Early repolarization syndrome: A cause of sudden cardiac death

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Abstract

Early repolarization syndrome (ERS), demonstrated as J-point elevation on an electrocardiograph, was formerly thought to be a benign entity, but the recent studies have demonstrated that it can be linked to a considerable risk of life-threatening arrhythmias and sudden cardiac death (SCD). Early repolarization characteristics associated with SCD include high-amplitude J-point elevation, horizontal and/or down-sloping ST segments, and inferior and/or lateral leads location. The prevalence of ERS varies between 3% and 24%, depending on age, sex and J-point elevation (0.05 mV vs 0.1 mV) being the main determinants. ERS patients are sporadic and they are at a higher risk of having recurrent cardiac events. Implantable cardioverter-defibrillator implantation and isoproterenol are the suggested therapies in this set of patients. On the other hand, asymptomatic patients with ERS are common and have a better prognosis. The risk stratification in asymptomatic patients with ERS still remains a grey area. This review provides an outline of the up-to-date evidence associated with ERS and the risk of life-threatening arrhythmias. Further prospective studies are required to elucidate the mechanisms of ventricular arrhythmogenesis in patients with ERS.

Key words: Early repolarization syndrome; Early repolarization; Sudden cardiac death; J-wave

Core tip: Early repolarization syndrome (ERS), demonstrated as J-point elevation on an electrocardiograph, was formerly thought to be a benign entity, but the recent studies have demonstrated that it can be linked to a higher risk of ventricular arrhythmias and sudden cardiac death. The prevalence of ERS varies between 3% and 24%, depending on age, sex and J-point elevation (0.05 mV vs 0.1 mV) being the main determinants. ERS patients are sporadic and they are at a higher risk of having recurrent cardiac events. Implantable cardioverter-defibrillator implantation and isoproterenol are the suggested therapies in this set of patients. On the other hand, asymptomatic patients with ERS are common and have a better prognosis. The risk stratification in asymptomatic patients with ERS still remains a grey area. This review provides an outline of the up-to-date evidence associated with ERS and the
risk of life-threatening arrhythmias. Further prospective studies are required to elucidate the mechanisms of ventricular arrhythmogenesis in patients with ERS.

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INTRODUCTION

Sudden cardiac death (SCD) is defined as natural death due to cardiac causes in a person who may or may not have previously recognized heart disease but in whom the time and mode of death are unexpected[1]. In the context of time, "sudden" is defined for most clinical and epidemiologic purposes as 1 h or less between a change in clinical status heralding the onset of the terminal clinical event and the cardiac arrest itself[1]. The overwhelming majority of SCD cases are related to cardiac arrhythmias[2]. The commonest electrophysiologic mechanisms leading to SCD are ventricular arrhythmias. About 10% of the cases of SCD are related to primary electrophysiological disorders with known (e.g., Brugada syndrome) or unknown (e.g., idiopathic VF) ion-channel abnormalities[3-8].

Early repolarization (ER), also recognized as "J-waves" or "J-point elevation" is an electrocardiographic (ECG) entity characterized by J-point elevation manifested either as either an abnormality consistent with elevation of the junction between the end of the QRS complex and the beginning of the ST segment in 2 contiguous leads[9,10]. Grant et al.[11] are considered to be the first who used the term ER to describe ST-segment deviations and related T wave inversion and premature repolarization. ER was unanimously and indisputably regarded as "normal," a "normal variant," or a "benign early repolarization" until 2000[12]. However, numerous more recent reports have suggested a relationship between ER and an increased risk of death from cardiac arrhythmias[8,13-19].

ERS is an electrocardiographic (ECG) entity characterized by J-point elevation manifesting either as either QRS slurring (at the transition from the QRS segment to the ST-segment) or notching (a positive deflection inscribed on terminal S wave), ST segment elevation with upper concavity and prominent T-waves in at least two contiguous leads[20] (Figure 1).

PREVALENCE

The ERS is commonly seen in athletes, cocaine users, hypertrophic obstructive cardiomyopathy and defects and/or hypertrophy of interventricular septal defects[21-24]. Prevalence of ERS varies between 3% and 24% in the general population, depending on the population studied and methods used for ECG interpretation. Young individuals, especially those predisposed to vagotonia, males, African Americans, and athletes are subpopulations known to have a higher prevalence of ERs[19,20]. Tikkanen et al.[13] demonstrated that the location (inferior vs lateral leads) as well as J-point elevation of > 0.2 mV are linked to a significant risk of death from cardiac arrhythmias (adjusted relative risk, 2.98; 95%CI: 1.85-4.92; P < 0.001).

