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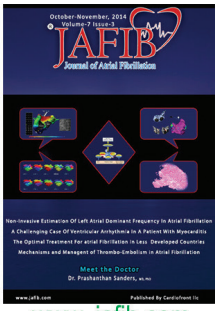

Evaluation Of Patients With Early Repolarization Syndrome

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Abstract

In recent years, the early repolarization pattern has emerged as a risk factor for malignant ventricular arrhythmias and sudden cardiac death. The identification of the subset of patients who are at high risk of sudden death represents a significant challenge to the clinician. Multiple clinical and ECG features have been associated with an increased risk of sudden death, however the majority of risk factors confer a small increase in absolute risk. The present article reviews current evidence and potential management strategies in patients with early repolarization.

Introduction

The early repolarization pattern on the surface electrocardiogram (ECG) is a relatively common finding. The prevalence of early repolarizationin the general populations has been reported to be as high as 13%, although estimates have varied significantly between studies.[1-4] A higher prevalence has been reported in young males and individuals of African descent. The characteristic feature of the early repolarization pattern is elevation of the J point, which is the junction between the QRS complex and the ST segment.[5] J point elevation may manifest as slurring or notching of the terminal portion of the QRS complex.

The pattern of early repolarization described above has long been regarded as a benign ECG variant.[6] However in recent years, compelling evidence has emerged from a number of studies to suggest that early repolarization is associated with an increased risk of malignant ventricular arrhythmias and sudden cardiac death (Figure 1).In 2007, a seminal study from Haissaguerre et al,[7] which involved 206 patients with idiopathic ventricular fibrillation (VF) and 412 control subjects, demonstrated a significantly higher prevalence of early repolarization in the VF group (31% in VF patients as compared to 5% in control patients).Two subsequent studies provided corroborating evidence linking early repolarization and arrhythmic sudden death. Rosso et al reported an approximately three-fold increase in the risk of sudden death associated with early repolarization (from 3.4/100,000 to 11/100,000).[8] In a large population-based study with follow-up extending beyond 30 years, Tikkanen et al also reported that early repolarization is associated with a significantly increased risk of sudden cardiac death.

It is important to note that the definition of early repolarization has varied between population-based studies that have investigated the prognosis of this ECG variant. For instance, in a study from the 1960s, Wasserburger et al described early repolarization as an elevation of the ST segment at the J point of between 1 and 4 mm with an associated ST segment concavity in the mid and left precordial leads.[9] Subsequently, in the 1970s, Kambara and colleagues described it as an upward concave RS-T segment elevation, primarily in the precordial leads. They also described an associated slurring of the downstroke of the R wave, the presence of distinct J points, or both.[10] Both studies described early repolarization as a benign ECG variant. In contrast, the studies reporting an association between early repolarization and sudden death refer to a specific distinct entity. In these studies, early repolarization is defined as a pattern of J point elevation of >1 mm in 2 contiguous inferior and/or lateral leads[7] (Figure 1). The variations in the definition of early repolarization may account for some of the discrepancies in sudden death risk between studies.

While the aforementioned studies have reported an association between early repolarization and sudden death, it is important to emphasize that the prevalence of sudden death amongst patients with this ECG pattern is very low. The identification of the subset of patients who are at high risk of sudden death represents a significant challenge. The present article reviews current evidence and potential management strategies in patients with early repolarization.

Genetic Basis Of Early Repolarization Syndrome

Multiple studies have previously demonstrated that ERS is a heritable disease.[7,11,12] The genetic substrate underlying ERS is currently poorly defined. While single gene mutations have been identified in isolated cases, a large proportion of the observed heritability remains unaccounted for.The first mutation underlying ERS was identified in a young patient from the original series from Haissaguerre et al. The mutation was located in a conserved residue

