

REVIEW

Early Repolarization: Not Benign Any More- The J-Wave Syndromes

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ABSTRACT

An early repolarization (ER) pattern characterized by J-point elevation, slurring of the terminal part of the QRS and ST-segment elevation has been traditionally considered to be totally benign over the past decades. A flurry of data derived from recently published studies demonstrate that an ER pattern in inferior or inferolateral leads, named early repolarization syndrome (ERS), is associated with increased risk for sudden cardiac death (SCD), being responsible for some cases of idiopathic ventricular fibrillation (IVF). Current evidence supports the notion that although ERS and Brugada syndrome (BrS) show discrete differences, they also share similar clinical, electrocardiographic and pathophysiological features, especially concerning the presence of amplified J-waves; thus, they can be considered to represent a continuous spectrum of phenotypic expression, termed J-wave syndromes. Research has provided us with fascinating insights into the underlying mechanisms responsible for repolarization abnormalities and we presently have more evidence to implement reliable risk stratification methods to patients with ER. However, many unanswered questions remain and still need to be addressed in future studies.

KEY WORDS: *J-wave syndromes; early repolarization; sudden cardiac arrest; idiopathic ventricular fibrillation; Brugada syndrome*

ABBREVIATIONS

BrS = Brugada syndrome
ECG = electrocardiogram
ER = early repolarization
ERS = early repolarization syndrome
ICD = implantable cardioverter
defibrillator
IVF = idiopathic ventricular fibrillation
LQTS = long QT syndrome
SCD = sudden cardiac death
SQTS = short QT syndrome
VF = ventricular fibrillation

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Manuscript received April 24, 2012;
Revised manuscript received July 24,
2012; Accepted August 24, 2012

INTRODUCTION

Since 1903 when Willem Einthoven invented the electrocardiogram (ECG), a lot of progress has been made concerning its interpretation, the recognition of several heart disorders and their underlying mechanisms. ECG waveforms reflect the electrical activity of ventricular cardiac cells as a whole and are categorized into two general groups: depolarization that is represented by the QRS complex and repolarization depicted by the J, T, and U waves. Due to its involvement in potentially lethal arrhythmias, ventricular repolarization and especially its ionic and cellular basis has been the center of attention of many researchers during the past two decades.¹ As a result, several primary arrhythmic disorders causing sudden cardiac death (SCD) have been recognized including ST-segment elevation in the right precordial leads (Brugada syndrome -BrS) and QT interval abbreviation (short QT syndromes) or prolongation (long QT syndromes), especially when these entities are accompanied by ventricular premature beats with relevantly short coupling intervals.²

Early repolarization (ER) is defined as an ECG pattern characterized by a prominent J-point and ST-segment elevation, notching or slurring of the terminal

Conflict of Interest: none declared

portion of the R wave (J wave) with upward concavity ending in a positive high amplitude symmetric T-wave in most ECG leads.³ While the role of BrS and short (SQTS) or long QT syndromes (LQTS) in provoking life-threatening arrhythmias is now clearly established, early repolarization (ER)³ has been consistently considered a benign variant of the normal ECG lacking specific clinical importance.³⁻⁶ Early repolarization is a common ECG finding observed in 2-10% of the general population showing a greater prevalence in young healthy men and athletes.^{3,4,6-9} However, recently published studies have questioned this long-standing concept, demonstrating a possible connection between some forms of ER and J waves, found in otherwise healthy subjects, and the appearance of idiopathic ventricular fibrillation (IVF) and SCD.¹⁰⁻¹³ Early repolarization presents several clinical, pathophysiological and ECG similarities with the BrS. Interestingly, BrS was also believed to have minimal arrhythmic potential when firstly described as ST-elevation in the right precordial leads,¹⁴ but its arrhythmogenicity has been well proven over the past 20 years. Thus, despite the fact that BrS and ER syndrome (ERS) show differences concerning the morphology and location of the prominent J-wave deflection, they are thought to represent a continuous spectrum of phenotypic expression termed *J-wave*

syndromes.^{1,3,12,15-17} All these clinical situations, either congenital or acquired, share common ionic mechanisms and the observed phenotype and their potential to become a substrate for ventricular arrhythmias and SCD is mostly dependent on the extent and the type of the particular ion channel affected.

