

Electrocardiographic Early Repolarization A Scientific Statement From the American Heart Association

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The early repolarization (ER) pattern (ERP), initially described as elevation of the ST segment of ≥ 1 leads on the 12-lead ECG, has long been considered a benign phenomenon. However, more recent studies have demonstrated positive, negative, and neutral associations between an ERP and various end points, including all-cause, cardiac, and arrhythmic mortality. These recent studies have used more complex or heterogeneous definitions of ER, including J-wave or J-point elevation and QRS complex notching or slurring, with or without concomitant ST-segment elevation. Other studies have identified an increased prevalence of ERP in survivors of spontaneous ventricular fibrillation (VF) or cardiac arrest.

As a result, considerable confusion remains concerning the definition of ERP, its prognostic significance, and whether additional evaluation or treatment is warranted. These issues are especially important because the prevalence of ERP may be as high as 10% in the general population and even higher in some healthy subgroups. The writing group performed a comprehensive literature search and developed recommendations based on the results of the current literature. We searched MEDLINE (via PubMed), EMBASE, and the Cochrane Library to identify relevant primary scientific articles, guideline statements, and review articles in the literature. Search terms included, but were not limited to, early repolarization, J-point elevation, J wave, Haissaguerre syndrome, sudden cardiac death, idiopathic ventricular fibrillation, ventricular fibrillation, cardiac repolarization reserve, sudden unexplained death syndrome, and Osborn waves. We also reviewed the

references of highly cited documents and citing documents. The recommendations were voted on, and 80% agreement was required for inclusion.

The purposes of this document are as follows:

- To provide a concise overview of the ER literature, emphasizing variation in definitions of benign and malignant forms of ER
- To provide guidance and recommendations to physicians on appropriate recognition and risk management
- To identify critical areas for future collaborative research efforts

Definition of ER

The challenge in studying ER is the lack of agreement on definition. Historically, the term ER was first used to describe ST-segment elevation in the absence of chest pain¹⁻³ (Figure 1) to differentiate these findings from acute myocardial infarction or pericarditis. In the absence of chest pain, these findings were considered benign.^{4,5} ERP can represent distinct pathological conditions, including acute myocardial injury or infarction, Takotsubo cardiomyopathy, pericarditis, and hypothermia (Osborn waves).^{6,7} In the absence of these conditions, ERP is considered a variant of the normal electrocardiographic pattern, given its frequency in the population.⁸ The study of ER is complicated by the presence of not 1 but several key characteristics that must be considered, including the localization and number of leads in which ERP is present,

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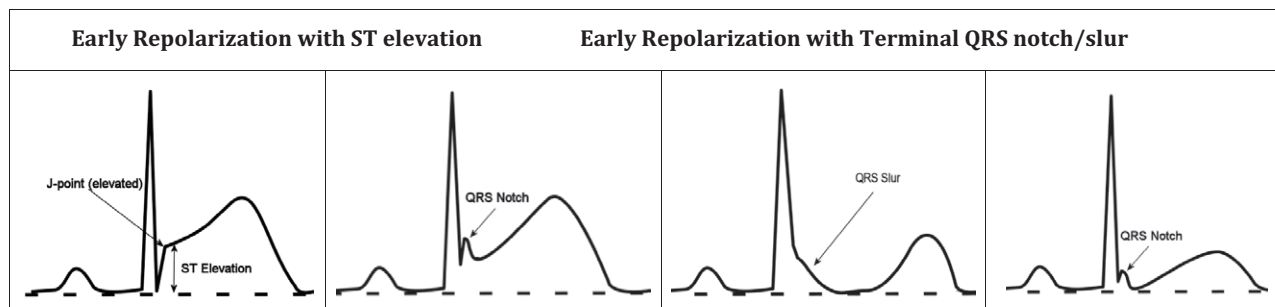


Figure 1. Examples of early repolarization pattern.

the character of the QRS complex and J point (notching or slurring), the magnitude and duration of the J-point elevation, the elevation of the ST segment, and concomitant electrocardiographic findings such as J-wave augmentation or short coupled premature ventricular contractions.^{9,10}

Currently, the term ER is used to refer to nonspecific ST-segment elevation in algorithms used in commercial ECG machines.^{11,12} The 2009 American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society recommendations for the standardization and interpretation of the ECG define ER as “a normal variant commonly characterized by J-point elevation and rapidly upsloping or normal ST segment.”¹³

