Early Repolarization Syndrome
– A New Electrical Disorder Associated With Sudden Cardiac Death –
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Early repolarization (ER), consisting of a J-point elevation, notching or slurring of the terminal portion of the R wave (J wave), and tall/symmetric T wave, is a common finding on the 12-lead electrocardiogram. For decades, it has been considered as benign, barring sporadic case reports and basic electrophysiology research that suggested a critical role of the J wave in the pathogenesis of idiopathic ventricular fibrillation (VF). In 2007–2008, a high prevalence of ER in patients with idiopathic VF was reported and subsequent studies reinforced the results. This review summarizes the current state of knowledge concerning ER syndrome associated with sudden cardiac death. (Circ J 2010; 74: 2039–2044)

Key Words: Early repolarization; Idiopathic ventricular fibrillation; J wave; Sudden cardiac death

Sudden cardiac death (SCD) is defined as an unexpected natural death from a cardiac cause within a short time period, generally ≤1 h from the onset of symptoms, in a person without any prior condition that would appear to result in instantaneous fatality. The majority of SCD events are associated with structurally diseased heart. Ventricular tachycardia (VT) degenerating first to ventricular fibrillation (VF) and later to asystole appears to be the most common pathophysiologic cascade involved in fatal arrhythmias recorded as the primary electrical event at the time of SCD, particularly in patients with advanced heart disease. In patients without structural heart disease, polymorphic VT and torsades de pointes caused by various genetic or acquired cardiac abnormalities, such as ion-channel abnormalities, or acquired long-QT syndrome commonly contribute to the initiation of life-threatening arrhythmias. Primary electrophysiologic disorders with known (long QT syndrome, Brugada syndrome, catecholaminergic polymorphic VT, short QT syndrome) or unknown (early repolarization (ER) syndrome, idiopathic VF) ion-channel abnormalities are responsible for 10% of SCDs.

For decades, ER, which is characterized by an elevation of the junction between the end of the QRS complex and the beginning of the ST segment (ie, the J point) from baseline on standard 12-lead electrocardiogram (ECG), has been considered to be benign ECG manifestation. However the presence of this pattern, especially in the inferior or lateral leads, has recently been recognized in some studies as associated with vulnerability to VF. This review summarizes our current state of knowledge of ER syndrome.

Electrocardiogram of Early Repolarization

Definition of Early Repolarization
The ER pattern is a common electrocardiographic variant characterized by J-point elevation manifested either as 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 2 contiguous leads. In most of the studies elevation of the J point and/or ST-segment from the baseline by at least 0.1 mV was considered definitive of ER (Figure).

Diagnosis of Early Repolarization Syndrome Associated With Idiopathic VF
To evaluate the association between ER and idiopathic VF, patients with other known diseases have to be distinguished from patients with idiopathic VF. On the basis of published guidelines, patients are classified as having idiopathic VF if they have no identifiable structural heart disease demonstrated by echocardiographic biventricular dimensions and function, no detectable coronary artery disease on coronary angiography or exercise testing, and no known repolarization abnormalities. Secondly, cases of primary electrical disorders should be excluded if the QT interval corrected for heart rate (QTc) is less than 340 ms (short QT interval) or more than 440 ms (long QT interval) at baseline and before arrhythmia. Patients with the Brugada syndrome, defined as right bundle branch block and ST-segment elevation (≥0.2 mV) in ≥2 precordial leads V1-3, without intervention or following infusion of a sodium-channel blocker, should also be excluded. In addition, patients with catecholaminergic arrhythmias, defined as arrhythmias during catecholamine
infusion or exercise testing, should be excluded. To avoid confusion with the pattern commonly seen in highly trained athletes (J-point elevation + ST elevation in V2-4), the term “inferolateral J wave elevation syndrome” is probably more appropriate for the ER associated with VF.

Prevalence in the General Population and in Patients With Idiopathic VF
The prevalence of ER in the general population varies from less than 1% to 13%, depending on age (predominant in young adults), race (predominant in black populations), sex (predominant in males), and the criterion for J-point elevation (0.05 mV vs 0.1 mV).7,8,17,18,20,21 The most comprehensive study to date evaluating the prevalence and prognostic significance of ER in a community-based general population of 10,864 middle-aged subjects reported the prevalence of ER as 5.8% (5.0% in the control group studied in our report8), including 3.5% in the inferior leads, 2.4% in the lateral leads, and 0.1% in both, using the same ECG criteria.17 With J-point elevation ≥0.2 mV, the prevalence dropped to 0.33% (0.7% in the control group studied in our report8).

