

Six-Year Outcome of Subjects Without Overt Heart Disease With an Early Repolarization/J Wave Electrocardiographic Pattern



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“Early repolarization” (ER) is a frequent finding at standard electrocardiogram (ECG). In this study we assessed whether ER is associated with an increased risk of events, as recently suggested by some studies. We prospectively enrolled 4,176 consecutive subjects without any heart disease who underwent routine ECG recording. ER was diagnosed in case of typical concave ST-segment elevation ≥ 0.1 mV; a J wave was diagnosed when the QRS showed a notch or a slur in its terminal part. In this study we compared the 6-year outcome of all 687 subjects with ER/J wave and 687 matched subjects without ER/J wave (controls). Both groups included 335 males and 352 females, and age was 48.8 ± 18 years. Overall, 145 deaths occurred (11%), only 11 of which attributed to cardiac causes. No sudden death was reported. Cardiac deaths occurred in 5 (0.8%) and 6 (0.9%) ER/J wave subjects and controls, respectively (odds ratio [OR] 0.85, 95% confidence interval [CI] 0.26 to 2.80, $p = 0.79$). Both ER (OR 1.68, 95% CI 0.21 to 13.3, $p = 0.62$) and J wave (OR 0.91, 95% CI 0.28 to 3.00, $p = 0.88$) showed no association with cardiac death. Total mortality was 11.5% in the ER/J wave group and 10.6% in the control group (OR 1.10, 95% CI 0.78 to 1.56, $p = 0.58$). Both ER (OR 0.44, 95% CI 0.16 to 1.24, $p = 0.12$) and J wave (OR 1.20, 95% CI 0.85 to 1.70, $p = 0.30$) showed also no association with all-cause death. In subjects without any evidence of heart disease, we found no significant association of ER/J wave with the risk of cardiac, as well as all-cause, death at medium-term follow-up. © 2017 Elsevier Inc. All rights reserved. (Am J Cardiol 2017;120:2073–2077)

The pattern of “early repolarization” (ER) at the electrocardiogram (ECG) has long been considered a benign finding.^{1–4} Recent studies, however, reported that ER portends an increased risk of sudden death,^{5–11} as well as cardiovascular and total mortality,^{9,12–15} raising clinical and medicolegal concerns among cardiologists.^{16,17} Subsequent data, in fact, suggested that the increased risk might be related to prominent J waves rather than the ST-segment elevation typical of ER,¹⁸ but other studies failed to detect any increased risk associated with ER/J wave.^{19–24} Previous studies, however, were not designed to prospectively investigate the prognostic role of ER/J wave, and the definition of ER, J point, and J wave also varied. In 2010, we started a fully prospective study, specifically designed to assess the clinical implication of ER/J wave pattern in subjects without any evidence of cardiac disease.²⁵ In this study, we report the 6-year follow-up of subjects with the ER/J wave pattern compared with that of a matched subgroup of subjects without ER/J wave pattern enrolled in the study.

Methods

Between January and July 2010, we prospectively collected all ECGs performed at the Cardiology Outpatient Service and at the Center for prehospital evaluation of patients programmed to undergo elective noncardiac surgery of our University Hospital (Policlinico A. Gemelli, Rome, Italy) to assess prevalence and predictors of ER/J wave, and start prospective follow-up of patients. The design of the study, the clinical characteristics of subjects, and the methods of ECG analysis have been described in detail elsewhere.²⁵

Consecutive subjects who had no evidence of heart disease, according to clinical history, ECG tracing and, when required, noninvasive diagnostic investigation (mainly, echocardiography and exercise stress test) were enrolled in the study. Subjects were excluded in case of a cardiac rhythm other than sinus, intraventricular conduction disturbances, presence of a pacemaker, or any other ECG finding that could interfere with an accurate assessment of the ER/J wave pattern.

A physician collected detailed information about the clinical history of each subject with the aid of a standardized questionnaire. Data acquired included age, gender, cardiovascular risk factors, symptoms suggestive of arrhythmias, reason for ECG recording, and drug therapy. Hypertension was defined as blood pressure $\geq 140/90$ mmHg or use of antihypertensive drugs; hypercholesterolemia was defined as blood cholesterol levels >200 mg/dL or use of anticholesterolemic drugs; diabetes was defined as fasting

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glucose blood levels of ≥ 126 mg/dL or use of antidiabetic drugs; smoking was defined as any usual cigarette smoking; obesity was defined as a body mass index ≥ 30 kg/m².

All subjects gave written informed consent to participate in the study, which was approved by our Institutional Review Board.

As there were significant differences in age and gender between subjects with and without ER/J wave in our whole population,²⁵ we designed the present study as an age- and gender-matched case-control study, to try to minimize biases related to these 2 major clinical variables.

Overall, a total of 4,176 subjects were recruited for the study. In the present study we compared 6-year clinical outcome of all 687 subjects who were classified to have ER/J wave (16.5%) with that of 687 subjects who were classified not to have ER/J wave at enrollment (control group). Control subjects were strictly matched for age and gender to ER/J wave subjects in a 1:1 ratio.

The methods of ECG analysis and diagnosis of ER and J wave have previously been described in detail.²⁵ Shortly, the ECGs were independently analyzed by 2 expert cardiologists, who were unaware of the clinical history of the subjects, and any discordance was solved with the supervision of a third expert electrocardiologist.