ERP was originally considered a normal variant with a benign outcome.^{14,15} However, in the 1980s, abnormalities of the J point were associated with idiopathic VF and sudden death in isolated case reports.¹⁴ In 2000, Gussak and Antzelevitch¹⁶ published experimental models demonstrating that under conditions predisposing to ST-segment elevation, ERP resembled Brugada syndrome in arrhythmogenicity. The arrhythmogenic hypothesis gained support in 2008 with the seminal publication by Haïssaguerre and colleagues¹⁷ reporting that survivors of idiopathic sudden cardiac arrest were found to have terminal QRS slurring or notching at a greater frequency than control patients. These slurs and notches were described as ER, and the authors did not require the presence of ST-segment elevation in their definition (Figure 1). A series of population studies subsequently used the ER term to refer to terminal QRS slurring or notching without requiring ST-segment elevation.^{18–20} Thus began the semantic confusion that continues to this day.

To complicate matters further, several studies have identified ER in reference to the J point. Traditionally, the J point has been characterized as the junction at the end of the QRS complex and beginning of the ST segment, a definition used by the 2009 American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society ECG standardizations document.¹³ Despite differences in magnitude and location, because the ER syndrome (ERS) and Brugada syndrome are characterized by similar clinical features and J-wave abnormalities, they are often described as representing parts of a continuum of J-wave syndromes.²¹ Historically, terminal QRS slurs and notches have been considered part of the QRS complex, a finding supported by the 1985 Common Standards of Electrocardiography Working Party.²² More recently, ERP has been defined by QRS slurring and notching, with the J point defined as the top of the terminal QRS slur or

peak of the QRS notch, and is recognized as being the result of phase 1 of the action potential.²³

The lack of consensus in definitions of ERP and of J-point abnormalities results in difficulty in the interpretation of the 2013 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society expert consensus on the inherited arrhythmia syndromes.²⁴ In this document, the ERP was defined as ≥ 1 -mm J-point elevation in ≥ 2 contiguous inferior or lateral leads. The authors recognize that ERP could refer to ST-segment elevation. However, the consensus document focuses on J-point elevation without a precise definition. The authors most likely refer to the J point as the top of the QRS slurs or notches described by Haïssaguerre et al¹⁷ and those found in familial cases of idiopathic VF,²⁵ but these definitions are not clear.²⁶

We believe it is critical to standardize the definitions of ER. We propose that the definition of ER is an umbrella term that can mean any of the following: ST-segment elevation in the absence of chest pain, terminal QRS slurring, or terminal QRS notching (Figure 1). Clinical studies that use the term ER should clearly state which of these electrocardiographic patterns is being used. Some have suggested elimination of ER terminology altogether.²⁷ Others have suggested using the term J-wave pattern to differentiate ST-segment elevation from QRS slur/notch.²⁸ Neither of these approaches has been widely adopted.

We propose that when the term ER is used, it should be qualified further such as ER with ST-segment elevation or ER with terminal QRS slur/notch and clearly defined with the proposed terminology below.

Terminology

The following definitions are proposed to help standardize the terminology used in conjunction with ER (Figure 2).

- ERP: An umbrella term that can refer to ST-segment elevation in the absence of chest pain, terminal QRS slur, or terminal QRS notch. When used, this term should be qualified or defined further with the terminology below.
- ST-segment elevation: The elevation above the isoelectric baseline of the segment between the end of the QRS and the beginning of the T wave. The differential for ST-segment elevation is broad and includes myocardial infarction and pericarditis. ST-segment elevation in the absence of chest pain can be referred to as ERP with ST-segment elevation.
- Terminal QRS notch: A low-frequency deflection at the end of the QRS complex. These notches were initially described by Osborn⁷ as J waves (referring to injury)

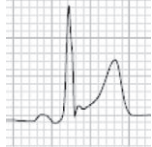
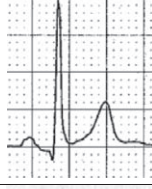
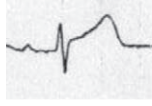
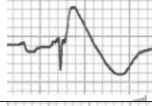


Early Repolarization Patterns	Description	Example
Terminal QRS Notching	Low frequency deflection at the end of the QRS.	
Terminal QRS Slurring	An abrupt change in the slope of the last deflection at the end of the QRS.	
ST elevation	Elevation of the ST segment above the isoelectric baseline.	
Other Repolarization Patterns	Description	Example
Brugada Type 1	Downward coved ST segment elevation, usually in V1-V3.	
Brugada Type 2	ST segment elevation with a saddleback appearance, usually	
Epsilon Wave	Low frequency, positive terminal deflection associated with ARVC, usually in V1-V3.	

