A Clinical Approach to Early Repolarization

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The term early repolarization (ER) is defined electrocardiographically by either (1) a sharp well-defined positive deflection or notch immediately following a positive QRS complex at the onset of the ST-segment, or (2) slurring at the terminal part of the QRS complex (also termed J-waves or J-point elevation, Figure 1). Specifically, the ER pattern is present when J-point elevation of ≥0.1 mV is seen in 2 adjacent leads with either a slurred or notched morphology. Although ER was historically considered benign, this perception changed as numerous studies established an association with increased risk of death and idiopathic ventricular fibrillation (VF). The incidental discovery of early repolarization now poses numerous questions, including defining and quantitatings the risk of sudden death. With the emerging reports of a genetic contribution, defining the genetic basis, inheritance, and the role of screening relatives broadens the implications of early repolarization beyond the index case. Insights into the molecular mechanism of early repolarization and therapeutic strategies continue to highlight its evolving significance.

This review seeks to provide a concise summary of the current evidence surrounding these issues, contextualize its clinical significance, and present an approach to the clinical evaluation and management of these patients. This review will emphasize that the majority of individuals with ER are at no or minimal risk for arrhythmic events. In others the ER substrate may potentially increase arrhythmic risk associated with underlying cardiac pathology. Very rarely, clinicians will encounter individuals in whom ER is a manifestation of a primary arrhythmogenic disorder.

Prevalence and Arrhythmic Risk

The first study to seriously question the convention that ER is a benign phenomenon compared 206 patients with idiopathic VF with 412 healthy subjects, and demonstrated that the ER pattern was more prevalent in subjects with idiopathic VF (31% versus 5%, P<0.01). ER was greater in magnitude in cases than controls. Patients with idiopathic VF who had ER were more likely to experience syncope or cardiac arrest during sleep. This defines the ER syndrome, where syncope or cardiac arrest is attributed to ER after systematic exclusion of other etiologies. The site of origin of ectopic activity that initiated VF was consistent with the location of the repolarization abnormality on the ECG, supporting the primary arrhythmogenic substrate of ER. During a follow-up of 61±50 months, implantable cardioverter-defibrillator monitoring showed a 2-fold higher incidence of recurrent VF in case subjects with ER than in those without. Another concurrent case–control study also demonstrated a higher prevalence of ER (42%) among survivors of idiopathic VF compared with controls (13%, P<0.01).

Subsequent large population studies reported the prevalence of ER to be between 6% and 13%. ER was associated with increased relative risk of cardiac and all cause mortality. Inferior J-point elevation ≥0.2 mV (Figure 1) was associated with further increased risk (relative risk, 3.15; P<0.01). It is noteworthy that J-point elevation of ≥0.2 mV is rare in the normal population (observed in only 0.3%). Even though ER is common, idiopathic VF is rare. The incidence of idiopathic VF in an individual aged <45 years is estimated to be 3:100,000. This risk increases to 11:100,000 when J-waves are present. Although ER increases the relative risk of arrhythmic events, the absolute risk remains very low. Therefore the incidental identification of ER should not be interpreted as a high-risk marker. Clinical decisions are driven by the presence and severity of symptoms and comorbidities (see below).

The prevalence of J-point elevation among young athletes is reported to be between 22% and 44%. One case–control study found that ER was 4 times more prevalent among athletes with a history of cardiac arrest than among healthy athletes. However, in this study the prevalence of ER in the control group of athletes was substantially lower at 7.9% in comparison with other studies. Young healthy athletes demonstrate an ST-segment pattern/morphology which does not appear to be associated with an increased arrhythmic risk. The presence of ER increases the probability of arrhythmic death from approximately 2 per million to 3.5 per million in this population of competitive athletes. Of note, the association of ER with arrhythmic risk is typically at rest or during sleep, and not during physical activity.