HISTORICAL PERSPECTIVE

The J-deflection presenting as either QRS slurring or notching was first described in 1936 by Shilpey et al.[25] and was considered a normal ECG variant. In 1938, Tomaszewski[26] presented the case of an accidently frozen man whose ECG demonstrated a very slowly inscribed deflection between the QRS complex and the earliest part of the ST segment, representing a J wave. In 1953, Osborn[27] described a “current of injury” later named “the Osborn wave” in acidic and hypothermic dogs at rectal temperatures < 25 °C.

In 1961, Wasserburger et al.[28] further defined ER as a 1-4 mm takeoff of the ST-segment at the end of the QRS complex with a distinct notch or slur on the downslope of the R wave in the mid to left precordial leads.

In 1999, Gussak et al.[29] suggested that ER may be malignant in some cases, based on observations that an ER pattern in arterial perfused wedge preparations can easily convert to one which gives rise to polymorphic ventricular tachycardia.

In 2000, evidence supporting above hypothesis was provided by Kalla et al.[30] and Takagi et al.[31]; they reported VF in patients with prominent J-wave and ST segment elevation in inferior leads without structural heart diseases and postulated that idiopathic VF with an ER pattern in inferior leads may represent a variant of the Brugada syndrome. In 2008, Haïssaguerre et al.[32] and Nam et al.[33] described a strong relationship between J-waves and many different forms of ventricular arrhythmias in the absence of known heart disease.

CELLULAR, MOLECULAR AND GENETIC CONSIDERATIONS

The pathophysiologic basis of the ER is currently not fully understood. The most discussed hypothesis incriminates that this may be related to either an increased susceptibility or vulnerability to cardiac arrest in critical ischemic conditions such as acute coronary syndromes[33], or to subtle changes in the cardiac action potential[34]. ER in its simplest form occurs in early phase of the cardiac action potential and is caused by the cardiac transient outward potassium current (Ito). If a situation arises where there is a reduced density of the Ito channels in the endocardium compared with the epicardium, the action potential of the endocardium may be prolonged to such an extent that it may injure the heart. This may result in sudden cardiac death.
epicardium or mid-myocardium\textsuperscript{[35]}, a large Ito current can occur that results in electrocardiographic ER and large voltage gradients that may generate J wave elevation (Figure 2) and have the propensity to initiate life threatening arrhythmias\textsuperscript{[34,35]}.

Another hypothesis regarding the mechanism causing ER suggests an association of localized depolarization abnormalities with repolarization anomalies, as it happens in type 1 Brugada syndrome\textsuperscript{[36-39]}.

The genetic basis of ER syndrome continues to be elucidated, with the evidence restricted to either case reports or preliminary studies that fall short of clearly identifying the genetic basis of ER\textsuperscript{[40,41]}. The reported implicated gene mutations involve the KCNJ8 gene (responsible for the ATP sensitive potassium channel Kir6.1 - I\textsubscript{ATP} current), CACNA1C, CACNB2, CACNA2D1 genes (responsible for the cardiac L-type calcium channel - I\textsubscript{Ca.L} current), and the SCN5A gene (responsible for the sodium channel - I\textsubscript{Na} current)\textsuperscript{[40-44]}. All of these might enhance the underlying inward - outward current imbalance responsible for accelerated epicardial repolarization.
the term “J-Wave Syndrome” has been suggested to describe ERS and Brugada Syndrome as a spectrum of a clinical condition. Antzelevitch et al. described three subtypes of ERS, and highlighted a pattern of risk profile: (1) type 1: It shows ER in the lateral precordial leads that is seen in healthy male athletes and has the lowest risk of malignant arrhythmias (Figure 3); (2) type 2: It shows ER in the inferior and inferolateral leads and is associated with a greater risk of malignant arrhythmias; and (3) type 3: It shows ER pattern in all ECG leads (Figure 4) and has the highest risk of malignant arrhythmias and electrical storms.

The Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society (HRS/EHRA/APHRS) consensus statement on the diagnosis and management of primary inherited arrhythmia syndromes recommended criteria for the diagnosis of ER is shown in Table 1.

DIFFERENTIAL DIAGNOSIS

Early Repolarisation syndrome have a wide differential including Brugada Syndrome, short and long QT syndromes as well as other conditions causing ST segment elevation (ST segment elevation MI, acute pericarditis and idiopathic VF). Brugada syndrome (BS), perhaps the closest clinical entity to ERS, is a primary repolarisation disorder characterized by a prominent J-wave causing a pattern of incomplete right bundle branch block and ST-segment elevation in the right precordial leads (V1-V3) (Figure 5) and significant risk of sudden cardiac death in individuals with no known structural heart disease. BS, an autosomal dominant condition, is more common in males and has a variable penetrance. Symptoms of BS include syncope with or without any warning signs, seizures and nocturnal agonal respiration; however, ECG remains the cornerstone of diagnosis of BS. However, the Brugada ECG feature of provocation by sodium channel blocker is not observed in ER. In fact, sodium channel blockers in most patients with ER
artery bypass grafting.