Figure 2. Examples of early repolarization and other repolarization electrocardiographic patterns. ARVC indicates arrhythmogenic right ventricular cardiomyopathy.

during experimental hypothermia and later were called Osborn waves.

- Terminal QRS slur: An abrupt change in the slope of the last deflection at the end of the QRS.
- J point: The point where the QRS ends and the ST segment begins.¹⁵ There is debate about whether terminal QRS slurs and notches should be considered part of the QRS segment, as recommended by the Common Standards of Electrocardiography Working Party.²² We propose that the J point should be measured with the peak representing the peak of the notch or onset of a slur when present (Figure 1).
- J-point elevation: An elevation of the J point ≥ 1 mm above the isoelectric baseline.
- J wave: Initially used by Osborn⁷ to refer to notching at the end of the QRS seen during experimental hypothermia. However, it has more recently been used to refer to the presence of notches or terminal QRS slurs. For clarity, if this term is used, it should be further defined with the terminal QRS slur and notch terminology.
- Brugada pattern: A series of ST-segment abnormalities, including downward coved and saddleback ST-segment elevations, associated with sudden cardiac death. These patterns were clearly defined in the Brugada syndrome consensus statement²⁹ and are located in precordial leads V₁ through V₃. Clinical studies, including those by Haïssaguerre et al,¹⁷ excluded these leads to differentiate ER from Brugada patterns.

- Epsilon wave: A low-frequency terminal QRS deflection present in the anteroseptal precordial leads in patients with arrhythmogenic right ventricular cardiomyopathy. The morphology can be variable but is often a broad, low-amplitude terminal QRS notch.
- Pattern versus syndrome: Pattern refers to an electrocardiographic characteristic, whereas syndrome is a collection of clinical findings (which may include certain electrocardiographic characteristics) that share a pathophysiological mechanism. A Brugada pattern, for example, refers to the electrocardiographic characteristic, whereas Brugada syndrome is the disease entity that requires the presence of a type I Brugada pattern and clinical signs such as syncope or ventricular arrhythmias.
- ERS: Defined as occurring in patients with ERP who have survived idiopathic VF with clinical evaluation unrevealing for other explanations. Familial cases have been described²⁵ and associated with rare genetic variants in several ion channel-encoding genes.³⁰⁻³² In the 2013 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society inherited arrhythmia expert consensus statement, ERS was defined by J-point elevation of 1 mm in ≥ 2 contiguous inferior or lateral leads in the setting of idiopathic VF.²⁴ As noted earlier, the definition was unclear because the J point was not clearly defined.²⁶ Because terminal QRS slurs and notches are common, the consensus statement recommended that the

diagnosis of ERS in family members should not be based on electrocardiographic findings alone.

- J-wave syndrome: Terminal QRS slurs or notches associated with cardiac arrest. This is often used as an umbrella term that includes Brugada syndrome and often implies clinical events (ERS).³¹

Biological Basis and Genetics

The underlying biological mechanisms and pathogenesis of ERP and ERS have been areas of substantial focus over the past 2 decades, and many elegant studies have contributed to our current understanding.^{16,23,33–35} Some controversy exists as to whether the electrocardiographic findings represent ER, late depolarization, or neither.^{36,37} The repolarization hypothesis suggests that the presence of the ERP reflects regional heterogeneity in the dispersion gradient of myocardial refractoriness prompted by a net outward shift in repolarizing current.³⁴ Shifts favoring decreased inward sodium or calcium channel current or increased transient outward potassium current (I_{to}), for example, may drive this dispersion of refractoriness. Augmented dispersion of repolarization predisposes to phase 2 reentry, allowing premature ventricular contractions to trigger VF. A transmural voltage gradient from ventricular epicardium to endocardium, caused by the prominence of epicardial I_{to} , results in the J wave. Increased net repolarization current results in an augmented voltage gradient causing an accentuation of the phase 1 notch of the action potential and J waves or ST-segment elevation.²³ Meticulous studies of canine left ventricular wedge preparations have shown accentuation of the action potential notch in the epicardium enhanced by vagal tone, associated with increased level of I_{to} current, and reversed by quinidine and isoproterenol, supporting the repolarization hypothesis.³⁵ The depolarization hypothesis proposes that slowed conduction in the right ventricular outflow tract with fractionated and late potentials contributes to arrhythmogenicity.³⁸