Mechanism of Early Repolarization and Idiopathic Ventricular Fibrillation

Osborn reported that dogs subjected to hypothermia developed spontaneous VF that was preceded by the development of J-waves. The J-wave was attributed to a current of injury (hence the term J) and later coined the term Osborn wave.
Figure 2 depicts a schematic of the action-potential (AP) ionic determinants underlying ER. The normal epicardial AP differs from the endocardial in having a prominent phase 1 notch or spike-and-dome morphology (Figure 2A). The difference is primarily attributable to a larger transient-outward K⁺-current (Ito) in the epicardium, which results in greater net repolarizing (outward) current flow during phase 1. In ER, a further enhancement in epicardial net outward current, results in an enhancement of the endocardial-to-epicardial AP differences that manifests as J-waves which reflects current flow from depolarized endocardium to substantially-repolarized epicardium during phase 1 (Figure 2B). Some clues to the underlying mechanisms are provided by gene mutations associated with ER, including genes encoding inward Na⁺ or Ca²⁺ or outward K⁺ currents. Although the functional properties of the mutations have not all been determined, it seems likely that ER results from a net increase in outward current caused by a loss of inward-channel function or a gain...
in outward-channel function. It remains unclear whether these mutations are more functionally important in the epicardium, or whether they simply exaggerate the magnitude of preexisting epicardial-endocardial differences by increasing overall net outward current flow.

Local discrepancies in the AP durations likely play a major role in arrhythmogenesis in the ER syndrome. Because the effect of early repolarization acceleration on the overall AP duration can vary from slight to major AP duration reductions over a relatively narrow range of current-values, it is possible for major differences in repolarization to exist over fairly short distances in the epicardium (Figure 3A). Precisely how the repolarization gradients in ER (Figure 3A) translate into arrhythmogenesis is presently unclear. One widely-held concept is that the AP dome of cells with relatively intact morphologies propagates to adjacent, rapidly repolarized cells to produce phase-2 reentry (Figure 3B). Another notion is that current flow from depolarized epicardial cells to adjacent repolarized cells causes the latter to depolarize and reach threshold, generating spontaneous focal activity that triggers local reentry (Figure 3C). In either case, irrespective of the initiating mechanism, local transmural reentry facilitated by steep AP duration gradients likely maintains the tachyarrhythmia.

An understanding of the underlying ionic mechanisms can help in comprehending the response to interventions. For example, adrenergic activation with isoproterenol is effective in suppressing ER arrhythmias, likely by enhancing inward currents (particularly L-type Ca\(^+\)+-current) that offset the net outward K\(^-\)-current excess. Quinidine (which suppresses outward currents, particularly I\(_{\text{to}}\)) is also effective. Vagal influences generally antagonize adrenergic effects and are probably responsible for events that are triggered by contexts like meals and during sleep.

**Genetic Basis**

In the absence of a common monogenic familial ER syndrome like that recognized for long QT syndrome, understanding the genetic basis of ER is in its infancy with only a handful of reports implicating single genes. The reported implicated gene mutations involve the \(KCNJ8\) gene (responsible for the ATP sensitive potassium channel Kir6.1 - I\(_{\text{KATP}}\) current), \(CACNA1C\), \(CACNB2\), \(CACNA2D1\) genes (responsible for the cardiac L-type calcium channel - I\(_{\text{Ca.L}}\) current), and the \(SCN5A\) gene (responsible for the sodium channel - I\(_{\text{Na}}\) current; Figure 2). All of these might enhance the underlying inward–outward current imbalance responsible for accelerated epicardial repolarization as illustrated in Figure 2B.

The first report of a patient with the \(KCNJ8\) S422L mutation was a case report of a 14-year-old female who experienced numerous episodes of idiopathic VF unresponsive to \(\beta\)-blockers, verapamil, and multiple antiarrhythmic medications. VF recurrences were associated with marked accentuation of ER. Subsequent functional studies demonstrated that compared with wild-type Kir6.1 channels, I\(_{\text{KATP}}\) is increased significantly in the S422L variant, which involves the substitution of nonpolar lysine for the highly-conserved polar amino-acid serine located in the intracellular C terminus. This gain of function variant appears to be pathogenic in ER and idiopathic VF but is not present in the majority of cases of ER syndrome.