J WAVE - HISTORY, EPIDEMIOLOGY AND MECHANISMS

The “J wave” is usually defined as a positive “hump-like” deflection immediately after a positive QRS complex at the onset of the ST-segment. Due to the fact that the J-wave deflection is often hidden within the QRS complex,¹ most authors include in the definition of ER both a gradual transition of the terminal part of the QRS complex with upright concavity causing a “slurring” of the QRS and an ECG pattern with a sharp and well-defined hump noted immediately after the R-wave, resulting in a “notching” of the terminal QRS complex, called “J-point elevation” (Fig. 1).¹⁸ Both patterns need to be ≥ 1 mm (0.1 mV) above the isoelectric line and present in at least two contiguous leads.^{19,20}

The pattern of ER and J deflection presenting as slurring

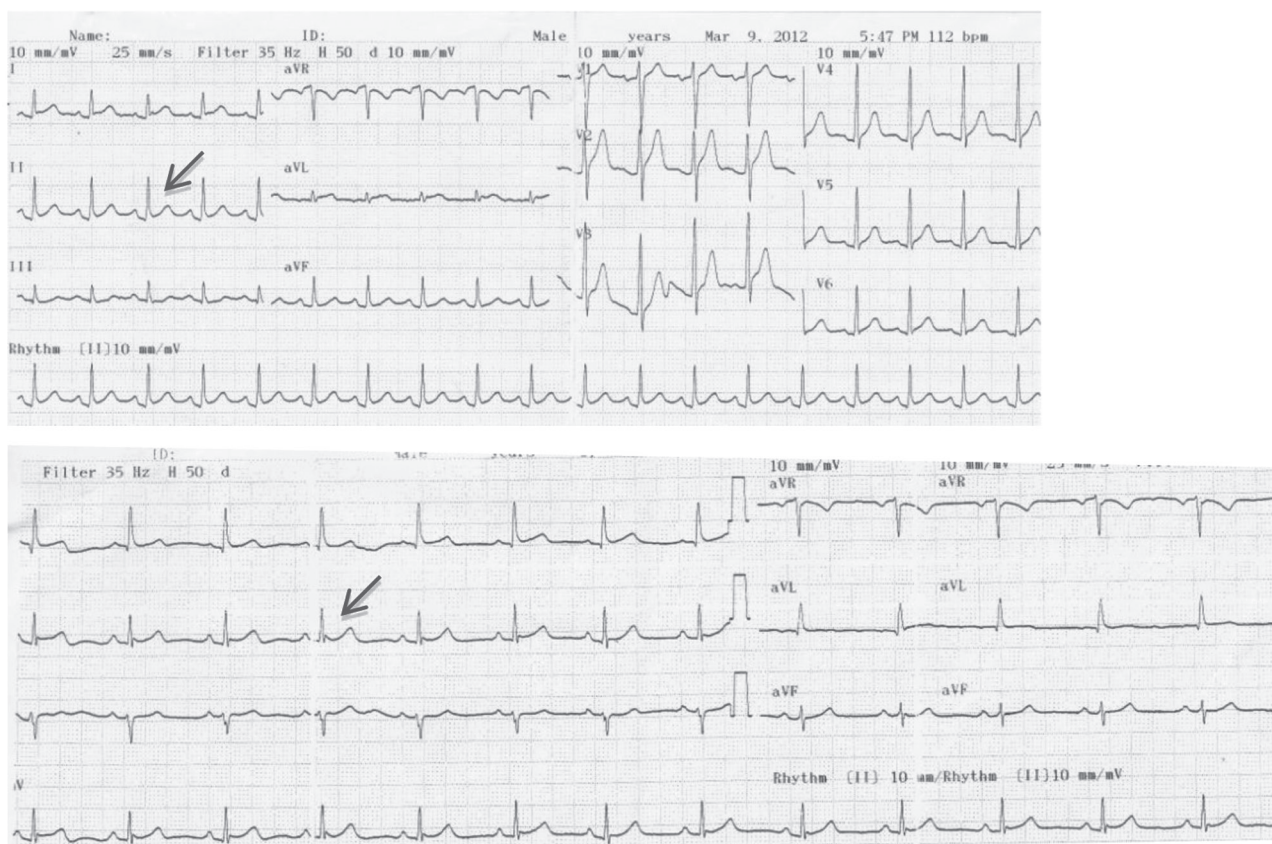


FIGURE 1. The two major patterns of early repolarization. Terminal QRS slurring (upper ECG) and notching (lower ECG) (arrows).