Several observations have raised speculation that a genetic basis for ERP exists. First, ERP has been reported to occur more frequently among relatives of individuals who experienced idiopathic sudden cardiac arrest than control subjects.²⁵ Second, a widespread heritable basis for ERP has been reported.^{18,39} Data from the Framingham study and British cohorts suggest that there is evidence of heritability of ERP with a 2- to 2.5-times increased risk in siblings and offspring of subjects with inferolateral ERP.^{18,39} Third, ERP has been observed as a feature of other genetic arrhythmia syndromes such as Brugada syndrome^{40–42} and short-QT syndrome.⁴³ Furthermore, some genetic variants reported to be associated with ERP have been associated with other arrhythmia syndromes, including Brugada syndrome.^{44,45}

Indeed, rare genetic variants in genes governing cardiac repolarization have been observed in candidate gene screening studies performed in affected individuals, including *KCNJ8*,^{30,45} *SCN5A*,³² and L-type calcium channel subunits.³¹ In contrast, despite the widespread heritable component reported to underlie ERP, a large-scale meta-analysis of genome-wide association studies did not identify any common variants significantly associated with ER.⁴⁶ The authors speculate that heterogeneity in the definition of ERP may have contributed to the null findings of this analysis. In aggregate, these observations

underscore the limited understanding of the genetic basis of the condition at present. It is conceivable that various genetic forms of ERP exist, ranging from highly penetrant mendelian forms of the condition to complex polygenic forms.

Certain clinical features may suggest a more malignant form of ERP, that is, ERS, with a heritable basis (Table 1). In patients exhibiting these elements, determining the causal genetic variation underlying the ERP phenotype might facilitate a molecular and confirmatory diagnosis for an otherwise idiopathic condition and enable targeted carrier testing to determine whether asymptomatic relatives are at risk for the same condition. Nevertheless, as a result of limited understanding of the genetic basis of ERP or ERS, genetic testing for the condition may be associated with low sensitivity and specificity, as well as a risk of discovering a genetic variation of unknown clinical significance. Therefore, although genetic testing may be reasonable in cases of ERP in which the index of suspicion is high for a malignant heritable pathogenesis, the clinical utility of such testing requires prospective evaluation.

Epidemiology of ER

As previously noted, systematic study of ER has been hampered by the absence of an established consensus definition, and significant variability in its description exists across observational studies. Published observational studies suggest that the prevalence of ERP ranges between 1% and 18%.^{4,19,20,47,48} One of the first studies to describe ERP was an investigation of 4-lead ECGs in 200 men and women published in 1936, which reported a frequency of 25% in men and 16% in women.⁴⁹ Subsequent studies have shown that ERP is more frequent in blacks, men, younger individuals (age <40 years), and athletes.^{4,48}

Although early reports demonstrated no increased risk of death in patients with ERP,⁴ the landmark case-control study by Haïssaguerre and colleagues¹⁷ suggested an increased prevalence of ERP in 206 subjects with VF (J point ≥ 0.1 mV) compared with 412 control subjects (hazard ratio, 2.1; 95% confidence interval, 1.2–3.5; $P < 0.001$). Another case-control study by Rosso et al⁵⁰ also revealed that inferolateral ER was more frequent in 45 patients with idiopathic VF compared with 121 age- and sex-matched control subjects. Additional studies have demonstrated an association between ERP and arrhythmia in patients with known structural heart disease. For example, an increased risk of VF has been observed in patients with ERP after myocardial infarction compared with age- and sex-matched control subjects.⁵¹ Although an increased frequency of ERP has been reported in case-control studies, the data from large epidemiologic studies have been mixed.