**Figure 3.** Mechanism of arrhythmogenesis in early repolarization (ER). A, Schematically depicts the normal endocardial (Endo, brown) and epicardial (Epi\(_1\), red; Epi\(_2\), green) action potentials (APs). Small differences in net phase-1 repolarizing current/s can create major differences in Epi AP-duration as shown. B, Arrhythmogenesis by propagation of the AP-dome. Depolarizing-current flow from Epi\(_2\)-APs to Epi\(_1\)-APs causes propagation (solid purple arrow) of the dome to Epi\(_1\)-cells, activating Endo tissues (dotted purple arrow) and setting up transmural reentry (black arrows). C, An alternative notion for the mechanisms initiating arrhythmia in ER. Depolarizing current-flow from Epi\(_2\)-APs to Epi\(_1\)-APs (purple solid line) causes Epi\(_1\) to depolarize and reach threshold, causing focal activation of Epi\(_1\)-cells that spreads to Endo tissue and initiates transmural reentry.
Loss of function mutations of the cardiac L-type calcium channel have also been implicated (CACNA1C, CACNB2, and CACNA2D1 genes). This study reported that 4/24 (17%) of ER probands had mutations in highly conserved residues, suggesting pathophysiological significance. However, confirmation of the pathogenic nature of these variants awaits functional expression studies.

Nonsynonymous variants affecting highly conserved residues of the SCN5A gene have been identified in 3 unrelated patients with ER and idiopathic VF (resulting in A226D, L846R, and R367H). Expression studies demonstrated loss of function. The diagnosis of ER syndrome and the exclusion of Brugada syndrome in this study is disputed.

Rare variants involving the above genes have also been associated with Brugada syndrome. Additionally, some characteristics of ER resemble features of the Brugada ECG/syndrome (Figure 4), including J-waves, pause/bradycardia-dependent accentuation, the dynamic nature of the ECG pattern, local re-excitation via phase 2 re-entry, and suppression of the ECG features and arrhythmia with isoproterenol and quinidine. However, the Brugada ECG feature of provocation by sodium channel blocker is not observed in ER. There is also no recognized structural counterpart in ER like that recently described within the epicardium of the right ventricular outflow tract in malignant forms of Brugada syndrome. Some individuals with Brugada syndrome may also have ER (approximately 12%). Thus there appear to be basic pathophysiological differences that delineate these 2 as possibly related but distinct entities.

**Clinical Manifestations**

ER is most often an incidental ECG finding that may be present intermittently. Repeated measurements from 542 subjects with ER demonstrated the subsequent absence of ER in ~20%. Even in the cardiac arrest population, 58% of patients whose arrest was attributed to ER syndrome had ≥1 ECG that did not demonstrate the ER pattern during their hospitalization. There is no proven provocative test to identify concealed ER. Limited data report conflicting evidence for an association between syncope and ER. Syndrome may exceptionally rarely present as syncope. Such patients may also have a vagal prodrome. Tilt table testing may be of assistance to establish whether vagal stimulation is associated with VF or if high-risk ER features are provoked (ie, >2 mm J point elevation with horizontal/downsloping ST segment – detailed below). The utility of such an approach is not established. Furthermore, vasovagal syncope is relatively overwhelmingly more common in comparison to ER syndrome (Figure 5).

Based on arrhythmic risk associated with the spatial distribution of ER, a classification scheme has been proposed. Type 1 (ER in the lateral precordial leads) is common among healthy male athletes and is thought to be largely benign. Type 2 (ER in the inferior or inferolateral leads) is associated with a moderate level of risk. Type 3 (ER globally in the inferior, lateral, and right precordial leads) appears to be associated with the highest risk. Brugada syndrome is classified as type 4 (j-wave/point elevation in the right precordial leads). This classification system has been criticized because of the lack of a cogent common pathophysiological substrate across the 4 types. Additionally, the ST characteristics are incremental to the location with a clear higher risk associated with the horizontal or down-sloping pattern.

