

EARLY REPOLARIZATION SYNDROMES

Definition

Early repolarization pattern is defined electrocardiographically by (1) an end QRS notch (J wave) or slur on the downslope of a prominent R wave with and without ST-segment elevation; (2) the peak of the notch or J wave (J_p) ≥ 0.1 mV in ≥ 2 contiguous leads of the 12-lead ECG, excluding leads V1–V3; and (3) QRS duration (measured in leads in which a notch or slur is absent) < 120 ms (Figure 1).¹⁻³ **Early repolarization syndromes** (ERS) refer to sudden cardiac death or documented VT/VF in individuals with an early repolarization pattern. The term **J-wave syndromes** usually denotes inherited conditions such as the ERS and the Brugada syndrome, that are due to mutations affecting calcium, potassium, and sodium channels (Table 1 of Chapter 57) and may contribute to overlap syndromes.^{1,4,5} The **J-wave deflection** occurring at the QRS-ST junction (also known as Osborn wave) was first described in 1953, and is seen in many conditions such as acute ischemia (especially in true posterior myocardial infarction), hypothermia, hypercalcemia, brain injury, acidosis, and early repolarization syndromes.⁶

Genetics and Pathophysiology

An increase in net repolarizing current, due to either a decrease of inward Na^+ or Ca^{2+} currents (I_{Na} , and $I_{\text{Ca,L}}$), or augmentation of outward currents, such as I_{to} , $I_{\text{K-ATP}}$, and $I_{\text{K-ACh}}$, lead to augmentation of the J wave or the appearance of ST-segment elevation that is more prominent during slow heart rates.¹⁻³ Physiological heterogeneity of electrical properties and transmural gradients in ion channel distribution in the endocardial, midmyocardial (M cells), and epicardial layers result in regional differences in electrophysiological properties. Ventricular epicardial (particularly RV) and M cells, but not endocardial action potentials, display a prominent phase 1 due to a large transient outward potassium current (I_{to}) giving rise to the typical spike-and dome or notched configuration of the action potential and inscription of the J wave in the ECG. The degree of accentuation of action potential notch leading to loss of the dome depends on the magnitude of I_{to} . When I_{to} is prominent, as it is in the right ventricular epicardium, an outward shift of current causes phase 1 of the action potential to progress to more negative potentials at which the L-type calcium current ($I_{\text{Ca,L}}$) fails to activate, leading to all-or-none repolarization and loss of the dome. Loss of the action potential dome usually is heterogeneous, resulting in marked abbreviation of the action potential at some sites but not at others. The dome then can propagate from regions where it is maintained to regions where it is lost, giving rise to local transmural reentry and closely

coupled extrasystoles (phase 2 reentry). When the extrasystole occurs on the preceding T wave results in an R-n-T phenomenon that initiates polymorphic VT or VF.¹

Overlap with other syndromes may be seen. Mutations in the SCN10A gene may produce patterns of Brugada, early repolarization and conduction disease,⁴ and a high prevalence of early repolarization in short QT syndrome has also been reported.⁷ It has been proposed that Brugada syndrome, ERS, and idiopathic VF may form part of a spectrum of subtle subepicardial cardiomyopathy. Impaired sodium current, along with genetic and environmental susceptibility, may precipitate a reduction in epicardial conduction reserve, facilitating current-to-load mismatch at sites of structural discontinuity, giving rise to electrocardiographic changes and the arrhythmogenic substrate.⁸

Clinical Significance

The early repolarization pattern has long been considered to be a benign ECG manifestation (1-18% in the general population), that is seen more commonly in young healthy men and athletes (up to 40%), and its clinical significance has been questioned.⁹ In a report on professional athletes, a correlation between J point elevation and interventricular septum thickness was observed, thus suggesting a possible mechanistic role of exercise induced left ventricular hypertrophy as the basis for J point elevation, and no cardiac death was observed in a median of 13 years follow-up.¹⁰ Many healthy athletes have early repolarization with a rapidly ascending pattern. Inferolateral ESR pattern is seen in 25-35% of competitive athletes, and inferior only in 4% and is considered a dynamic phenomenon related to physical activity.¹⁰⁻¹² In the CARDIA study, the presence of early repolarization in young adults was not associated with higher risk of death during long-term follow-up.¹³ The possibility that false tendons, ie discrete, fibromuscular structures that transverses the LV cavity, are related to the genesis of J waves has also been raised.¹⁴