or notching of the terminal part of QRS complex was first described in 1936 by Shipley and Hallaran and was considered a normal ECG variant.²¹ In 1938, Tomaszewski²² presented the case of an accidentally frozen man whose ECG depicted a very slowly inscribed deflection between the QRS complex and the ST segment, representing a J wave. In 1953, Osborn²³ described a “current of injury” –later named “the Osborn wave”- in acidotic and hypothermic dogs at rectal temperatures less than 25 °C followed by several publications in the next 10 years considering this pattern a normal variant. In 1961, Wasserburger and Alt²⁴ further defined early repolarization as a 1 to 4 mm takeoff of the ST segment from the isoelectric line accompanied by downward concavity of the ST segment and symmetrically limbed T wave often of large amplitude in the mid to left precordial leads. A publication by Klatsky et al further strengthened this long-held belief showing that the prevalence of ER in a cohort of 73,088 healthy volunteers was 0.9% and that the patients with ER were less likely to develop severe arrhythmias and did not experience excessive morbidity compared with the control group.⁶

While J waves are commonly observed in several animal ECGs, in humans they are usually partially or completely buried in the QRS complex under physiological conditions. Prominent J waves on the ECG are often observed in specific conditions like hypothermia, electrolyte imbalance, myocardial ischemia, right ventricular dysplasia, pulmonary embolism, brain injury, tricyclic antidepressant intoxication, BrS, and ER (Table 1).^{5,25-28} However, J waves are often misdiagnosed as intraventricular block in some normal individuals with ER.¹⁸ Male sex is strongly associated with ER; not only men represent more than 75% of the ER cases but also depict greater J-point elevation than women do.^{8,21} ER pattern is more common in blacks^{6,15,18} and young athletes especially those who participate in competitive sports.^{6,8} The latter observation is probably related to the strong influence of autonomic tone on ER variability.²⁹ Several clinical investigators have reported that ER pattern may follow a circadian variation and is more prominent when parasympathetic tone is high, e.g. postprandial, during rest or sleep, in athletes, and, conversely diminishes when adrenergic tone is high, as observed during exercise.³⁰⁻³² Finally, several reports showing a positive association between Sokolow-Lyon index and ER have been published.^{33,34}

Whether the inscription of the J wave on the surface ECG reflects ER or delayed depolarization has been a matter of debate. Most electrophysiologists concede that the J wave is an ER phenomenon justifying its occurrence to be coincident with phase 1 of the epicardial action potential which precedes the endo- and mid-myocardial phase 1, thus generating an early gradient in the repolarization currents within the ventricles.^{13, 35} More evidence in favor of this notion is its aforementioned rate-dependant morphological fluctuation (increased pattern at slow heart rate, decreased pattern at faster heart rate) and its varying amplitude concurrently with the ST segment. Other

TABLE 1. Conditions with prominent J waves on the ECG

| |
|---|
| Hypothermia |
| Hypercalcemia |
| Hyperkalemia |
| Hypoxia |
| Acidosis |
| Myocardial ischemia |
| Arrhythmogenic right ventricular cardiomyopathy |
| Pericardial effusion |
| Pectus excavatum |
| Pulmonary embolism |
| Brain injury |
| Subarachnoid hemorrhage |
| Mediastinal tumors |
| Tricyclic antidepressant intoxication |
| Brugada syndrome |
| Early repolarization (syndrome) |
| Short QT syndrome |

researchers did not find late potentials on high-amplification ECG and invasive endocardial mapping¹⁹ and preliminary data obtained from electroanatomic maps of epicardial activation and repolarization, indicate that patients who show ER on the surface ECG have abnormal repolarization, rather than abnormal late activation. On the contrary, recently published data by Abe et al³² derived from the use of a newly developed signal-averaging system to record depolarization (late potentials) or repolarization markers (T-wave alternans and QT dispersion), might support the idea that J waves are more related to depolarization. J waves were significantly associated with all late potential parameters but not with T-wave alternans and QT dispersion.