In patients with documented idiopathic VF and a structurally normal heart, the prevalence of ER was 31%.8 Prevalence rates up to 60% have been reported in smaller studies;22 The prevalence of the ER pattern with J-wave elevation ≥0.2 mV in patients with idiopathic VF was found to be 16%.8

History of Early Repolarization
Early Repolarization in the Past
The J-point deflection occurring at the QRS-ST junction (also known as the Osborn wave or J wave) was first described by Tomaszewski in 1938.23 An ER pattern that was slurring or notching of the terminal part of QRS complex on the ECG was first described in 1936.24 However, it was a wide- and long-held belief that ER on ECG was not associated with any adversity. This long-held concept was reconsolidated by Klatsky et al in 2003 in a study involving 73,088 patients who underwent voluntary health examination, including ECG, in Oakland, California, between 1983 and 1985.15 The authors concluded that the prevalence of ER in their cohort was 0.9% (670/73,088) and that the patients with ER were less likely to experience arrhythmias. The overall rate of hospitalization and outpatient visits was not higher than in the control population.15

Early Repolarization in the Current Era
During the past decade, a number of clinical reports (mostly from Japan) have described patients who had sudden cardiac arrest associated with abnormal J waves; however, ER was reported as the only “abnormal” finding in patients diagnosed with idiopathic VF,25–38 Meanwhile, the potential arrhythmogenicity of ER was also demonstrated in experimental studies.39–42 These observations pointed towards a potentially non-benign nature of ER. More definitive clinical evidence and a turning point in our perception of ER came in 2007–2008 when we reported a high prevalence of ER in patients...
with idiopathic VF. ER was observed in 31% (64/206) of idiopathic VF cases vs 5% (21/412) of well-matched healthy subjects (P=0.001). Furthermore, based on data from implantable cardioverter-defibrillators (ICD), 64 idiopathic VF survivors with ER experienced higher VF recurrence than 142 VF survivors without ER (41% vs 23%, P=0.008). Subsequently, Rosso et al compared the ECGs of 45 idiopathic VF cases with those of 124 age- and sex-matched control subjects and 121 young athletes and found that ER was more common among the patients with VF than among the control subjects (42% vs 13%, P=0.001). This was particularly true for J-point elevation in the inferior leads (27% vs 8%, P=0.006) and was true for J-point elevation in leads I to aVL (13% vs 1%, P=0.009). In contrast, J-point elevation in V1-6 occurred with equal frequency among patients and matched-control subjects (6.7% vs 7.3%, P=0.86). In another study by Nam et al, baseline ECGs of 11 of 19 (57.9%) patients with VF showed ER in contrast to 3.3% of 1,395 controls representing the general population.

Although case-control studies do not establish causation, strong evidence in favor of an association between ER and VF-related SCD has emerged. Tikkkanen et al systematically reported the long-term outcome of ER in the general population. The authors assessed the prevalence and prognostic significance of ER on routine ECG performed during a community-based investigational study of coronary artery disease among 10,864 middle-aged subjects. The mean follow-up was 30±11 years with the primary endpoint of cardiac death and secondary endpoints of all-cause mortality and arrhythmic death. The prevalence of ER was 5.8% in this cohort. Importantly, ER in the inferior leads was found to be associated with an increased risk of cardiac death (adjusted relative risk, 1.28; 95% confidence interval (CI), 1.04 to 1.59, P=0.03) and was true for J-point elevation in leads I to aVL (13% vs 1%, P=0.009). In contrast, J-point elevation in V1-6 occurred with equal frequency among patients and matched-control subjects (6.7% vs 7.3%, P=0.86). In another study by Nam et al, baseline ECGs of 11 of 19 (57.9%) patients with VF showed ER in contrast to 3.3% of 1,395 controls representing the general population.