**Diagnosis of Ventricular Fibrillation Resulting From Early Repolarization Syndrome**

The mere presence of the ER pattern on ECG should not lead to a classification of ER syndrome in the absence of symptoms. ER syndrome causing VF may be diagnosed when other etiologies have been excluded and when J-point elevation is augmented immediately preceding VF. These patients may also display a high-risk ER ECG pattern (see below). ER syndrome causing VF is probable when other etiologies have been systematically excluded and a high-risk baseline ER pattern exists or increased parasympathetic tone provokes high-risk ER characteristics (eg, nocturnally) or cardiac arrest occurs during sleep/at rest.

Systematic assessment of survivors of sudden cardiac death without evidence of infarction or left ventricular dysfunction is reported to establish a causative diagnosis in ~50% of cases. Systematic evaluation includes cardiac monitoring, echocardiogram, evaluation of coronary arteries, signal-averaged ECG, exercise testing, cardiac MRI, and intravenous epinephrine and sodium channel blocker challenge. Targeted genetic testing should also be considered when a chanelopath phenotype is suggestive. A careful review of all available ECGs for evidence of ER is warranted, particularly around the time of the cardiac arrest (Figure 5).

The role for extensive investigations in assessing patients with chest pain, syncope, or palpitations need to be guided...
after thorough clinical assessment and independent of early repolarization in the absence of unexplained sudden cardiac death in the family. Given the rarity of idiopathic VF, ER identified in a patient with chest pain, palpitations, or syncope in the majority of the population would be an incidental finding. Although genotype data are emerging in case report fashion, current guidelines do not recommend genetic testing. Even when a familial malignant phenotype is present, genetic testing has not been of assistance.

**Prognostic Variables of the Early Repolarization Pattern**

A number of electrocardiographic and demographic variables have been suggested to modify the arrhythmic risk in ER. Despite the increased relative risk of arrhythmia associated with some of the presented variables, the subsequent increased absolute risk in the general population is still small and the exceedingly low incidence of idiopathic VF renders these variables alone devoid of meaningful clinical utility. There is no risk stratification strategy for asymptomatic patients with ER that would allow for the identification of higher risk individuals with the ER pattern who might be candidates for treatment. Autonomic tone also modulates this risk. Some reports suggest that ER should be viewed as an adjunctive prognostic variable in the presence of other cardiac pathologies (see below).

**Electrocardiographic Markers**

In addition to the inferior location and greater amplitude of ER, a horizontal or down-sloping ST-segment after ER portends a higher risk in both the general population and in patients with idiopathic VF. The ST-segment pattern is defined as ascending when there is >0.1 mV elevation of the ST-segment within 100 ms after the J-point and the ST-segment merges gradually with the T wave or as horizontal/descending when the ST-segment elevation is ≤0.1 mV within 100 ms after the J-point and continues as a flat ST-segment until the onset of the T wave. The highest risk occurs with the combination of ER of high amplitude (≥0.2 mV) in the inferior limb leads and a horizontal or descending ST-segment. The prevalence of the horizontal/descending ST-segment in controls (∼3%) compared with the incidence of idiopathic VF renders this variable alone devoid of meaningful test accuracy. Additionally, some individuals at risk demonstrate the up-sloping ST-segment pattern, compromising the accuracy of this marker. The incidence of idiopathic VF attributable to ER with a horizontal ST-segment is estimated to be 0.03% – 100-fold less than the prevalence. Thus the absolute risk remains extraordinarily low, unless symptoms suggest pathogenicity and ER syndrome is diagnosed. ECG features alone lack sensitivity, specificity, and predictive accuracy to have clinical utility at present.