A large study of 10864 individuals in Finland found that inferolateral ER (≥ 1 mm in 2 consecutive leads) was present in 5.8% of the population and was associated with an increased risk of sudden cardiac death, particularly in those with inferior ER ≥ 2 mm (relative risk, 2.92; 95% confidence interval, 1.45–5.89).²⁰ Similar findings were observed in a cohort of 6213 patients from Germany and 15 141 subjects in the Atherosclerosis Risk in Communities (ARIC) study.^{19,52} In contrast, Uberoi and colleagues⁴⁸ found no association with ERP and increased cardiovascular mortality in 29 281 patients within the VA Palo Alto Health Care System. Meta-analysis of observational studies has revealed increased arrhythmic risk;

Table 1. Features That May Raise Suspicion for a Malignant and Heritable Form of ER

Family history of sudden cardiac arrest or early unexplained death
Personal evaluation and workup suggestive of a channelopathy (eg, short-QT syndrome, Brugada syndrome)
Personal history of unheralded syncope suggestive of an arrhythmogenic pathogenesis (particularly when at rest or recumbent)

ER indicates early repolarization.

however, the magnitude of this risk is low, with an estimated absolute risk difference of 0.0007%/y.⁵³

From a population perspective, ERP can properly be called a normal variant, given its overall frequency. However, the preponderance of evidence suggests an association with an increased risk of arrhythmic death, particularly in those with inferior ER ≥ 2 mm. Despite these associations, large epidemiological studies suggest that the risk is low. Data from Rosso et al⁵⁰ suggest that the finding of ERP in a young adult would increase the probability of idiopathic VF from 3.4 in 100000 to 11 in 100000. It has been hypothesized that ERP may represent a marker of arrhythmogenesis that requires a “second hit” or a proarrhythmic trigger such as ischemia or a critically timed extrasystole. Several population studies suggest that ERP confers an increased risk of VF in the setting of ischemia and myocardial infarction.^{54,55} At present, the implications of ERP in a given patient without a history of arrhythmia are hard to discern and require further study.

Overall Risk Assessment/Recommendations for Further Evaluation

Although ERP is a common electrocardiographic finding, idiopathic VF is a rare disease.⁵⁶ On the other hand, cardiac arrest is often the presenting symptom in idiopathic VF.^{57,58} Consequently, distinguishing the small fraction of patients at risk for potentially lethal ventricular arrhythmias from the vast majority of patients with ERP who are not at risk for sudden death is a formidable challenge. This section summarizes the clinical and electrocardiographic characteristics that may aid in this risk stratification process.

Clinical Characteristics

Sex

Male sex predominates among patients with cardiac arrest related to ERP.^{17,50} However, the same is true for asymptomatic healthy control subjects with ERP,^{17,50} especially healthy athletes.⁵⁰ Therefore, male sex is of limited value for risk stratification. Conversely, the finding of prominent J waves (see below) in a female patient may call for further evaluation.

Familial History of Sudden Death

There are reports of families with unexplained sudden death or malignant arrhythmias documented in family members in whom ERP was the only abnormality found despite extensive evaluation.⁵⁹ Consequently, recognition of ERP in the ECG of an asymptomatic family member of a sudden death victim generally causes concern.⁵⁸ However, one should recall that ERP is a familial trait in the absence of familial sudden death.¹⁸ Therefore, one should not assume that an asymptomatic individual with ERP and a positive familial history of

sudden death is similarly at risk, especially if the ECG of the proband (as often happens) is unavailable. Furthermore, one should recall that the majority of patients with ERS actually do not have a familial history of sudden death.⁵⁷ For example, in the largest case series,¹⁷ only 16% of patients with cardiac arrest and ER had a familial history of sudden death.

In clinical practice, a familial history of unexplained sudden death at a young age calls for systematic evaluation of all surviving family members regardless of the presence or absence of ERP. ERP has been observed in patients with short-QT syndrome.^{43,60} Whether ERP is an “innocent bystander” or reflects an additional substrate or negative modifier is not known. It has been observed, however, that patients with idiopathic VF frequently have QT intervals in the low-normal range⁶¹ or have apparently normal QT intervals that fail to increase during low heart rates.⁶² These data suggest that the cause of idiopathic VF in some patients, including those with ER, is a genetic mutation encoding for short-QT syndrome or “short-QT syndrome with not-so-short QT intervals.”⁶³

History of Syncope

Every patient with a history of syncope needs assessment of his/her risk for sudden death, taking into consideration that in young individuals benign vagal syncope is common and arrhythmic syncope is rare.⁶⁴ The clinical history, more than the electrocardiographic characteristics (see below) of ERP, should dictate the extent of the evaluation. This is important because one third of patients with benign vagal syncope have ERP.⁶⁵ A history of syncope at rest is strongly associated with ERS and is attributable to pause-dependent augmentation of J waves that precede episodes of VF.⁵⁰

