Early Repolarisation Changes in ECG: Are they Benign or Malignant?

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Abstract
Till recently, ST segment elevation in the absence of conduction abnormalities or chest pain occurring particularly in young bradycardia individuals has been considered a normal variant called early repolarisation (ER). However, recent studies suggest a more worrisome picture as patients with history of idiopathic ventricular fibrillation showed increased prevalence of ER in ECG. ER is an ECG pattern characterised by elevation of the QRS-ST junction (J point) ≥ 2 mv from baseline in the inferior (II, III, aVF) or lateral (I, aVL, V4-V6) leads manifested as QRS slurring or notching. The ER pattern describes the patient with appropriate ECG findings in the absence of symptomatic arrhythmias. The Early Repolarisation Syndrome (ERS) applies to the patient with both appropriate ECG findings and symptomatic arrhythmias. The current experimental data support the concept that J-point elevation is a marker of increased transmural heterogeneity of ventricular repolarisation, which increases the vulnerability to ventricular tachyarrhythmias. Male gender, history of syncope or sudden cardiac death (SCD) in family, ER in inferior leads or global ER pattern, terminal notching of QRS complex, J wave amplitude of more than 0.2 mv, horizontal or downward direction of ST segment elevation signify higher risk features for SCD in ER patients. Patients with ER pattern on ECG should have complete cardiac evaluation. The management options for ERPS include anti arrhythmic drugs, implantable cardioverter-defibrillator (ICD) and radiofrequency ablation. There is a need for the physicians to be aware of this entity, hitherto considered as variant of normal ECG pattern especially in young adults and understand its implications, identify high risk subsets and manage with appropriate strategy.

Introduction
Sudden cardiac death (SCD) is a major cause of mortality in the general population. The most common cause of sudden cardiac death is ventricular fibrillation (VF). Coronary artery disease, cardiomyopathy, congenital and valvular heart disease, primary electrophysiological abnormalities are the major causes of VF causing SCD. Some cases are identified as idiopathic VF when no specific aetiology is known. Till recently, ST segment elevation in the absence of conduction abnormalities or chest pain occurring particularly in young, bradycardia individuals has been considered a normal variant called early repolarisation (ER).¹ However, recent studies suggest a more worrisome picture as patients with history of idiopathic VF showed increased prevalence of early repolarisation in ECG.²,³ ER is a common ECG finding that affects 5% of population. So, its potential arrhythmic significance is very challenging. How should the physician advise a patient with ER pattern which was considered normal till recently? How can ER related SCD be predicted and prevented? In this article we will review the available information, possible mechanisms, clinical features and management strategies pertaining to ER.

Historical Background
ER pattern was first described as a normal variant by Shirpley and Hall in 1936.⁴ Investigators in 1950s and 1960s have labelled the ER ECG pattern as normal RS-T segment elevation variant or juvenile ST variant and observed that ER tends to be associated with young age, male sex, black race and regression of ECG changes during exercise and this ECG pattern doesn’t appear to be associated with increased risk of mortality.⁵,⁶ After initial reports in 1984 in South East Asian population,⁷ a large number of case reports in 1990s described an association between ER pattern and idiopathic VF.⁸,⁹ In a large case control study by Haïssaguerre et al found that ER was six times more common in 206 idiopathic VF patients than in 412

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matched controls and idiopathic VF subjects with ER were at increasing risk of SCD. Tikkanen et al studied the prevalence and prognostic significance of ER on 12-lead ECG in a community-based general population of 10,864 middle aged subjects during a mean follow-up of 30±11 years. J-point elevation of at least 0.1 mV in inferior leads was associated with an increased risk of death from cardiac causes.

Genetics, Pathophysiology and Mechanisms

Under normal conditions, cardiac action potential durations are similar and small variations in the timing of local depolarisation and repolarisation produce the electrocardiographic QRS complexes and T waves. During the ST-segment, all cardiac cells are depolarised, so little current flows (Figure 1). If one region (Region A in Figure 1) is affected by ER there is a large voltage gradient between adjacent region (Region B in Figure 1), which is still at plateau phase, and initial region (Region A) which is at the resting phase. A current flow toward the ER region creates positive ST-segment displacement (ST-segment elevation) in ECG leads reflecting electrical activity in the initial region. To generate the typical ER pattern, it is necessary that some regions of the myocardium repolarise earlier than others as depicted in Figure 1. Generalized ER would cause uniform shortening of the QTinterval, not the ST-segment elevation and J waves that characterise ER. The first gene variants described in patients with ER and SCD, agree with the notion of ionic-current imbalances favouring accelerated repolarisation as causes of the characteristic ECG pattern and arrhythmia susceptibility. The first mutation identified in a patient with ER-related VF was found in the KCNJ8 gene encoding the inward-rectifier ATP-dependent potassium channel. Propagation of the action potential dome from the sites where it is maintained, to the sites where it is lost may result in reexcitation of local tissue. This phase 2 re-entry could induce closely coupled ventricular extra systole, thereby creating the possibility to induce a re-entrant arrhythmias.