Table 2 gives a list of conditions with J-wave on the ECG.

| Condition | Description |
|-----------|-------------|
| Benign ERS | 
| Malignant ERS | 

The identification of high-risk patients with ERS remains challenging. Currently, surface ECG is the only available tool in order to differentiate between the benign and the malignant forms of ERS. A horizontal or descending ST-segment elevation has been associated with adverse outcomes (compared with a rapidly ascending ST-segment elevation) following J-point elevation. Other abnormalities, such as localization of the PR segment, which is not present in ER. While patients with acute myocardial injury due to ST elevation myocardial infarction (STEMI) can initially have J-point elevation with concave ST segment elevation, the ST segment elevation typically becomes more pronounced and convex (rounded upward) as the infarction persists. However, the primary distinguishing factor between ER and acute myocardial injury is the presence of clinical symptoms such as chest pain or dyspnea. ER and notching of the terminal QRS need to be considered in risk stratification for arrhythmias in patients with coronary artery disease and after coronary artery bypass grafting.

Table 2 gives a list of conditions with J-wave on the ECG.

**BENIGN OR MALIGNANT**

The identification of high-risk patients with ERS remains challenging. Currently, surface ECG is the only available tool in order to differentiate between the benign and the malignant forms of ERS. A horizontal or descending ST-segment elevation has been associated with adverse outcomes (compared with a rapidly ascending ST-segment elevation) following J-point elevation. Other abnormalities, such as localization of the ER pattern in inferior or inferolateral (compared with lateral) leads or extension of ER into a BrS pattern, may also represent a worse prognosis.

The benign type of ERS is commonly associated with young age group, left ventricular hypertrophy on ECG,
The current consensus is that these patients do not require specific investigations or therapeutic interventions. Among the survivors of SCD due to idiopathic VF, the reported rate of recurrent VF ranges between 22% and 37% at two to four years. Because these patients have no structural heart disease, they have an excellent prognosis for long-term survival if VF is treated. As a result, such patients are best treated with an implantable cardioverter-defibrillator (ICD). HRS/EHRA/APHRS consensus statement on the diagnosis and management of primary inherited arrhythmia syndromes recommendations for therapeutic interventions in ERS are shown in Table 3.

It has been demonstrated that patients with VF and ER have a higher prevalence of recurrence of VF than VF patients without ER (43% vs 23%, P < 0.001) during a five years follow-up. In a multicenter observational cohort study of 122 patients (90 males, mean age 37 ± 12 years) with ER in the inferolateral leads and more than three episodes of idiopathic VF (including those with electrical storm), isoproterenol was effective for the acute suppression of VF, immediately suppressing electrical storms in seven of seven patients. In terms of long-term therapy, VF recurrences have been demonstrated to be effectively suppressed by quinidine therapy. Encouraging results recently emerged from a study by Gurabi et al, who demonstrated that in addition to quinidine, clobazol, and milrinone suppress the hypothermia-induced VT/VF in a canine left ventricular model.

However, there exists a “gray area” in between the two ends of the spectrum, where no clear guidelines exist. Examples include patients with syncope who may have a “malignant” ER pattern and/or a significant family history of sudden cardiac death. The current guidelines suggest that ICD implantation may be
considered in high-risk individuals with unexplained syncope[50].

SCREENING FAMILY MEMBERS
There are no current recommendations can be given to do ECG screening of the families of individuals with asymptomatic ER pattern or individuals with strong family history of ER or ER with VF. There are no recognized provocative tests that would help in diagnosing concealed ER in family members of patients with ERS, although preliminary observation advocate that concealed ER cases may be recognized by Valsalva maneuver[50,66].

CONCLUSION
In the recent years, ER syndrome has been associated with a significant risk of life-threatening arrhythmias and cardiac death. It is currently not possible to identify asymptomatic individual patients with ER who are at a higher risk of having cardiac arrhythmias with any clinically useful degree of accuracy. It is also not possible to identify asymptomatic individuals with a primary arrhythmogenic disorder attributable to ER. All patients with ER should continue to have modifiable cardiac risk factors addressed.

Until we have a better knowledge, physicians are left with the observation that in patients with ER in the inferolateral leads, life-threatening ventricular arrhythmias may occur and may lead to sudden cardiac death. Since there are a large number of patients who fit such a criteria but do not appear to have excess risk of arrhythmias, further data is needed to reveal how to identify the group of patients who would be at a significant risk and what measures can be taken to prevent it.

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