As already stated, the inscription of the J wave immediately after ventricular depolarization indicates the presence of a transient transmural voltage gradient at the beginning of ventricular repolarization (Fig. 2). Antzelevitch's team was the first to propose a difference in repolarization phases 1 and 2 of the action potential between canine ventricular epicardium and endocardium as the basis for the ECG J wave.^{35,36} The authors reported that the action potentials observed in ventricular epicardium commonly display a noticeable notch (spike and dome), mostly mediated by a 4-aminopyridine-sensitive tran-

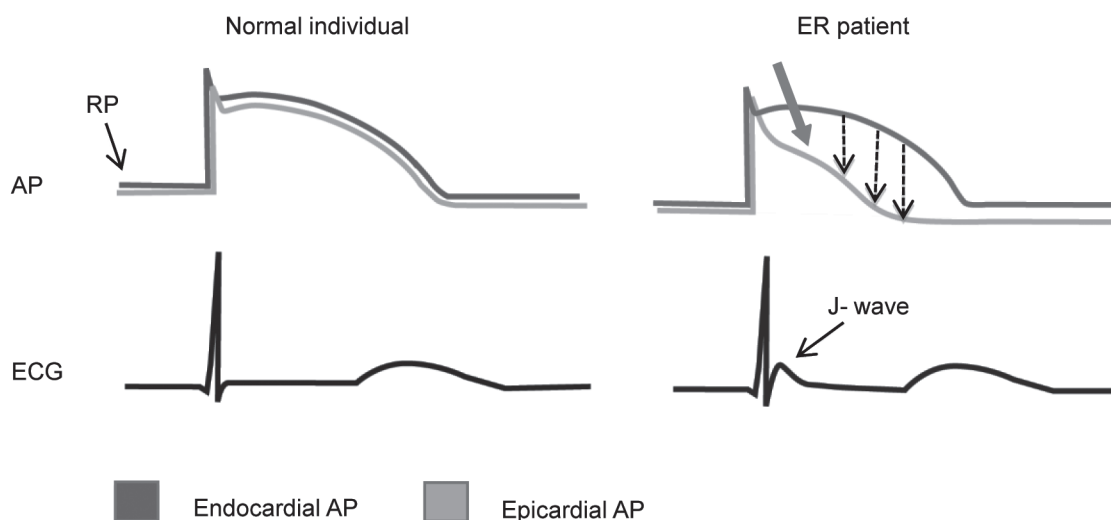


FIGURE 2. Schematic representation of the possible mechanism underlying J-wave occurrence. Action potentials from epicardium and endocardium from normal individuals (left) and early repolarization (ER) patients (right) as well as the respective electrocardiograms are shown. A prominent phase 1-notch and the loss of epicardial dome in phase-2 (thick arrow) results in transmural dispersion of repolarization (dashed arrows) and appearance of the J-wave and ST-segment elevation on the surface ECG. AP: action potential, ECG: electrocardiogram, ER: early repolarization, RP: resting potential.

sient outward current (I_{to}). On the opposite, endocardial cells have a much smaller density of I_{to} resulting in the absence of a notch in the endocardium. As a consequence, a transmural voltage gradient may be produced during early ventricular repolarization, presented as a J wave or J point elevation on the surface ECG. Preliminary evidence supporting this hypothesis was first obtained when Yan and Antzelevitch published the results of their experiments in an arterially perfused canine ventricular wedge preparation.¹³ When the transmural activation was from the endocardium to epicardium, as in normal hearts, a prominent J wave coincident with the epicardial action potential notch was seen on the surface ECG. Conversely, if the epicardium was activated first and then spread to the endocardium, the J wave disappeared, being buried within the QRS complex. Researchers also demonstrated a linear correlation between the magnitude of the J wave and I_{to} -mediated action potential notch in epicardium. These significant observations also explain the aforementioned influence of several environmental, epidemiological and other factors to J wave size, through their action on I_{to} kinetics. For example, males have more prominent I_{to} current in ventricular epicardium than females³⁷ and show a 3-fold prevalence of ER. Hypothermia-induced prominent J waves are apparently the result of a marked accentuation of the spike and dome morphology of epicardial action potentials following the selective effect of cold temperatures on the activation kinetics of L-type Ca^{2+} current, while I_{to} is affected less.¹³ Similarly, tachycardia reduces I_{to} due to its slow recovery from inactivation and results in a decrease in the J wave size.¹⁰

