Early repolarization and short QT interval in healthy subjects

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BACKGROUND An early repolarization (ER) pattern is common in ECGs from patients with ventricular fibrillation (VF). These patients with ER have shorter QT intervals. Morphological variants of the ER pattern also have been associated with idiopathic VF, but their prevalence in healthy subjects is unclear.

OBJECTIVE The purpose of this study was to study the prevalence of ER and its morphological variants, and its association with the QTc interval in healthy subjects.

METHODS Digital ECGs from 1886 healthy subjects from Phase I clinical trials were analyzed by a central ECG laboratory.

RESULTS ER, defined as J-point elevation ≥0.1 mV in ≥2 contiguous leads, was present in 514 subjects (27.3%), of whom 505 (98.2%) were males. The prevalence of ER declined progressively with increasing age. ER pattern was seen in lateral leads (I, aVL, V_4–V_6) in 26.1%, in inferior (II, III, aVF) or inferolateral leads in 8%, and was global in 1.9%. The terminal portion of the QRS complex was notched in 43.1% and slurred in 56.9%. Notching was common in inferior/lateral leads, and slurring was common in anterior leads. A non-ascending ST segment was seen in 71% of ECGs with a notched pattern but in only 12.3% of ECGs with a slurred pattern. The ER group had slower heart rates (9.3 ± 13.3 bpm [mean difference ± SD], $P < .001$) and shorter QTc intervals (QTcB = 20.2 ± 25.6 ms, QTcF = 11.0 ± 21.9 ms; $P < .001$). Four subjects in each group had a short QT interval (QTcF <350 ms).

CONCLUSION ER and all of its variants are common in healthy young males with slower heart rates and slightly shorter QTc intervals. A short QT interval (QTcF <350 ms) is rare.

KEYWORDS Arrhythmia; Cardiac repolarization; Early repolarization; Electrocardiography; Short QT interval; Sudden cardiac death

ABBREVIATIONS **ER** = early repolarization; **VF** = ventricular fibrillation

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Introduction

Early repolarization (ER) is a widely recognized ECG pattern characterized by J-point elevation in the ST segment, usually in the inferior or lateral leads of a 12-lead ECG.[1] Until recently, it was generally regarded as a normal variant[2] of limited clinical significance that could be mistaken for conditions such as acute myocardial infarction, pericarditis, or intraventricular conduction defects.[3] Recent studies have now identified a possible link between ER and the risk of malignant ventricular arrhythmias.[4–7] Haïssaguerre et al[5] found ER in 31% of survivors of idiopathic ventricular fibrillation (VF) compared to 5% of healthy controls. Tikkanen et al[6] prospectively studied a cohort of middle-aged Finnish individuals and observed higher mortality from cardiac causes in subjects with ER at baseline. The ER pattern probably results from transmural repolarization heterogeneity from endocardium to epicardium resulting from a longer duration of action potentials in subendocardial cells than in subepicardial cells,[3,4] which in turn could predispose to cardiac arrhythmias. More recently, subtypes of the ER pattern have been described based on leads showing ER, morphology of the terminal part of QRS complex (notching or slurring), and shape of the ST segment (horizontal/downsloping and ascending/concave) in an attempt to differentiate between malignant and benign variants of ER.[8,9]

Interestingly, the studies by Tikkanen et al[6] and Haïssaguerre et al[5] found that the QTc interval was shorter in patients with ER. In 2004, Viskin et al[10] reported that the QTc interval is shorter in survivors of idiopathic VF than in healthy controls. However, the extent of QT shortening in these studies was small, and whether shorter QT interval itself contributes to the development of ventricular arrhythmias in individuals with ER is being debated.[2,11–13] Watanabe et al[14] studied patients with short QT syndrome and found ER in 65% of patients with ventricular arrhythmias compared to 10% of healthy controls. However, Gross[13] suggested that the shorter mean QTc interval found in some of the ER cohort studies[5,6] may have resulted from the inclusion of a few unrecognized patients with familial short QT syndrome.[10] Although several studies have reported on the prevalence of ER in the healthy population, most of

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those studies preceded the reports that drew attention to this association. Because the prevalence of ER and its various morphological patterns and their association with the length of the QTc interval in healthy subjects are not clear, we studied ECGs from volunteers participating in Phase I clinical trials who had been screened to exclude comorbid conditions.

Methods

Subjects

We retrospectively studied ECGs from 1886 healthy subjects (1433 males and 453 females, age 18–92 years) participating in 41 Phase I clinical trials for which Quintiles Cardiac Safety Services was the central ECG laboratory. For each subject, a single drug-free ECG that served as a baseline for the trial was included in the present study. All ECGs were recorded using digital ECGs (ELI 250, Mortara Inc, Milwaukee, WI) with 1000-Hz sampling rate, 25 mm/s speed, and 10 mm/mV amplitude.