Mechanisms of Early Repolarization

Experimental Studies

The exact mechanism for ER is still unknown. In 1991, Antzelevitch et al first proposed transmural differences in the early phases of the cardiac action potential (phases 1 and 2) as probably responsible for inscription of the ECG J wave. Subsequently, they obtained direct evidence in support of this hypothesis in arterially perfused canine ventricular wedge preparations in 1996. Briefly, an arrhythmicogenic platform is created by disproportionate amplification of the repolarizing current in the epicardial myocardium due to a decrease in the inward sodium or calcium channel currents or an increase in the outward potassium currents mediated by the \( I_{\text{Na}} \), \( I_{\text{K,ATP}} \), \( I_{\text{K,ACH}} \) channels. The trigger and substrate for development of phase 2 reentry and VT/VF eventually emerge from the transmural dispersion in the duration of cardiac action potentials.

Genetic Testing

Because ER was not associated with an increased risk of SCD until recently, the genetic markers to differentiate benign and arrhythmic forms of ER have not been identified. The importance of the genetic background in ER has recently been suggested by our report, which showed that 16% of cases with VF and ER have a family history of SCD. Given the high frequency of the genetic background underlying the ER pattern in the population, it is probably polygenic and influenced by environmental factors.

As described previously, rare monogenic forms of ER have been reported using a candidate gene approach. ER on ECG suggests a shift in transmural voltage gradient between the epicardium and endocardium as a causal mechanism. An increase in the \( I_{\text{K}}, I_{\text{K,ACH}}, I_{\text{K,ATP}} \) current or a decrease of the sodium \( I_{\text{Na}} \) and/or calcium \( I_{\text{Ca}} \) current could lead to this phenomenon. Recently, we identified the first genetic abnormality associated with idiopathic VF and inferolateral ER, which was a rare variant in KCNJ8,8 responsible for the pore-forming subunit Kir6.1 of the \( I_{\text{K,ATP}} \) channel, using a candidate gene approach in a 14-year-old girl who was resuscitated following an episode of sudden death caused by VF with ER More recently, Medeiros-Domingo et al investigated 101 patients with J-wave syndromes, including 87 cases of Brugada syndrome and 14 of ER syndrome, and 1 case in each group hosted the identical missense mutation, KCNJ8, S422L. It was supported by the finding that KCNJ8 is a novel J-wave syndrome-susceptibility gene. Burashnikov et al identified a missense variant in the J2 subunit of the cardiac L-type calcium channel in patients with the ER syndrome. Expression studies for this variant are not available as yet.

Early Repolarization or Delayed Depolarization?

Although the J wave is synonymously used with the ER abnormality, the mechanistic evidence elucidating the inscription of the J wave on the surface ECG is incomplete. Basic investigators propose the inscription of J wave as coincident with phase 1 of the cardiac action potential in the epicardial region of the ventricular myocardium, which precedes phase 1 in the endo- and mid-myocardial cells, generating an early gradient in the repolarization currents within the ventricles, thereby justifying the J wave as an ER phenomenon. In accordance with that, some clinical investigators have concluded that the J wave should be considered as a repolarization phenomenon, rather than as late depolarization, because of its slower inscription, spontaneous/rate dependant fluctuation in a morphologic pattern (increased pattern at slow heart rate, decreased pattern at faster heart rate) or amplitude in the face of stable QRS complexes, and amplitude varying concurrently with the ST segment. These investigators did not find late potentials (LPs) on high-amplification ECG and invasive endocardial mapping further reinforced their view. Recently Abe et al analyzed 22 idiopathic VF patients using a newly developed signal-averaging system to record LPs (depolarization marker), T-wave alternans (TWA) and QT dispersion (QTD) (repolarization markers). J waves were significantly associated with all LP parameters, but TWA and QTD were not. They concluded these findings might support the idea that...
J waves are more strongly associated with a depolarization abnormality than with a repolarization abnormality.

**Risk Stratification of VF**

As described earlier, although ER is a common entity, unexplained SCD in young adults is very rare. Rosso et al claimed that the presence of a J wave on the ECG of a young adult would increase the probability of VF from 3.4±100,000 to 11±100,000, which is a negligible rise.16 They, therefore, concluded that the incidental discovery of a J wave on routine screening should not be interpreted as a marker of “high risk” for sudden death, because the odds for this fatal disease would still be approximately 1±10,000.14 However, needless to say careful attention should be paid to subjects with “high risk” ER.

