Early Repolarization Syndrome - An Overview and Recent Expert Consensus Statement by Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA), and the Asia Pacific Heart Rhythm Society (APHRS)

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Early repolarization (ER) pattern in ECG has been considered as benign finding over last 60 years. It is common ECG pattern characterized by J-point and ST segment elevation in 2 or more contiguous leads. This was first described as early repolarization by Grant et al in 1951 (1) was considered as benign. Osborne demonstrated that in dogs with hypothermia leads to the development of J waves followed by spontaneous ventricular fibrillation (VF) (2). ER pattern in particularly anterior precordial leads is usually considered benign but recently this pattern in the inferior and/or lateral leads has been reported as a risk to idiopathic VF in case-control studies and now characterised as Early repolarization (ER) syndrome (3-9).

The incidence of ER pattern ECG in inferior and lateral leads has reported between 1-13% in different studies with higher incidence in more recent studies (4-12). It is more common in physically active young individuals, athletes, Afro-crabbian, South East Asians and young males (12-14). Other factors which are found to be associated with ER pattern ECG are high vagal tone, hypothermia, hypercalcemia, bradycardia, prolonged QRS duration, short QT interval, and left ventricular hypertrophy assessed by the Sokolow-Lyon index (13). Although Brugada syndrome has typical ECG changes in anterior precordial leads, there have been about 11-15% cases of Brugada syndrome reported with ER changes in inferolateral leads similar to ER syndrome. (15)

J point elevation and ST segment elevation either notched or slurred are the key features of ER syndrome (Figure 1). The magnitude of the J-point elevation may have prognostic significance (10). Furthermore, J point elevation in idiopathic VF patients is of greater amplitude and ECG lead distribution compared to those with an established cause of cardiac arrest [8]. VF risk increases by 3 times in ER pattern ECG individuals, but the overall risk remains low due the rarity of VF in the general population. Transient changes in the presence and amplitude of J-point elevation poses a higher risk for VF (3). A horizontal or descending ST-segment following J-point elevation is associated with a worse prognosis in the general population (16).

Figure 1 : Standard 12-lead ECG of 29 years old male, survivor of Out of Hospital VF arrest showing ER pattern in inferior and lateral leads(1mm J point elevation in lead I, II, V5 & V6). No other cause of VF arrest identified and patient had ICD implanted before discharge from hospital.
The most commonly explained hypothesis is development of voltage gradient during repolarization across the ventricular wall generated by Ito channels heterogeneity. ST segment corresponds temporally to plateau phase, the normal ECG ST segment aspect indicating the absence of a significant voltage gradient during ventricular repolarization (17). It is proposed that in ER, compared to ventricular endocardial cells, ventricular epicardial cells are richly innervated with Ito channels which specific outward potassium currents channels. This generates repolarization in epicardial cells earlier than in endocardial cells, creating transmural gradients. These gradients between epicardial and endocardial sites results as J point elevation on ECG, which has become a hallmark for the classification of ER syndrome. Another possible explanation is localized depolarization abnormalities with repolarization anomalies as happens in type 1 Brugada syndrome (2, 18, 19, 20). Nevertheless both mechanisms could be a cause for ER syndrome, but further research is required based on molecular techniques with correlation with imaging, voltage mapping, genetic studies, and autopsy studies of the ventricular area corresponding to the electrocardiographic changes.

There has been reported familial association in ER syndrome and idiopathic VF with one of studies suggesting 23% of relatives of sudden cardiac death (SCD) individuals with J-point elevation in the inferolateral leads (21). Autosomal dominant inheritance pattern with incomplete penetrance is suggested in ER syndrome (13, 22). Mutation in KCNJ8 (ATP-sensitive potassium channel) (23, 24) L-type calcium channel genes, (25) as well as loss-of-function mutations in SCN5A (26) have also been associated with idiopathic VF with ER syndrome. There is also a mutation in KCND3 genes reported which is outward potassium channel Ito (Kv4.3) coding gene (27).Further conclusive studies are still required to evaluation of inheritance pattern and genetic associations.

Clinical presentation of ER syndrome is often unexpected malignant arrhythmias as first presentation (3). Ventricular ectopics with a positive QRS morphologic pattern in leads V1 to V2, indicating origin from the left ventricle and short-long-short sequence interval initiating VF (Figure 2). This is usually preceded by increase in the amplitude of early repolarization pattern (7).Additional triggers, such as acute ischemic events also precipitate VF with pre-existing early repolarization (10, 11). Other causes of sudden cardiac death should be excluded with appropriate investigations before considering diagnosis of ER syndrome. Primary inherited arrhythmia syndromes such as short QT syndrome, and Brugada syndrome, long QT syndrome should also be excluded in survivors of cardiac arrest from VF or polymorphic ventricular tachycardia. (8) So far there is no recommended method or test to unmask ER pattern however ECG monitoring with 12 lead Holter is useful to identify ER pattern during bradycardia.

![Figure 2: EGM from ICD of patient mentioned in figure 1 showing ventricular ectopic initiating VF](image-url)
There are no formal guidelines for diagnosis and management of ER syndrome however there is recent HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes have included ER syndrome. The document recommends following (28):

- ER syndrome is diagnosed by the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/ Polymorphic VT.
- ER syndrome can be diagnosed in a SCD victim with a negative autopsy and medical chart review with a previous ECG demonstrating J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG.
- ER pattern can be diagnosed by the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG.

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<th>Class</th>
<th>Recommendations</th>
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<td>Class I</td>
<td>ICD implantation is recommended in patients with a diagnosis of ER syndrome who have survived a cardiac arrest.</td>
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| Class IIa | Isoproterenol infusion can be useful in suppressing electrical storms in patients with a diagnosis of ER syndrome.  
Quinidine in addition to an ICD can be useful for secondary prevention of VF in patients with a diagnosis of ER syndrome. |
| Class IIb | ICD implantation may be considered in symptomatic family members of ER syndrome patients with a history of syncope in the presence of ST segment elevation >1mm in 2 or more inferior or lateral leads.  
ICD implantation may be considered in asymptomatic individuals who demonstrate a high-risk ER ECG pattern (high J-wave amplitude, horizontal/ descending ST-segment) in the presence of a strong family history of juvenile unexplained sudden death with or without a pathogenic mutation. |
| Class III | ICD implantation is not recommended asymptomatic patients with an isolated ER ECG pattern. |

The document also supports the acute use of isoproterenol in electrical storm for suppression of recurrent VF, and quinidine for long-term suppression. The recommended initial dose of isoproterenol at 1.0 μg/minute, targeting a 20% increase in heart rate or an absolute heart rate > 90 bpm, titrated to haemodynamic response and suppression of recurrent ventricular arrhythmias (28).

The document does not provide guidance regarding further management of asymptomatic individuals with ER pattern ECG particularly with regards to their follow up and provocation testing as no established test available. In addition there are no recommendations given to screen the families of individuals with asymptomatic ER pattern. However familial investigation might be facilitated by using the valsalva manoeuvre to reveal the electrocardiographic pattern in family members but this needs further assessment for validation (29). The definition of strong family history still requires further elaboration.

Overall ER ECG pattern is now identified as recognised risk for cardiac arrest due to VF and polymorphic VT but risk of sudden cardiac death from ER syndrome in general population remains low. This should be considered in survivor of VF cardiac arrest if ECG changes are present and no other cause of arrest identified. Document is first of its kind and will be very useful to clinicians in diagnosis and management of ER syndrome however further research is required in understanding pathophysiology, genetics, family screening and risk stratification.

References


