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The Electrophysiological Substrate of Early Repolarization Syndrome

Noninvasive Mapping in Patients

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ABSTRACT

OBJECTIVES This study sought to map the epicardial electrophysiological (EP) substrate in early repolarization (ER) syndrome patients using noninvasive electrocardiographic imaging (ECGI), and to characterize substrate properties that support arrhythmogenicity.

BACKGROUND The ER pattern is a common ECG finding. Recent studies established a definitive clinical association between ER and fatal ventricular arrhythmias. However, the arrhythmogenic substrate of ER in the intact human heart has not been characterized.

METHODS Twenty-nine ER syndrome patients were enrolled, 17 of whom had a malignant syndrome. Characteristics of the abnormal EP substrate were analyzed using data recorded during sinus rhythm. The EP mapping data were analyzed for electrogram morphology, conduction, and repolarization. Seven normal subjects provided control data.

RESULTS The abnormal EP substrate in ER syndrome patients has the following properties: 1) abnormal epicardial electrograms characterized by presence of J waves in localized regions; 2) absence of conduction abnormalities, including delayed activation, conduction block, or fractionated electrograms; and 3) marked abbreviation of ventricular repolarization in areas with J waves. The action potential duration (APD) was significantly shorter than normal (196 ± 19 ms vs. 235 ± 21 ms; $p < 0.05$). Shortening of APD occurred heterogeneously, leading to steep repolarization gradients compared with normal controls (45 ± 17 ms/cm vs. 7 ± 5 ms/cm; $p < 0.05$). Premature ventricular contractions (PVCs) were recorded in 2 patients. The PVC sites of origin were closely related to the abnormal EP substrate with J waves and steep repolarization gradients.

CONCLUSIONS ER is associated with steep repolarization gradients caused by localized shortening of APD. Results suggest association of PVC initiation sites with areas of repolarization abnormalities. Conduction abnormalities were not observed. (J Am Coll Cardiol EP 2017;■:■–■) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AD = activation duration

AP = action potential

APD = action potential duration

ARI = activation-recovery interval

AT = activation time

BrS = Brugada syndrome

ECG = electrocardiogram

ECGI = electrocardiographic imaging

EGM = electrogram

EP = electrophysiological

ER = early repolarization

ERS = early repolarization syndrome

LV = left ventricle/ventricular

PVC = premature ventricular contraction

RT = recovery time

RV = right ventricle/ventricular

SR = sinus rhythm

VF = ventricular fibrillation

The early repolarization (ER) pattern on the electrocardiogram (ECG) is characterized by a J-wave ≥0.1 mV in inferior and/or lateral leads (1). It resolves during exercise and fast pacing, but accentuates during bradycardia. The prevalence of the ER pattern in the general population is estimated to range between 1% and 13% (2,3). It is thought to be more common in males, young athletes, and people of African descent.

For decades, the ER pattern was considered a benign ECG manifestation. Since the 1980s, this view has been challenged on the basis of sporadic observations that linked the J-wave with ventricular arrhythmia (4–6). In a recent study with a large cohort of patients, the prevalence of the ER pattern was significantly higher in patients with idiopathic ventricular fibrillation (VF) compared with control subjects (1). This was the first study that provided clinical evidence supporting a definitive association between the ER pattern and an increased risk of ventricular arrhythmia. Following this study, additional population-based studies provided corroborating evidence (2,7–9). The critical role of the ER pattern in initiating VF has been supported by observations of a consistent and marked J-wave accentuation preceding the onset of arrhythmia (1,10) and by electrophysiological (EP) mapping data that suggested an association between the origin of ectopy that initiated VF and the location of repolarization abnormalities (1). Meta-analysis on 16 studies involving 334,524 subjects suggests that the ER pattern is associated with an increased risk for sudden cardiac arrest, cardiac death, and death from any cause (11).

Studies in patients with ER syndrome (ERS) have been so far confined to investigation of the body-surface ECG characteristics and extrapolating possible mechanisms. However, ECG characteristics have been shown to be inadequate measures of underlying repolarization properties (12). Reports of invasive catheter mapping in patients with ERS provide limited information about the abnormal EP substrate (1,13). Understanding the mechanism of ER and how it may predispose patients to an increased risk of arrhythmias requires detailed characterization of the EP substrate in the intact heart of ERS patients. Similarly, risk stratification for arrhythmia and differential diagnosis between benign and malignant ERS require noninvasive mapping of the EP substrate in individual subjects. Recent developments in noninvasive electrocardiographic imaging (ECGI) (12,14–21) have demonstrated its ability to obtain high-resolution panoramic EP data of epicardial activation and repolarization, and their alteration by disease and interventions in humans (17–21). In the current study, we characterize the epicardial EP substrate in ERS patients on the basis of high-resolution ECGI data obtained during sinus rhythm (SR), in an effort to provide insights into the substrate properties that support arrhythmogenicity in these patients.

METHODS

PATIENT POPULATION. ERS patients from Washington University and Bordeaux University Hospital were enrolled. The clinical diagnosis is ER pattern on the ECG, defined as an elevation of the J-point (J-wave) ≥0.1 mV in at least 2 contiguous leads. The J-wave is manifested either as QRS slurring or notching in the inferior lead, lateral lead, or both. The patients should have at least 1 of the following: idiopathic VF, unexplained syncope, or familial incidence of unexplained sudden cardiac death. Patients with structural heart disease, coronary artery disease, or other conditions, including long QT syndrome, short QT syndrome, and Brugada syndrome (BrS) were excluded. All patients had structurally normal hearts and normal ventricular function. Data from 7 healthy subjects provided normal controls (14). These were healthy adults, ranging in age from 21 to 43 years. All control subjects had normal 12-lead ECGs and no known history of heart disease. Protocols were approved by the institutional review boards at both centers; written informed consent was obtained from all patients.

NONINVASIVE MAPPING. During ECGI, body-surface ECG potentials were acquired simultaneously from 256 electrodes using a multichannel data acquisition system (Biosemi, Amsterdam, the Netherlands). Next, the patient underwent thoracic computed tomography with ECG gating to obtain the epicardial geometry and torso electrode positions. Body surface potentials were baseline corrected and bandpass filtered (0.05 to 400 Hz) to remove high-frequency noise and DC component. If necessary, a 60-Hz notch filter was applied to remove power-induced noise. The pre-processed signals and the patient-specific heart-torso geometry were processed with ECGI algorithms to reconstruct epicardial potentials, unipolar electrograms (EGMs), and maps of epicardial activation and repolarization. ECGI has been validated extensively in torso-tank and canine experiments, and in human studies. It provides high-