**Clinical Features**

In such a situation, we consider that close follow-up should be offered to patients with ER and a history of unexplained syncopal or a family history of unexplained sudden death. Abe et al reported that the prevalence of ER in 222 patients with syncope and no organic disorder was 18.5%, which is almost 10-fold that in 3,915 healthy controls (2%).16 Therefore, the possibility of ER-associated syncopal episodes cannot be excluded in at least some of these patients. The genetic basis of ER is still largely unknown. Also, in patients with VF and ER, a positive family history of sudden death was not excluded in at least some of these patients. The genetic basis of ER is still largely unknown. Also, in patients with VF and ER, a positive family history of sudden death was not significantly higher than in those without ER (16% vs 9%, P=0.17).4 Nevertheless, it does not imply that family history is not an important aspect of the background to ER patients.

**Magnitude of the J Wave**

We also found that the magnitude of the J-wave elevation in the case group was significantly higher than that in the control subjects (2.0±0.8 mV vs 1.2±0.4 mV, P<0.001).8 In the study by Tikkanen et al, subjects with J-point elevation >0.2 mV on inferior leads not only bore a higher risk of death from cardiac causes (adjusted relative risk, 2.98; 95%CI, 1.85–4.92, P<0.001) as compared with a J-point elevation >0.1 mV, but also had a markedly elevated risk of death from arrhythmia (adjusted relative risk, 2.92; 95%CI, 1.45–5.89, P=0.01).17 This finding indicates that the magnitude of the J-point elevation could be a discriminator of risk. It is worthy to note that a J-point elevation >0.2 mV seems to be rare in the normal population. Three-quarters of the subjects with a J-point elevation on baseline measurement had the same pattern several years later.17 However, it is necessary to point out that the magnitude of the J-wave elevation can fluctuate, even without drug provocation or exercise, which means that a low-magnitude J wave should not be considered as a static entity.

**Spontaneous Dynamicy**

We performed serial ECGs during electrical storm (including frequent ventricular ectopy and episodes of VF) in 18 subjects and all showed a consistent and marked increase in the amplitude of the J wave during the period of storm when compared with the baseline pattern (from 2.6±1 mm to 4.1±2 mm, P<0.001).8 Besides spontaneous accentuation of the J-wave amplitude preceding the electrical storm, spontaneous beat-to-beat fluctuation in the morphologic pattern of ER was also observed.8 Nam et al investigated the initiation of VF episodes and reported a dramatic, but very transient, accentuation of J waves prior to the development of electrical storm in 5 patients.20 The available data suggest that transient J wave augmentation portends a high risk for VF in patients with ER.

**Distribution of the J Wave**

In normal subjects, most of the ER is confined to the inferior leads, lateral leads or left precordial leads. As reported by Tikkanen et al, of 630 subjects with ER, only 16 (2.5%) had ER in both the inferior and lateral leads.17 Focusing on patients with VF, we found that 46.9% of patients with VF and ER showed the ER pattern in both inferior and lateral leads.8 Similarly, the global presence of ER was observed in none of the 46 subjects with ER without VF (selected from among 1,395 individuals from the general population), but was in 45.5% of patients with ER who developed VF.20 The implications of a global J wave are unknown, but, theoretically, this characteristic obviously means a much more diffuse repolarization abnormality.

**Morphology of the J Wave**

Recently, Merchant et al compared the baseline ECGs of 9 patients with VF/VT and ER (so-called malignant ER) and 61 age- and sex-matched controls with normal ER (so-called benign ER).52 The results demonstrated that QRS notching was more prevalent among cases than controls in leads V1 (44% vs 5%, P=0.001), V5 (44% vs 8%, P=0.006) and V6 (33% vs 5%, P=0.013). They concluded that left precordial terminal QRS notching is more prevalent in malignant variants of ER than in benign cases and could be used as a tool for risk stratification of subjects with ER. However, the case number in that study was small and included 3 patients with idiopathic monomorphic VT without VF.52

**Correlation Between J-Point Location and Origin of Arrhythmia**

We presented a definitive association between ER and idiopathic VF by mapping the ventricular ectopy initiating the VF in patients with ER and idiopathic VF.8 In 6 patients with ER recorded in inferior leads alone, all cases of ectopy originated from the inferior left ventricular wall. In the subjects with widespread global ER, as recorded in both inferior and lateral leads, ectopy originated from multiple regions.8,53 These findings prove that the ER abnormality may be either limited to a single region in the ventricles or can extend beyond to involve more than 1 region simultaneously. The link between this ECG pattern and malignant arrhythmias is supported by both the accentuated repolarization before the onset of arrhythmia in the case subjects and the origin of triggering beats from the region of ER. For patients who are diagnosed with idiopathic ventricular arrhythmias and ER, an alarm should be raised if the origin of arrhythmia, as identified by the morphology of VF-initiating ventricular ectopy, is discordant with the location of ER.