Mechanistic considerations may explain clinical aspects of ER. J waves are enhanced by hypothermia, which can also cause VF. Ionic currents have characteristic temperature sensitivities, potentially accounting for hypothermic J waves. Most ionic currents show time-dependent activation, inactivation, and/or recovery properties and are strongly influenced by heart-rate changes, potentially accounting for rate-dependent ER manifestations. The ER pattern is labile: autonomic tone and heart rate likely play major roles in ER variability. The current experimental data support the concept that J-point elevation is a marker of increased transmural heterogeneity of ventricular repolarisation, which increases the vulnerability to ventricular tachyarrhythmias.

Why is ER located primarily in inferior leads of ECG in some individuals and lateral leads in others? The answer could be that localisation must reflect regional control of repolarisation, which is presently poorly understood.

ER-ECG Diagnosis

ECG abnormality constitutes the hallmark of ER. It includes repolarisation and depolarisation abnormalities in the absence of identifiable structural cardiac abnormalities, or other conditions, or agents that are known to cause ST-segment elevation. ER is an ECG pattern characterised by elevation of the QRS-ST junction (J point) ≥ 2 mV from baseline in the inferior (II, III, aVF) or lateral (I, aVL, V4-V6) leads manifested as QRS slurring or notching (Figure 2).

Classification of Early Repolarisation Pattern

Based on arrhythmic risk associated with the localisation of ER changes on surface ECG, a classification has been proposed.

Type 1: ER localised to lateral precordial leads. Common among healthy male athletes and is thought to be largely benign.

Type 2: ER seen in the inferior or inferolateral leads and associated with a moderate level of risk. Tikkanen et al noted that in addition to inferior localisation and greater amplitude of ER, a horizontal or
down sloping ST-segment after ER portends a higher risk for SCD.14.

Type 3: ER seen globally in the inferior, lateral, and right precordial leads, associated with the highest relative risk, though the absolute risk of sudden death remains small.

The ER pattern describes the patient with appropriate ECG findings in the absence of symptomatic arrhythmias. The Early Repolarisation Syndrome (ERPS) applies to the patient with both appropriate ECG findings and symptomatic arrhythmias. ERPS causing VF may be diagnosed when other etiologies have been excluded and when J point elevation is augmented immediately preceding VF. Autonomic tone and heart rate variability likely play major risks in ER. The ER associated idiopathic VF events are more likely to occur with increased parasympathetic tone such as sleeping or after meals. Conversely, adrenergic stimulation suppresses ER and associated arrhythmic risks.

ER-High Risk Features: These include male gender, history of syncope, or SCD in family, ER in inferior leads or global ER pattern, terminal notching of QRS complex, J wave amplitude of more than 0.2 mv, horizontal or downward direction of ST segment elevation.2,3 Patients with ERPS should be evaluated with Holter monitoring, exercise test, tilt table test, cardiac MRI and intravenous drug challenge with adrenaline and sodium channel blockers.

Therapies for Early Repolarisation Syndrome

Drug Therapy

Antiarrhythmic drug quinidine has been shown to be beneficial in arrhythmias induced by ERPS. The benefit from quinidine is generally attributed to Ito inhibition, which is consistent with the notion that early phase 1 voltage gradients underlie arrhythmogenesis of ER. Arrhythmic storm occurs in about 10% of patients with ER-related SCD. Isoproterenol infusion, titrated to increase heart rate beyond 90 and up to 120 beats/min, suppresses arrhythmic events, as do other heart rate-increasing interventions (such as atrial or ventricular pacing). There was no suggestion of benefit from other anti-arrhythmic drugs like beta blockers, verapamil, mexilitine, amiodarone and class Ic agents.

**Implantable Cardioverter-Defibrillator (ICD)**

For ER patients resuscitated from idiopathic VF, ICD implantation is required. In patients with ICD and frequent nonsustained ventricular tachyarrhythmias and/or ICD shocks, adjuvant antiarrhythmic therapy with quinidine may be helpful.

**Radiofrequency Ablation**

In electrophysiology laboratory, premature beats triggering VF can be localised to regions showing ER in some patients and ablation of such zones can prevent VF recurrence.2

**Inheritance of ER and Family Screening**

ER demonstrates heritability in the general population and within the family.15 Familial transmission appears more frequent when mother was affected. Currently it is not possible to identify asymptomatic individuals and families with ER at increased risk of SCD with any clinically useful degrees of accuracy. In symptomatic patients and their families the Valsalva maneuver may assist in identifying concealed ER cases. Patients with ER should have underlying cardiovascular disease aggressively managed as there is no ER associated proven risk modifying intervention.

**Conclusion**

The ERPS as a primary arrhythmogenic disorder causing VF is relatively rare.16 However, ERPS patients should undergo thorough cardiac evaluation as discussed to establish the probable diagnosis and further management (Figure 3). At present clinically useful risk stratifying tools or an established provocative test for identifying malignant ER
are not available. Patients with asymptomatic ER with no family history of malignant ER, possibly those with ER ECG changes restricted to lateral precordial leads can be reassured that the available evidence indicates no increased risk. All patients with ER should continue to have modifiable cardiac risk factors addressed. There is a need for further data to enable more accurate risk estimation in all ER subjects and to offer preventive therapy when risk is elevated. There is an urgent need for all the physicians to be aware of this entity, hitherto considered as variant of normal ECG pattern especially in young adults.

References