Electrocardiographic Characteristics

The Type and Location of ER

Although the classic description of benign ER invokes the presence of ST-segment elevation in the inferolateral leads, the arrhythmogenic form of ERP involves tall J waves with limited ST-segment elevation, mainly in the inferior leads.⁶⁶ The existence of malignant arrhythmias in patients with J waves in multiple leads has led to the perception that widespread J waves in many leads have malignant implications.³⁴ However, the majority of patients with idiopathic VF have J waves limited to the inferior leads.^{17,50}

Amplitude of the J Waves

J waves in patients with idiopathic VF are of greater amplitude than those seen in healthy control subjects matched for age and sex, and the association between J-wave amplitude and risk is statistically significant.¹⁷ However, the absolute difference between the mean amplitude of arrhythmogenic and the innocent J waves is < 1 mm at standard gain, and there is significant overlapping between them.¹⁷ Therefore, except for the giant waves rarely seen in idiopathic VF,^{30,67} the amplitude of the J waves is of limited value for risk stratification.

Augmentation of J-wave amplitude immediately after sudden pauses is characteristic among patients with idiopathic VF, but this phenomenon is seen primarily in patients who have tall J waves already at baseline.⁶⁸ J-wave amplitude should be evaluated during Holter recordings because patients with idiopathic VF demonstrate significantly taller J waves during slow heart rate at night.⁶⁹

However, it is important to recognize that there is no cutoff value for J-wave amplitude that will accurately identify all patients at risk.

The Morphology of the ST Segment

Ample evidence demonstrates that the contour of the ST segment in patients with ER provides important prognostic information.⁷⁰ As first described by Tikkanen et al,⁷¹ J waves followed by a rapidly ascending ST segment are consistently a benign finding. In contrast, the pattern of J waves followed by a horizontal or descending ST segment is associated with increased arrhythmic risk.⁷⁰ As one moves from patient populations at very low risk for arrhythmic complications (ie, healthy athletes) to patient groups at high risk for malignant arrhythmias (ie, patients with idiopathic VF), the type of ST-segment abnormality changes. Whereas $\approx 95\%$ of asymptomatic athletes with ER have the rapidly ascending ERP, $\approx 70\%$ of patients with idiopathic VF have the horizontally descending form.⁷⁰ Consequently, the terms benign ER and malignant ER are used to describe the rapidly ascending and horizontally descending patterns, respectively. However, it is important to emphasize that the term malignant ER implies a relative rather than an absolute risk. In other words, although careful analysis of the ST-segment morphology is useful for risk stratification, the added value is generally not sufficient for clinical decision making. For example, for the asymptomatic patient with ERP, an ascending ST segment is certainly reassuring, but a horizontal form should not be interpreted as a sign of high risk. The risk of cardiac arrest resulting from idiopathic VF for an asymptomatic young adult with ER is only 1 in 3000 even when the ST segment is horizontal.⁵⁶

Future Research Needs/Conclusions

The existing literature indicates substantial heterogeneity in the definitions and prognostic implications of ERP. We submit that a concerted effort to understand the epidemiology, prognostic associations, genetic underpinning, and biological basis of ER is warranted. We therefore propose several focused areas of future research that may help inform our understanding and management of this electrocardiographic finding.

Definitions of ER

The various definitions of ERP described in the literature (inferior, lateral, mid precordial, notching, slurring, J-point elevation, etc) limit the direct comparison of studies of this condition. In many cases, descriptors are not mutually exclusive and thereby contribute to confusion among scientists and practitioners. An ideal definition of ER would encompass both clinically meaningful and biologically relevant features.

- We propose efforts to classify ER using outcome-driven approaches to define meaningful and prevalent variant patterns.

Epidemiology of ER

Population-based observations indicate that the prevalence of ERP varies widely, depending on the patient subset and on the definition of ERP. The long-term outcomes of ER in clinically relevant subgroups of interest (young athletes, relatives of cardiac arrest survivors, etc) and clinical precipitants of arrhythmogenesis have not been well defined.