**LPs by a Signal-Averaged System Using 24-h Holter Electrogram**

Abe et al reported that patients with idiopathic VF and J waves had a high incidence of LPs showing a circadian variation with night ascendancy.49 TWA and QTd were not useful, but detection of LPs by a signal-averaged system using 24-h Holter electrogram was a useful technique for identifying those at high risk for arrhythmic events.

**Invasive Induction of VF**

Induction of VF was attempted in 132 VF patients from 2 dif-
different ventricular sites and up to 3 extrastimuli.\textsuperscript{8} The patients with ER did not show significantly higher inducibility than those without ER.\textsuperscript{8} Moreover, a low rate of VF inducibility (34\%) in the patients with a clinical history of VF makes the electrophysiologic study less sensitive for risk stratification of symptomatic patients.

**Management of VF Associated With Early Repolarization**

**Drug Therapy**

**Management of Electrical Storm During the Acute Phase**

We reported the effect of drug therapy for electrical storm in patients with ER and idiopathic VF in a multicenter study.\textsuperscript{51} Of 122 patients with VF and ER, 33 (27\%) experienced more than 3 episodes of VF and 16 experienced electrical storm (≥3 VF/24 h). In this population, electrical storm was unresponsive to \(\beta\)-blockers, lidocaine/mexiletine, and verapamil, but amiodarone was partially effective. In contrast, isoproterenol infusion immediately suppressed electrical storm. Acute control of arrhythmia could be achieved by deep sedation and/or isoproterenol infusion.\textsuperscript{52,53}

**Management of Recurrent VF During the Chronic Phase**

Patients with VF and ER have shown a higher incidence of VF recurrence than VF patients without ER (43\% vs 23\%; \(P<0.001\)) during 5 years of follow-up.\textsuperscript{8} We reported that during follow-up of 69±58 months, oral antiarrhythmic drugs were poorly effective in preventing recurrent VF: \(\beta\)-blockers, verapamil, mexiletine, amiodarone, and class IC antiarrhythmic drugs.\textsuperscript{54} However, quinidine was effective in 9 of 9 patients, decreasing recurrent VF from 33±35 episodes to nil for 25±18 months of follow-up.\textsuperscript{55} Interestingly, the ER pattern was closely linked to the period of occurrence of arrhythmia and was helpful in monitoring the efficacy of drug therapy. At the time of arrhythmia occurrence, ER was more pronounced than during the period without arrhythmia.

**Other Therapeutic Options**

Based on these observations, patients with VF and ER may be candidates for treatment over and above an ICD. To weather an electrical storm that is resistant to antiarrhythmic drugs, left ventricular assistance and cardiac transplantation may be required.

Catheter ablation of the ectopy initiating the VF could be another potential modality for the management of VF patients with ER who fail to respond to drugs. Catheter ablation eliminated all ectopies in 5 of 8 subjects; however, there were no data during long-term follow-up and further studies are necessary.\textsuperscript{8}

**Conclusion**

Current scientific evidence drawn from a large cohort of subjects with long-term follow-up suggests that ER, particularly if recorded in the infero-lateral leads, is not always as benign as traditionally thought. There is a high prevalence of ER in the patients experiencing first, recurrent and stormy episodes of idiopathic VF. We necessarily recommend careful evaluation of patients with ER in association with unexplained syncope, a family history of SCD or idiopathic ventricular arrhythmias. It is equally important to prospectively investigate the prognostic value of a J wave >0.2 mV, a global J wave and a notched J wave in the left precordial leads. For patients with recurrent VF, isoproterenol in acute cases and quinidine in chronic cases are effective antiarrhythmic drugs.

Future clinical and experimental studies should focus on understanding the exact mechanisms and reasons for this pattern, on establishing the method of risk stratification and ultimately on devising strategies to prevent premature death from cardiac causes in subjects with this pattern.

**Disclosure**

None.

**References**