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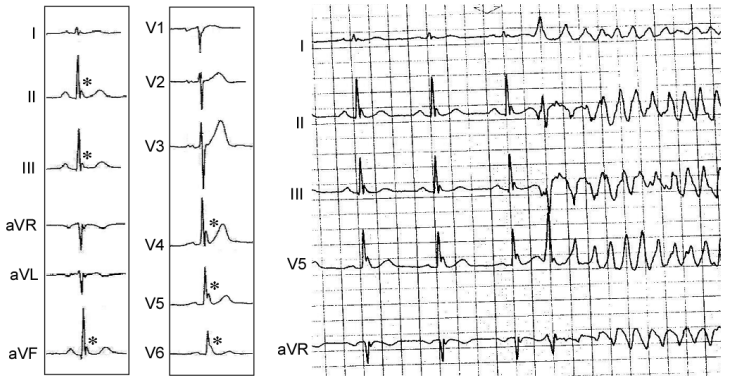

Figure 1: Early repolarization and induction of VF

Surface ECG of patient with early repolarization demonstrating notching in the inferior and lateral leads 24. Right image demonstrates a rhythm strip of the same patient with spontaneous induction of VF by a premature ventricular extrastimulus

in the KCNJ8 gene (S422L), which encodes an inwardly rectifying potassium channel. However the mutation was not functionally characterized.[13] In a subsequent study, Medeiros-Domingo et al who performed candidate-gene screening in 14 ERS patients and identified the mutation in one patient. The mutation was associated with a gain-of-function effect with an augmented IK-ATP current.[14] Further evidence implicating the KCNJ8-S422L variant came from a study by Barajas-Martinez et al. They also used a candidate-gene approach and identified a single ER patient with a KCNJ8- S422L mutation after screening 204 patients with a J wave syndrome.[15] They also reported a gain-of-function effect of the mutation.

Burashnikov et al performed candidate-gene screening in 24 ERS patients for mutations in genes encoding calcium channel subunits.[16] Four mutation carriers were identified; one mutation carrier had a CACNA1C mutation, two patients had CACNB2 mutations and one patient had a CACNA2D1 mutation. While the mutations were highly conserved, suggesting a potential pathogenic effect, they were not functionally validated. Watanabe et al performed candidate-gene screening for sodium channel (SCN5A) mutations in a cohort of 50 patients with ERS and ventricular fibrillation.[17] SCN5A mutations in highly conserved residues (A226D, L846R, and R367H) were identified in three unrelated ERS patients. Functional analysis of the mutations revealed loss-of-function type modulation with the mutant channels failing to generate an INa current.In a more recent study, Hu et al screened a cohort of 150 ERS and Brugada syndrome patients for mutations in ABCC9, which encodes the ATP-binding cassette transporter of IK-ATP (SUR2A).[18] Four ERS patients from the cohort were demonstrated to harbor a V734I-ABCC9 mutation. Functional analysis of the variant demonstrated a gain-of-function effect when co-expressed with the IK-ATP channel. The mutations identified to date have been summarized in Table 2.

Pathophysiological Mechanisms Underlying ERS

The first detailed insights into the mechanisms underlying ER came from Yan and Antzelevitch in 1996.[19] Using a wedge preparation from a canine ventricle they reported that the J wave is a manifestation of a transmural gradient of the action potential (AP) notch. Multiple ionic currents have been proposed to underlie the transmural dispersion of the AP notch including Ito, ICaL, IK-ATP and INa. Attenuation of the Ito current during administration the drug 4-AP significantly attenuates J wave amplitude.[19] Drugs that augment the IK-ATP current have been demonstrated to increase transmural dispersion of repolarization.[20] Further, as discussed above, mutations in genes encoding the IK-ATP channel have been reported to underlie ER.[13-15] Genetic studies have also identified mutations in genes encoding the ICaL, and INa currents, implying that these currents are potentially important mediators of altered repolarization in ER.[16, 17]

The predilection of the ER pattern for the inferior and lateral ECG leads is not fully understood. It has been speculated that the ER pattern manifests in the leads associated with the left ventricle because of the transmural orientation of the mean vector axis across the left ventricle and the septum.[19] In terms of the mechanism of arrhythmia in ER, an augmented transmural repolarization gradient is predicted to precipitate phase 2 reentry and premature ventricular ectopics. In turn, interaction of the premature ventricular ectopics with a susceptible ventricular substrate is predicted to cause transmural re-entry.[21, 22]

Risk Stratification Of Patients With Early Repolarization

A number of risk factors have been demonstrated to confer an increased risk of arrhythmic sudden death in patients with early repolarization.The following section outlines the evidence linking these risk factors with sudden death.