All subjects were screened by history, physical examination, and laboratory tests for abnormalities. Tests included hemoglobin; total, differential leukocyte, and platelet counts; and urine examination. Blood chemistry included serum bilirubin, transaminases, alkaline phosphatase, sodium, potassium, chloride, calcium, bicarbonate, blood urea nitrogen, creatinine, albumin, and glucose. Appropriate tests for viral hepatitis (hepatitis A, B, and C) and HIV were performed.

Subjects with a history of clinically significant cardiac disease were excluded from the study. Only normotensive subjects with resting blood pressure $\geq$90 mm Hg and $\leq$140 mm Hg systolic and $\geq$60 mm Hg and $\leq$90 mm Hg diastolic and normal resting heart rate ($\geq$50 bpm and $\leq$100 bpm) on screening were included. ECGs with bundle branch block or intraventricular conduction defects were excluded because of the difficulty in reliably identifying J-point elevation in these ECGs.

Female subjects were included only if they were not pregnant or lactating. Individuals with body mass index $<$18 or $>$30 kg/m^2, clinically significant abnormality at the screening medical assessment, history of drug/alcohol abuse, or use of tobacco/nicotine products in the 6-month period preceding the screening visit were excluded. All studies were approved by the respective institutional review boards, and all subjects consented to participate in the studies.

ECG analysis

All ECGs were analyzed manually by trained readers in a central ECG laboratory using onscreen analysis software (CalECG version 2.7, AMPS_LLC, New York, NY). ER was defined as J-point elevation $\geq$0.1 mV, visually determined onscreen using mouse-driven digital calipers, present in at least 2 contiguous leads.[5,15,16] ECGs with ER were further classified based on leads showing ER pattern: inferior (II, III, aVF), lateral (I, aVL, V_4–V_6), and anterior (V_1–V_3) leads, or global (anterior, lateral, and inferior leads).[12] ER was further classified as notched if there was a definite notch followed by a small rounded positive deflection at the junction of the QRS complex and the ST segment, or slurred if the transition occurred gradually without a notch[5] (Figure 1). ER pattern was also classified based on the shape of the ST segment as concave/rapidly ascending (defined as $>$0.1 mV elevation of the ST segment within 100 ms after the J point or persistent elevation $>$0.1 mV throughout) or horizontal/descending (defined as $\leq$0.1 mV elevation of the ST segment within 100 ms after the J point).[8,9]

QT interval was measured between QRS onset and the point where the T wave met the isoelectric baseline in 5 consecutive complexes in lead II. If the amplitude of the T wave in lead II was $<$1 mV, then QT interval was measured in lead V_5. R-R intervals were measured between the complex in which QT was measured and the preceding complex. QT interval was corrected for the effect of heart rate using the Bazett formula ($QTcB = QT/\sqrt{RR}$) and the Fridericia formula ($QTcF = QT/\sqrt[3]{RR}$). In the absence of a universal definition for a short QTc interval, 3 cutoff values (330,[14] 340,[17] and 350[18] ms) from previous studies were used. Long QTc interval was defined as QTc $>$450 ms.[19]

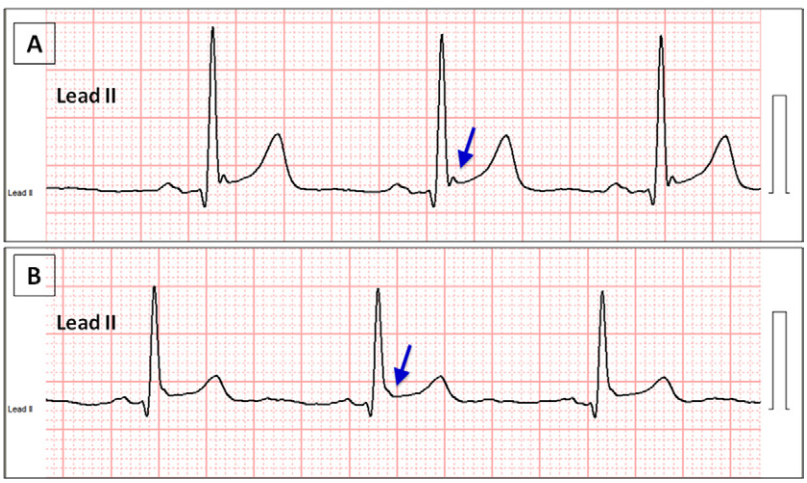

Figure 1 Single lead from ECGs from different healthy individuals showing notched **(A)** and slurred **(B)** patterns of the terminal portion of the QRS complex *(arrows)*. The shape of the ST segment is ascending (defined as $>$0.1 mV elevation of ST segment within 100 ms after the J point) in A and is non-ascending (defined as $\leq$0.1 mV elevation of the ST segment within 100 ms after the J point) in B.