Although both slurring and notching type ER are observed and may exist in the same patient, the prognostic value of one compared with the other has not been clearly established (Figure 1). Sex, Family History, and Ethnicity

Sex-stratified analysis has revealed an association of ER with cardiac mortality in males. A population-based case–cohort study of individuals of central European descent demonstrated males with ER in the inferior leads had a hazard ratio (HR) of 4.32 (P<0.01) compared with the risk in women for cardiac mortality. In one case–control study of patients with VF and ER, a positive family history of sudden death was not
significantly more common than in those without ER (16% versus 9%; \( P=0.17 \)). However, another study reported a higher prevalence (23%) of ER in family members of sudden arrhythmic death syndrome probands compared with matched unrelated healthy individuals from the general population (11% ER). Further studies are required to illuminate this element of ER.

Although ER is more common in individuals of African descent, there is no clear attributable risk associated with ethnicity and individuals of African descent are not over-represented in idiopathic VF cohorts. In a large population study, lateral or inferior ER in non-African descent individuals was independently associated with cardiovascular death (HR, 1.6; \( P=0.02 \)), whereas it was not associated with cardiovascular death in individuals of African descent (HR, 0.75; \( P=0.50 \)). This study also demonstrated that ER was more common in individuals of African descent (HR, 3.1; \( P<0.01 \)). The hazard of the inferior-only ER could not be estimated because there were no individuals of African descent deaths in this group. In contrast, in the non-African descent cohort, there was a statistically significant association between cardiovascular death and the inferior ER pattern (HR, 2.13; \( P<0.01 \)).

**Autonomic Tone**

Bradygrip-dependent augmentation of ER is observed in both VF cases and healthy controls (Figure 7). However, augmentation of the J-wave and the slope of the regression line (J-point elevation against heart rate) is greater in cases with VF compared with controls (\( P<0.01 \)). Tachycardia tends to normalize ER. VF often occurs at night when parasympathetic tone is augmented (9 of 11 episodes occurred between 18:00 and 6:00 hours in this study). Additionally, the amplitude of ER that may be unnoticeable during daytime sinus rates in patients with idiopathic VF becomes progressively augmented immediately before VF with bradycardia and an increase in vagal tone. Accentuation of ER resulting from compensatory pauses after extrasystoles along with the resultant short-long-short sequences may also contribute to VF.

In a preliminary report involving 3 French families with an apparent malignant familial ER pattern, the Valsalva maneuver was utilized to reveal concealed ER. However, the relationship between ER manifest by Valsalva and prognosis is not known.

**Early Repolarization Modifying Risk of Underlying Cardiac Pathology**

Although rare as a primary arrhythmic disorder, ER may be a much more common modifier in the context of structural heart disease and primary electric disorders. Patients with J-waves appear to be at an increased risk of ischemic VF in the event of a myocardial infarction/ischemia. Abbreviation of the epicardial action potential occurs during acute myocardial ischemia. Thus, patients with a gain of function variant/polymorphism leading to an increase in \( I_{KATP} \) may be expected to be more sensitive to acute ischemia-related arrhythmias by potentially accentuating the action potential gradient/heterogeneity. ER in the inferior leads has also been demonstrated to be associated with increased risk of life-threatening ventricular arrhythmias in patients with chronic coronary artery disease, after adjustment for left ventricular ejection fraction. ER in the inferior leads is also reported to predict higher risk of sudden death in nonischemic cardiomyopathy patients.

Limited evidence suggests that the coexistence of ER with a Brugada pattern ECG is an incremental predictor of arrhythmic events and a more severe phenotype. ER has also been demonstrated to be more prevalent in patients with arrhythmogenic right ventricular cardiomyopathy (31%) compared with in the general population, though this retrospective analysis identified no correlation with regard to cardiac arrest, syncope, or arrhythmic events. A high prevalence of ER in patients with short QT syndrome has been reported (65%). In multivariate models, ER was associated with arrhythmic events. Another study reported that among patients with idiopathic VF and ER, the QT interval was shorter compared with those with idiopathic VF but without ER, postulating an association between ER and QT interval shortening. Given the prevalence of the ER pattern, ER may be viewed as one of many arrhythmogenic factors that is rarely solely responsible for clinical events.