Table 2. Recommendations for the Management of ER

Recommendation	Class	LOE
Further evaluation for the incidental findings of an ERP on an ECG in an asymptomatic patient (without family history of sudden cardiac death) is not recommended.	III	C
In patients with unexplained syncope, incorporation of the presence of most ER electrocardiographic findings into risk stratification is not well established.	IIb	C
In patients with aborted sudden death or resuscitated VF who have electrocardiographic findings of ER, programmed ventricular stimulation performed on the basis of ER pattern alone is not recommended.	III	B
In patients with both unexplained syncope and first-degree family history of sudden death, the presence of ER may be considered in overall risk stratification during appropriate evaluation for arrhythmic causes of sudden death.	IIb	C

ER indicates early repolarization; LOE, Level of Evidence; and VF, ventricular fibrillation.

- We propose future large-scale prospective studies to determine the long-term outcomes and both precipitants and characteristics of arrhythmia associated with ERP.

Genetic and Biological Basis of ER

The biological basis of ERP remains incompletely understood. A heritable component has been observed for ERP in the community,¹⁸ although little is known about the common genetic determinants of the condition. Regional heterogeneity of repolarization may underlie the electrocardiographic manifestations of the condition, but the mechanisms underlying regional differences that manifest as ER are not well defined. Furthermore, it remains unclear how mechanisms of ER are modified in response to factors such as exercise training, heart rate, temperature, and age. The precise mechanisms of arrhythmogenesis in patients with ER remain largely speculative.

- We therefore propose large-scale, unbiased (eg, genome-wide association studies), family-guided genetic discovery approaches, as well as efforts aimed at understanding both the mechanisms underlying ER and the associated arrhythmogenesis.

Management of ER

Given the high prevalence of ERP and relatively low risks of arrhythmia in patients with the condition, counseling and management are particularly challenging. There is a critical need to understand whether individuals with ERP at significantly elevated risks of arrhythmia over a clinically meaningful time horizon can be identified and whether presently available tools have any utility in stratifying risk in individuals with ERP. The infrequency of arrhythmic events in individuals with ERP poses challenges for the identification of efficacious and cost-effective interventions that may reduce arrhythmic risk. Although both quinidine and isoproterenol may be effective for the management of patients with VF,^{17,72} data supporting their use remain limited to small samples with limited follow-up. The proper thresholds of risk at which to prescribe such medications remain unclear, and whether there is any role for medical therapy in a primary prevention setting

is unknown. It remains uncertain whether avoidable triggers (eg, medications) of arrhythmogenesis exist in patients with ERP. The prognostic implication of exercise training, which is associated with an increased prevalence of ERP, similarly remains unclear.⁷³

Recommendations for therapeutic interventions for ERS are described in the Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society Expert consensus statement on the diagnosis and management of patients with inherited arrhythmia syndromes.²⁴ As previously noted, the risk of SCD in asymptomatic patients without a family history of SCD is very low, and further investigation or treatment is unwarranted on the basis of current data. Recommendations for management are outlined in Table 2. Patients with potentially arrhythmic syncope or a family history of sudden cardiac death should be evaluated further with respect to high-risk clinical features (Figure 1).

- We advocate that large-scale registries with standardized follow-up be developed to identify triggers of arrhythmia, efficacious and cost-effective approaches to the risk stratification of individuals with ER, and interventions that may reduce arrhythmia risk.

Conclusions

This document highlights many of the challenges facing the interpretation of ER in the clinical setting and the lack of knowledge underlying the understanding of this very prevalent condition. It is essential that efforts to harmonize high-quality, longitudinal data are undertaken to address questions related to the clinical relevance of ERP. We submit that entities such as the American Heart Association will be critical for endorsing and facilitating the infrastructure necessary to develop a dedicated research program to support investigations related to ER.

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Kristen K. Patton	University of Washington	None	None	None	None	None	None	None
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Marco Perez	Stanford University	None	None	None	None	None	None	None
Jonathan Piccini	Duke University Medical Center	Boston Scientific†	None	None	None	None	Medtronic*	None
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Paul Wang	Stanford University School of Medicine	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10,000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10,000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.
†Significant.

Reviewer Disclosures

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Charles Antzelevitch	Lankenau Institute for Medical Research	None	None	None	None	None	None	J-Wave Consensus Conference participant*
William F. McIntyre	University of Manitoba (Canada)	None	None	None	None	None	None	None
Frank Yanowitz	University of Utah School of Medicine	None	None	None	None	None	None	None

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*Modest.

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Kristen K. Patton, Patrick T. Ellinor, Michael Ezekowitz, Peter Kowey, Steven A. Lubitz, Marco Perez, Jonathan Piccini, Mintu Turakhia, Paul Wang and Sami Viskin

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