127.81±28.64	123.03±21.61	0.321
DBP (mm Hg)	81.81±18.03	78.63±12.52	0.244
Dyslipidemia	21 (100)	1248 (93.1)	0.213
Total Cholesterol (mg/dL)	235.74±69.41	223.03±52.54	0.437
LDL (mg/dL)	138.43±52.34	134.73±43.04	0.702
HDL (mg/dL)	46.91±8.83	48.93±10.51	0.394
Triglyceride (mg/dL)	252.31±163.44	197.01±105.82	0.019
Smoking			0.851
Current smoker	1 (4.8)	53 (4.0)	
Former smoker	20 (95.2)	1288 (96.0)	
Waist circumference (cm)	100.81±12.40	99.91±11.63	0.720
BMI (kg/m^2)	28.62±5.12	28.31±4.64	0.771
Normal (19–24.9 kg/m^2)	5 (23.8)	311 (23.2)	
Overweight (25–29.9 kg/m^2)	8 (38.1)	573 (42.7)	0.903
Obese (≥30 kg/m^2)	8 (38.1)	457 (34.1)	
Metabolic syndrome	18 (85.7)	730 (54.4)	0.003

*Data are presented as the mean ± the standard deviation (SD) or frequencies (%).
ER, Early repolarization; FBS, Fasting blood sugar; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; LDL-C, Low-density lipoprotein; HDL-C, High-density lipoprotein; BMI, Body mass index

Table 3. Rates of the study endpoints based on early repolarization separated by sex*

Endpoints	Men (n=1334)			Women (n=1362)			Total (n=2696)		
	ER^+ (n=182)	ER^- (n=1152)	P	ER^+ (n=21)	ER^- (n=1341)	P	ER^+ (n=203)	ER^- (n=2493)	P
Unstable angina	10 (5.5)	113 (9.8) †	0.061	2 (9.5)	123 (9.2)	0.962	12 (5.9)	236 (9.5)	0.091
Myocardial infarction	7 (3.8)	46 (4.1)	0.922	3 (14.3)	30 (2.2) ‡	<0.001	10 (4.9)	76 (3.0)	0.140
Fatal	1 (0.5)	9 (0.8)	0.741	2 (9.5)	9 (0.7)†	<0.001	3 (1.5)	18 (0.7)	0.242
Nonfatal	6 (3.3)	37 (3.2)	0.953	1 (4.8)	21 (1.6)	0.293	7 (3.4)	58 (2.3)	0.321
Stroke	6 (3.3)	38 (3.3)	0.994	2 (9.5)	45 (3.3)	0.124	8 (3.9)	83 (3.3)	0.643
Fatal	2 (1.1)	11 (0.9)	0.851	2 (9.5)	10 (0.7) †	0.014	4 (2.1)	21 (0.8)	0.111
Nonfatal	4 (2.2)	27 (2.3)	0.901	0 (0.0)	35 (2.6)	0.451	4 (2.2)	62 (2.5)	0.653
Sudden cardiac death	2 (1.1)	31 (2.7)	0.191	2 (9.5)	18 (1.3) †	0.002	4 (2.2)	49 (2.3)	0.994
Cardiovascular-related mortality	5 (2.7)	51 (4.4)	0.290	6 (28.6)	39 (2.9) §	<0.001	11 (5.4)	90 (3.6)	0.192
All-cause mortality	10 (5.5)	115 (10.1)	0.093	7 (33.3)	109 (8.1) §	<0.001	17 (8.4)	224 (9.1)	0.772

*Data are presented as numbers and frequencies (%).
†P<0.05,
‡P<0.01,
§P<0.001 all with the χ^2 or Fisher exact test
ER, Early repolarization

Table 4. Adjusted models for early repolarization and the study endpoints

	HR	95% CI] †	P	HR	95% CI] ‡	P
Cardiovascular Events						
All	1.06	0.75-1.51	0.731	1.06	0.75-1.50	0.741
Men	0.81	0.54-1.23	0.334	0.82	0.54-1.25	0.364
Women	2.60	1.33-5.08	0.005	2.36	1.19-4.68	0.014
Cardiovascular-related mortality						
All	1.48	0.79-2.77	0.221	1.57	0.84-2.94	0.160
Men	0.73	0.29-1.83	0.502	0.75	0.29-1.90	0.544
Women	7.26	3.04-17.31	<0.001	4.97	1.95-12.6	0.001
All-cause mortality						
All	0.98	0.59-1.60	0.944	0.95	0.58-1.55	0.821
Men	0.66	0.35-1.28	0.223	0.66	0.35-1.28	0.224
Women	3.04	1.41-6.56	0.005	2.50	1.11-5.58	0.021

†Cox's proportional hazards model, adjusted for age.
‡Cox's proportional hazards model, adjusted for age, diabetes, hypertension, dyslipidemia, smoking, and waist circumstance
CI, Confidence interval; HR, Hazard ratio
Cardiovascular events are unstable angina, myocardial infarction, stroke, and sudden cardiac death.

cardiovascular-related mortality (28.6% vs 2.9%; P<0.001), and all-cause mortality (33.3% vs 8.1%; P<0.001). None of this association was observed in men.