Clinical History

Haissaguerreet al demonstrated that 39% of early repolarization syndrome (ERS) patients with cardiac arrest have a previous history of syncope. Further they reported that a history of aborted sudden death is associated with a 43% recurrence rate of ventricular arrhythmia.[7] In a subsequent study, Abe et al reported that 18.5% of patients with ERS had a previous history of syncope as opposed to only 2% in healthy controls.[23] More recently, Le Bloa et al reported that in 37 ERS patients with syncope, three patients had polymorphic VT during subsequent rhythm monitoring with an implantable loop recorder device.[24] Overall, these findings indicate that a history of unexplained syncope represents a potentially important risk factor for sudden death in ERS patients. Of note however, Bartczak and colleagues recently reported that amongst patients with syncope who are referred for tilt testing for suspected reflex syncope, the early repolarization variant was present in 31% of cases. These findings reflect the complexity of assessing ERS patients with syncope.[25]

The influence of a family history of sudden death on arrhythmic risk in ERS patients is presently unclear. Haissaguerre et al

Table 1: HRS/EHRA/APHRS guidelines for management of patients with early repolarization

Class of evidence	Treatment
Class I	•ICD implantation is recommended in patients with a diagnosis of ER syndrome who have survived a cardiac arrest
Class IIa	•Isoproterenolinfusion can beuseful 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 a definitive ER pattern on the ECG •ICD implantation may beconsidered in asymptomatic individuals who demonstrated 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 in asymptomatic patients with an isolated ER ECG pattern

Abbreviations: ER, early repolarization; ECG, electrocardiogram; ICD, implantable cardiac defibrillator.

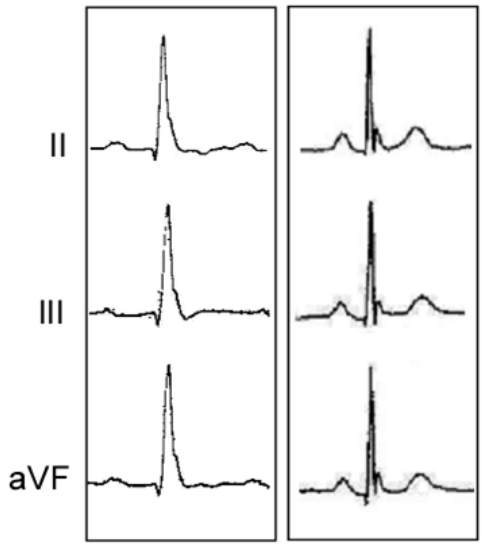

Figure 2: **ECG examples of slur and notch early repolarization patterns**

The panel on the left demonstrates typical slur pattern with. The panel on the right demonstrates a notch pattern.

demonstrated that 14% of idiopathic VF patients with the ERS pattern have a family history of sudden death.[7] However in other studies, the reported familial aggregation is lower.[8] In a subset of patients with early repolarization, the trait has been observed to transmit with a monogenic pattern of inheritance. Gourraud et al identified four pedigrees with an autosomal dominant pattern of inheritance of ERS with a high incidence of sudden death amongst affected individuals.[12] In a study involving 363 relatives from 144 pedigrees, Nunn et al reported that the ERS pattern is more prevalent in relatives of sudden arrhythmic death cases as compared to controls (23% vs. 11%).[11] Overall, these findings suggest that a family history could potentially predict arrhythmic risk. However, further research is necessary to determine the influence of family history on sudden death risk.

ECG Features

Multiple ECG characteristics have been demonstrated to confer an increased risk of sudden death in ERS patients. Individual ECG risk factors are discussed in more detail below.