**Therapies for Early Repolarization Syndrome**

**Drug Therapy**

A multicentre observational cohort study has demonstrated that isoproterenol in acute cases and quinidine in chronic...
cases is effective for suppression of VF related to ER syndrome. In this study (n=122, 90 males, mean age 37±12 years), patients with ER in the inferolateral leads with >3 episodes of idiopathic VF (including those with electric storms) had an antiarrhythmic drug prescribed by the treating physicians. Follow-up data were obtained for all patients using an implantable cardioverter-defibrillator. A successful oral antiarrhythmic drug was defined as elimination of all recurrences of VF with a minimal follow-up period of 12 months. Isoproterenol infusion immediately suppressed electric storms in 7 of 7 patients. Quinidine decreased recurrent VF from an average of 33 episodes to none over >2 years of follow-up. In addition, quinidine restored a normal ECG. Although this was a case series with empirical drug therapy, there was no suggestion of benefit from a number of other antiarrhythmic drugs (ie, β-blockers, verapamil, mexiletine, amiodarone, and class 1C agents; Figure 8).

Implantable Cardioverter-Defibrillator

An implantable cardioverter-defibrillator is indicated after cardiac arrest. There is no current risk stratification strategy for asymptomatic patients with ER in the general population and within families with ER. Syncope attributed to ER appears clinically uncommon and warrants an aggressive attempt to verify that syncope is related to arrhythmia (Figure 5). Implantable cardioverter-defibrillator therapy is highly effective in terminating ventricular arrhythmias in nearly all cases.

Inheritance of Early Repolarization and Family Screening

ER demonstrates heritability in the general population and within families. In 2 large population-based cohorts, siblings of individuals with ER had an increased unadjusted odds of ER (odds ratio, 2.22; P=0.047). A study involving 505 Caucasian nuclear families reported that individuals with ≥1 parent with ER had a 2.5-fold increased incidence of demonstrating the ER pattern. Familial transmission appeared more frequent when the mother was affected (3.8-fold versus 1.8-fold, P=0.1). Potential explanations for unequal transmission include transmission through mitochondrial DNA, effects mediated via sex chromosomes, and parental imprinting of autosomal genes. Heritability was also higher when ER was in the inferior leads or had a notched morphology. Another report of familial ER has suggested an autosomal dominant inheritance pattern with incomplete penetrance.
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Although the majority of individuals with an ER pattern in the general population have a benign course and evidence for heritability and familial ER is mounting, familial malignant forms of ER syndrome are exceptionally rare. Malignant familial forms of ER have been reported to be transmitted as an autosomal dominant trait in 3 large French families.31,32 These families represent a unique cohort, and findings should not be extrapolated to the general population. It must be noted that population studies argue for ER being a risk modifier, and the rare malignant familial ER syndrome suggests that ER is a primary arrhythmogenic disorder with a genetic basis. Unlike these families with a malignant form of familial ER syndrome, the majority of familial ER per se may not necessarily portend a substantially increased risk compared with the general population. This remains an active area of research.

It is currently not possible to identify asymptomatic individual patients/families with ER at increased risk of sudden death with any clinically useful degree of accuracy. There is also no evidence to suggest that the presence of ER without symptoms should alter management in an asymptomatic patient/family. Furthermore there is currently no recommendation to screen the families in individuals with asymptomatic ER. It is also not possible to identify asymptomatic individuals with a primary arrhythmogenic disorder attributable to ER. Patients with ER should have underlying cardiovascular diseases aggressively managed, given that there is no ER-associated proven risk-modifying intervention. In symptomatic patients and in their families the Valsalva maneuver may assist in identifying concealed ER cases.

**Conclusion**

The ER syndrome as a primary arrhythmogenic disorder causing VF is very rare. We lack clinically useful risk stratifying tools or an established provocative test for identifying malignant ER, despite some ECG features that are associated with a higher risk. As such, patients with asymptomatic ER and no family history of malignant ER should be reassured that their ECG is a normal variant, until such time as better tools enable risk stratification. All patients with ER should continue to have modifiable cardiac risk factors addressed.

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None.

**References**


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