The results of the Cox regression model analyses, controlled for possible confounders, are summarized in Table 4. In separate analyses concerning sex, ER was associated with significantly higher cardiovascular events (ie, unstable angina, MI, stroke, and SCD) (adjusted HR=2.36, P=0.014), cardiovascular-related mortality (adjusted HR=4.97, P=0.001), and all-cause mortality (adjusted HR=2.50, P=0.023) in women after adjustments for risk factors (ie, age, DM, hypertension, dyslipidemia, smoking, and waist circumstance). No significant association was found between ER and the study outcomes in men. The Kaplan–Meier survival curve of the study participants until the available endpoint is depicted in Figure 1.

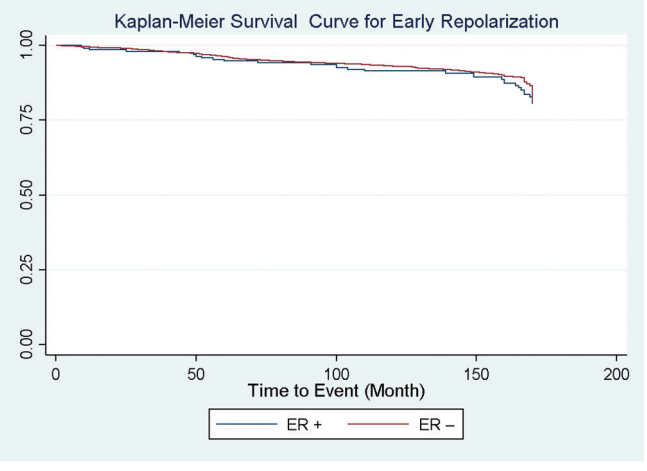

Figure 1. The figure depicts the Kaplan–Meier Survival curve for ER.
ER, Early repolarization

Discussion

The overall prevalence of ER was 7.5% in this 15-year population-based cohort study, and it was mainly found in men (6.7%). Like similar reports, younger males had a higher ER rate.[5, 6, 17-25] The prevalence of ER in the general population varies, ranging from 1%[20] to 13%[18] in previous studies. Differences between studies may be attributed to different definitions of ER and demographic features of the studied population, such as age, sex, and ethnic diversity. Furthermore, some studies have found heritability features of ER,[21,22] which may contribute to the different prevalence of ER in different populations. After 15 years of follow-up, a comparison of the frequency of each outcome between patients with persistent ER and individuals without ER revealed no significant differences. Although we found more ER^+ men, they were not at a higher risk for any cardiovascular event, cardiovascular-related mortality, or all-cause mortality. In contrast, ER^+ females were at a significantly higher risk of MI, fatal MI, SCD, cardiovascular-related mortality, and all-cause mortality, which could be confounded by the small number of patients in this group and higher rates of CVD risk factors in this group.

According to previous studies, ER is associated with fatal arrhythmias[13] and mortality[14] in patients with CVDs. However, the long-term prognosis of ER and its clinical importance in the general population without established CVDs are unclear.

The ER^+ French population was associated with cardiovascular mortality and all-cause mortality.[18] The ER^+ German population, especially the younger group, was at a higher risk of cardiac and all-cause mortality after nearly 20 years.[12] In contrast, in a sample of the adult general population in the United States (44% male), Klatsky et al[20] found a very low prevalence of ER (0.9%) and no increased risk for cardiovascular events or mortality in those with

ER.[20] Olson et al[19] suggested that ER was marginally associated with SCD (adjusted HR [95% CI] =1.31 [0.94–1.82]) after a mean follow-up of 13 years. Still this study found an interaction between ER and race/sex, which means whites and women had a higher risk of SCD when ER was present. Moreover, ER$^+$ women had a higher risk of coronary heart disease. Putting together, ER significantly increased the risk of SCD in white females (adjusted HR [95% CI] = 8.77 [3.19–24.13]).[19] Such sex effects were also found by Shulman et al[24] in a cohort study on the Hispanic population.

In the current 15-year population-based cohort study, we found an association between ER and cardiovascular events, cardiovascular-related mortality, and all-cause mortality in women but not in men. The mechanism of such possible sex effects is not clear. There may be a role for hormonal effects and other accompanying differences between sexes in cardiac electrophysiology.[26] Nonetheless, our results must be interpreted cautiously considering the small number of ER$^+$ women and the higher prevalence of DM, hypertension, and dyslipidemia in women than in men, even though these factors were controlled in the analyses. Besides demographic and established CVDs-related risk factors, the ER pattern is another debatable aspect. Some specific patterns of ER may have a higher risk of cardiovascular events and mortality.[11,12, 18, 23, 27, 28] Differences between studies regarding the long-term prognosis of ER in the general population may be due to different demographic characteristics of the studied population (eg, age, sex, and physical activity), various methods for the definition and observation of ER, its pattern, and the contribution of other cardiovascular risk factors, which can modulate the association between ER and cardiovascular outcomes.

Although our study is among the few large population-based cohorts evaluating the long-term prognosis of ER, it has some limitations. The sample size was not large enough for precise age-stratified analyses and for analyzing the interaction among age/sex and other CVD-related risk factors and the presence of ER in association with the study outcomes. Indeed, our findings are limited by the small number of ER$^+$ women and only a few cardiovascular events in this group. Furthermore, we did not perform Holter monitoring to detect arrhythmias like atrial fibrillation, and we based clinical judgments on follow-up ECGs.

Conclusion

In summary, the prevalence of ER in Iran's general population without overt CVDs is 7.5%, with a higher frequency among young men. We found no apparent association between ER and cardiovascular events, cardiovascular-related mortality, and all-cause mortality in men. However, after adjusting for known cardiovascular risk factors, we found an association between the presence of ER and cardiovascular events, cardiovascular-related mortality, and all-cause mortality only in women.

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