However, there has been evidence suggesting that the early repolarization pattern may be associated with a risk for VF, depending on the location of early repolarization, magnitude of the J wave, and degree of ST elevation.¹⁵⁻¹⁷ In a large study on a community-based general population of 10,864 middle-aged subjects, an early-repolarization pattern with J-point elevation of at least 0.1 mV in the inferior leads of a resting ECG was associated with an increased risk of death from cardiac causes.¹⁸ In addition, among patients with a history of idiopathic ventricular fibrillation, an increased prevalence of early repolarization, (up to 23%), defined as an elevation of the QRS-ST junction of at least 0.1 mV from baseline in the inferior or lateral lead, manifested as QRS slurring or notching, has been detected.^{15,19} A higher prevalence of J wave and/or QRS slurring (but not of ST elevation) has been found among athletes with cardiac arrest/sudden death than in controls.²⁰ A horizontal/descending

type (defined as ≤ 0.1 mV elevation of the ST segment within 100 ms after the J point) in the inferior leads, as opposed to a rapidly ascending ST segment type, may help to identify those individuals who are clearly at risk (Figures 1, and 2).^{21,22} Coexistence of an anterior early repolarization pattern (ie in leads V1-V3),²³ and early repolarization in the inferior leads, especially in cases without other QRS complex abnormalities, predict the occurrence of VT/VF.²⁴ The presence of low amplitude T waves, and a lower T/R ratio (T wave amplitude $\leq 10\%$ of the R wave amplitude) in lead II or V5, have also been reported as signs of malignant ERS.²⁵ In patients with a history of VF and inferolateral early repolarization, VF most commonly recurs when right precordial leads at high intercostal spaces display a Brugada pattern.²⁶ It has been estimated that the finding of early repolarization pattern in a young adult would increase the probability of idiopathic VF from 3.4 in 100 000 to 11 in 100 000.²⁷

Still, several obscure points remain with this syndrome. An early repolarization pattern in the inferolateral leads occurs in 5% of apparently healthy individuals,^{18,19} it may not be consistently seen, and even the horizontal/descending ST type was seen in 3% of controls.^{21,22} In the ARIC study, J-point elevation was associated with an increased risk of SCD in whites and in females, but not in blacks or males.²⁸ Finally, a large genome-wide association study has been unable to identify genetic variants associated with the pattern, possibly reflecting the phenotypic heterogeneity that exists among these individuals.²⁹ It seems, therefore, that the majority of individuals with ER and no family history of sudden cardiac death are at no or minimal risk for arrhythmic events.^{16 27}

Of note, a narrow QRS < 80 – 85 ms can be observed in a significant proportion of middle-aged healthy males and in similar patients with ischemic heart disease and does not seem to be linked to long-term prognosis.³⁰

Diagnosis

Specific diagnostic criteria for ER pattern and ER syndrome are presented in Table 1. Table 2 presents conditions for differential diagnosis. In addition, specific repolarization patterns that have been previously discussed should be also taken into account. The Brugada syndrome is characterized by J-point or ST-segment elevation in the right precordial leads, and approximately 12% of patients display typical early repolarization abnormalities. However, typically the ST-segment elevation is augmented in the right precordial leads by sodium-channel blockers, whereas in ERS the early repolarization pattern is usually attenuated.³¹ RVOT is the region involved in Brugada syndrome as opposed to the inferior LV wall in ERS. Leads affected in Brugada syndrome are V1-V3, whereas the inferolateral leads (II, III, aVF, V4-V6, I, aVL) are affected in ERS.¹ Intraventricular conduction defect-mediated notch

syndromes may present as J-wave syndromes, but the notch is tachycardia-dependent, and ischaemic or other structural heart disease is usually present.¹

Indications for genetic testing are presented in Table 3.

Therapy

The risk stratification and optimum management of these patients are not well defined and the recognition of the truly malignant forms is difficult (Table 4 and Figure 3). Electrophysiology testing does not appear useful for risk stratification, and is not generally recommended.³² VF is infrequently induced (22%) and has no predictive value for ICD therapy.³³ Patients with aborted sudden death in the absence of identifiable cause (idiopathic VF) are treated with ICD. Catheter ablation of the arrhythmogenic substrates with late depolarization abnormalities, and ablation of VF triggers emanating from the Purkinje system has also been reported.^{34,35} Quinidine, a drug that blocks I_{to} that is particularly expressed in the distal Purkinje cells, might be useful.³⁶

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