ER was specifically defined as the presence at the ECG of typical concave ST-segment elevation of 0.1 mV or higher in at least 2 contiguous inferior (DII-DIII-aVF), limb lateral (DI-aVL), and/or left precordial (V₄-V₆) leads. A “J wave” was diagnosed when the terminal part of the QRS, which, by definition, preceded the reference J point (identified as the point in which a clear linear ST segment started), showed a notch (notched QRS) or a widening (slurred QRS) in at least 2 contiguous leads. Specifically, a notched J wave was defined as a positive wave inscribed in the descending limb of the QRS with amplitude ≥ 0.1 mV with respect to the isoelectric line, whereas a slurred J wave was diagnosed when the widened terminal part of the QRS was ≥ 20 ms in duration and ≥ 0.1 mV in amplitude with respect to the isoelectric line. Intraobserver and interobserver agreement was excellent for diagnosis of both ER (Cohen κ 0.94 and 0.83, respectively) and J wave (Cohen κ 0.97 and 0.88, respectively).²⁵

The clinical state of subjects was assessed, whenever possible, by a structured telephone interview conducted by a physician. Clinical information was obtained directly from the subject or, in case of death, from relatives. The vital state of patients who could not be contacted by telephone was ascertained by consulting the website of the Health System of the Regione Lazio, Italy. For deceased subjects, the cause of death was ascertained by directly acquiring clinical information from patients' relatives or by obtaining the International Classification of Diseases codes reported in the death certificates.

Our primary aim was to assess the relation of ER/J wave with cardiac death (i.e., death caused by any acute or chronic heart disease) and sudden death (i.e., unexpected death occurring within 1 hour of any symptom onset or unwitnessed death), but the relation of ER/J wave with total mortality was also investigated.

A raw comparison with the most recent mortality data of the Italian population (year 2012), as available in the website

of the Italian Institute of Statistics (www.istat.it), was also performed.

Continuous and discrete variables were compared by Student's *t* test and Fisher's exact test, respectively. The association of individual variables with the 6-year end points was assessed by logistic regression. Multivariable logistic regression was applied both to adjust the relation of ER/J wave with end points for between-group significant or borderline ($p \leq 0.1$) variables and to identify variables independently associated with clinical outcome. To the latter aim, only variables with a *p* value ≤ 0.1 at univariate analysis were included in the multivariable model. *z*-Values of normal distribution were calculated to make a raw comparison of total and cardiac mortality observed in our population with that of the general Italian population. Results are expressed as mean $\pm$ SD or numbers and proportions. A *p* value < 0.05 was considered to be statistically significant. Data were analyzed with the statistical software package SPSS 21.0 (SPSS Italia, Inc., Florence, Italy).

Results

The clinical data of the 2 groups are summarized in Table 1. According to selection criteria, the 2 groups both included 335 males and 352 females with a mean age of 49 ± 18 years. There were no significant differences between the 2 groups for most variables. Controls, however, had a slightly higher body mass index and heart rate, and a higher frequency of a familial history of cardiovascular disease. Of 687 subjects with ER/J wave, 24 (3%) had ER only, 603 (88%) had J wave only, and 60 (9%) had both.

Follow-up was complete as to the vital state for 95% and 96% of ER/J wave and controls, respectively ($p = 0.15$). Overall, 145 deaths were recorded (11%). Most deaths were caused by neoplastic diseases (100 subjects, or 7.6%), whereas only 11 deaths (0.85% of the total population) could be at-

Table 1
Main clinical characteristics of the two groups of subjects

Variable	ER/J wave (n = 687)	Controls (n = 687)	p
Age (years)	48.8 $\pm$ 18	48.8 $\pm$ 18	1.00
Male/Female	335/352	335/352	1.00
Body mass index (Kg/m ²)	25.4 $\pm$ 4	26.0 $\pm$ 5	0.008
Heart rate (bpm)	70.0 $\pm$ 13	74.0 $\pm$ 13	0.001
Diabetes mellitus	74 (11%)	80 (12%)	0.67
Hypertension	193 (28%)	222 (32%)	0.10
Smoker	173 (25%)	146 (21%)	0.10
Family history of CVD	210 (31%)	256 (37%)	0.010
Family history of sudden death	5 (0.7%)	1 (0.1%)	0.22
Hypercholesterolemia*	156 (23%)	152 (22%)	0.85
Therapy			
Beta-blockers	65 (9.5%)	69 (10%)	0.72
Calcium-antagonists	28 (4.1%)	34 (5.0%)	0.44
ACE inhibitors/ARBs	130 (19%)	139 (20%)	0.54
Statins	61 (8.9%)	59 (8.6%)	0.92
Antiaggregants	67 (10%)	69 (10%)	0.86
Diuretics	65 (9.5%)	60 (8.8%)	0.71
Antiarrhythmics	13 (1.9%)	13 (1.9%)	1.00

ACE = inhibitors of angiotensin converting enzyme; ARBs = angiotensin receptor blockers; CVD = cardiovascular disease.

* Blood cholesterol levels > 200 mg/dL or use of anti-cholesterolemic drugs.

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