Inferior vs. Lateral J Wave Distribution

In a study involving a large cohort of ERS patients, Tikkanen et al demonstrated that inferior J point elevation is associated with a higher risk of sudden death (relative risk, 1.2843; P=0.03).[3] The specific risk of arrhythmic death was more elevated (relative risk, 1.43; P=0.03). Of note, the evidence linking lateral early repolarization with arrhythmic death was less robust. In a more recent study, Derval et al demonstrated that in patients with idiopathic VF, the J point elevation was more widespread as compared to that observed in patients with an established underlying cause of sudden death(4.3 ± 1.3 leads vs. 2.8 ± 0.8 leads; p=0.01).[26]

J Wave Amplitude

Tikkanen et al also reported that in a subset of patients with more pronounced J point elevation (>0.2 mV) in the inferior leads, the risk of sudden death was markedly elevated (relative risk, 2.983.94; P<0.001).[3] The relative risk of arrhythmic death was (3.94; P<0.001). Derval et al also demonstrated a higher J wave amplitude in idiopathic VF patients as compared to that observed in patients with an established underlying cause of sudden death (0.25 ± 0.11 mV vs. 0.13 ± 0.05 mV, p = 0.02).Further evidence linking augmented J point elevation came from Haissaguerre et al who demonstrated that in a significant proportion of ERS patients with VF, J point elevation is more pronounced immediately preceding episodes of ventricular arrhythmia.[7]

Horizontal vs. Ascending ST Segment

A horizontal or descending ST segment has been reported to be associated with a higher risk of sudden death as compared to a rapidly ascending ST segment. Tikkanen et al reported that subjects with early repolarization≥0.1 mV and a horizontal or descending ST segment had a relative risk of arrhythmic sudden death of 1.43. Amongst patients with inferior ER and a higher J wave amplitude (>0.2mV), the horizontal variant was associated with a relative risk of 3.14.[27] More pronounced J wave elevation was not demonstrated to alter risk in patients with ascending ST segment variant. In a smaller cohort of patients, Rosso et al provided further corroborating evidence linking the horizontal ST segment variant with increased risk of sudden death. They demonstrated that a horizontal ST segment has an odds ratio of sudden death of 13.8.[28] Finally, Rollin et al demonstrated that a horizontal ST segment is associated with an increased mortality HR of 8.75 (95% CI, 3.48 to 22.0).[29]

QRS Notching vs. Slurring

Notching of the terminal portion of the QRS has been reported to be more prevalent in patients with idiopathic VF. Merchant et al reported that QRS notching was more prevalent in the lateral leads in patients with ERS and VF as compared to controls (leads V4 (44% vs 5%, p = 0.001) and V5 (44% vs 8%, p = 0.006).Of note however, numbers of patients with ERS and VF in the study were small.[30] An example of an ECG illustrating notching is included in Figure 1.

Overall, the above findings suggest that the presence of inferior J point elevation of high amplitude with a horizontal down sloping pattern is the most ´malignant´ ECG in ERS patients. The evidence

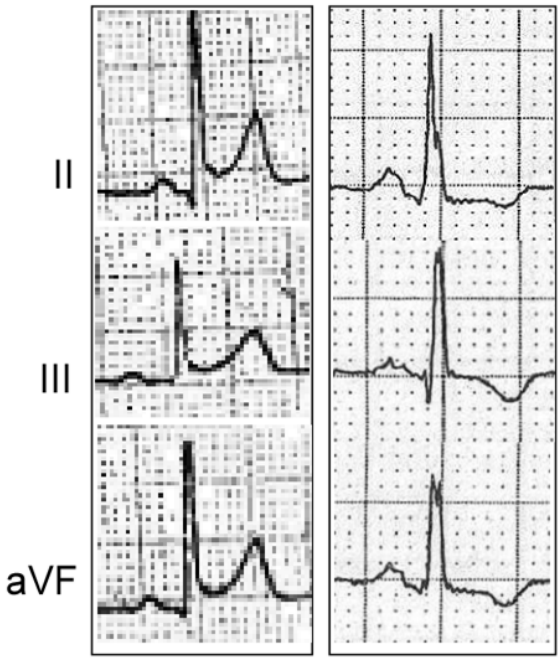

Figure 3: **ECG examples of horizontal and descending early repolarization patterns.**

The panel on the left demonstrates a typical horizontal ST segment. The panel on the right demonstrates an ascending ST segment pattern.

Table 2: Genetic mutations identified by candidate-gene studies in ERS

Gene	Variants	Gene product	Functional effect	No. patients	Comment	Ref
KCNJ8	S422L	Inwardly rectifying potassium channel	Gain-of-function effect with increased augmented IK-ATP current	221	3 unrelated ERS patients with same mutation identified in 3 different studies	13-15
CACNA1C	p.E850 del	L type calcium channel, alpha subunit	No functional analysis	24		16
CACNB2	S160T, R571C	L type calcium channel, beta 2 subunit	No functional analysis	24	2 unrelated ERS patients with different mutations	16
CACNA2D1	S956T	L type calcium channel, alpha 2/delta subunit 1	No functional analysis	24		16
SCN5A	A226D, L846R, R367H	Nav1.5 sodium channel alpha subunit	Loss-of-function effect with loss of INa current	50	3 unrelated ERS patients with different mutations	17
ABCC9	V734I	ATP-binding cassette transporter of IK-ATP (SUR2A)	Gain-of-function effect with augmented IK-ATP channel	150 (BrS and ERS)	4 unrelated ERS patients with same mutation	18

implicating this ECG pattern as a risk marker is less compelling.

Provocative Testing

Rotenet al investigated the effect of provocative testing with ajmaline in 31 patients with early repolarization and compared the response with 21 Brugada syndrome patients and 22 control patients. Interesting, in contrast to the observed response in Brugada syndrome patients, the degree of J point elevation was attenuated in early repolarization patients.[31] Corroborating evidence came from a study by Bastiaenenet al who demonstrated that ajmaline provocation results in diminished J point elevation, particularly in patients with lateral J point elevation and rapidly ascending ST segments.[32] Overall these findings indicate that sodium channel blockade does not play a role in risk stratification of early repolarization. Of note, in addition to sodium channel blockers, other pharmacological agents such as verapamil, epinephrine, ATP, cibenzoline, andpilsicainide have also have also been reported to have a negligible effect on the degree of J point elevation in ERS patients.[33]

Management Of ERS Patients

The early repolarization pattern is common in the general population and in the vast majority of patients, is associated with a benign prognosis. In asymptomatic patients with the early repolarization pattern, there is no indication for specific treatment.[34] In the small subset of patients who are deemed to be at high-risk, implantation of a cardiac defibrillator and/or pharmacological therapy maybe indicated.

Implantation of a cardiac defibrillator (ICD) is indicated in patients with early repolarization syndrome and previous aborted sudden death due to ventricular arrhythmia.[34] Patients with early repolarization and syncope on the other hand may represent a challenge. Extensive investigations to determine the cause of syncope are recommended. Patients with unexplained syncope may warrant close follow-up or rarely, ICD implantation. The presence of unexplainedsyncope with additional risk factors such as a ´malignant´ ECG with pronounced and wide spread J point elevation,a horizontal descending ST-segment,and a strong family history of sudden death at a young age may warrant ICD implantation.[34] Of note however, the evidence to support this strategy is less robust.

Pharmacological therapy maybe considered in early repolarization patients with an ICD and recurrent defibrillator shocks. A number of antiarrhythmics have been tried in this context. In a study by Haissaguerreet al involving 33 patients with early repolarization and recurrent ICD shocks intravenous isoproterenol was demonstrated to be effective in suppressing VF in the acute setting. Further, maintenance therapy with quinidine was demonstrated to suppress VF during longer-term follow-up.[33] By contrast, beta blockers, class 1C antiarrhythmics, and verapamil were demonstrated to be ineffective.The current recommendations for management of early repolarization patients from the HRS/EHRA/APHRS are summarized in Table 1.

Conclusion:

While the vast majority of patients with early repolarization on the ECG will have a benign course, in a small but important subset this ECG pattern is associated with potentially catastrophic consequences. The major current challenge for the clinician is identifying these patients prior to the first episode of VF. Multiple ECG features have been reported to confer an increased risk of sudden death. It is important to note however that the majority of these risk factors are associated with modest increases in absolute risk and are therefore of limited clinical utility in isolation.[35] Further research is currently necessary to develop more robust risk-stratification algorithms.

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