THE ST-SEGMENT

The ST-segment is the portion of the ECG observed between the end of the QRS complex and the beginning of the T-wave and normally stays at the same level as the T-P segment. Both the change in ST-segment morphology and its displacement, either upward (elevation) or downward (depression) of more than 1 mm from baseline, is considered abnormal and may have clinical implications. Due to the fact that the ST segment shows temporal correspondence with the plateau phase of the action potential, an isoelectric ST segment implicates the absence of a significant voltage gradient during phase 2 of ventricular repolarization.³⁰

Our baseline knowledge for ST-segment elevation is that it represents an “injury current” caused by a current flow from partially depolarized injured myocardial cells (e.g. myocardial infarction, pericarditis) to the uninjured ones.^{38,39} However, this mechanism is problematic and cannot explain ST-segment displacement in nonischemic or structurally normal hearts, as in the early repolarization syndrome and Brugada syndrome, conditions in which no “injured zone” is identified.⁴⁰ Temporally related to the phase 2 of the action potential, ST-segment elevation could actually be produced by a distinct difference in plateau potentials within the ventricles: the depression or loss of the action potential dome in the epicardium, but not endocardium, would result in a transmural voltage gradient during repolarization that could manifest as ST segment elevation on the surface ECG, as encountered in Brugada syndrome, ERS and possibly in that observed in acute myocardial ischemia.^{13,40}

THE J-WAVE SYNDROMES

The clinical syndromes characterized by J wave and ST segment elevation include the ERS, idiopathic ventricular fibrillation (IVF), and the Brugada syndrome.^{1,17,30} Although they share many ECG features as already discussed, their clinical implications vary. The ERS is likely benign, whereas IVF and the Brugada syndrome are associated with recurrent syncope and SCD.

1. EARLY REPOLARIZATION SYNDROME (ERS)

The major characteristic of ERS is a prominent J wave or J-point elevation, a concave upward ST segment elevation followed by a broad and upright T wave, predominantly observed in the left precordial and the inferior and less frequently in the anterior leads. The early repolarization syndrome has been considered to be a benign ECG phenomenon most commonly seen in young healthy men and athletes.^{4,8,24,30} As mentioned above, ERS shows several electrocardiographic similarities to the more arrhythmogenic BrS⁴¹ reflecting their similar underlying mechanisms for ST segment elevation. Prominent voltage gradients early in repolarization produce J waves while voltage gradients later in the action potential cause ST-segment elevation.³⁴ Both in the BrS and the ERS, J wave and ST segment are liable to modification with fluctuations in heart rate and autonomic tone.³⁶ However, the ionic basis responsible for the outward shift of currents during action potential phases 1 and 2 resulting in partial loss of the left ventricular epicardial action potential dome in the ERS is currently undetermined. Pinacidil is a potassium channel opener that leads to partial loss of the I_{to} -mediated action potential dome in canine left ventricular epicardium. The maintenance of endocardial action potential dome results in a concave upward or saddleback ST elevation on the ECG, similar to the human type.⁴² Several experimental data have demonstrated that complete loss of the I_{to} -mediated action potential dome in canine left ventricular epicardium rarely occurs due to a much smaller I_{to} compared to canine right ventricular epicardium, possibly explaining the benign nature of ERS.¹

Interestingly, some individuals show ER primarily in the inferior leads while others in lateral leads, a phenomenon not readily explained by current knowledge. Researchers believe that *ER localization* reflects differences in regional control of repolarization and seems to play a significant role in risk stratification for ventricular arrhythmias. According to its arrhythmogenic potential and ER localization, Antzelevitch and Yan¹⁷ proposed the classification of ERS into three subtypes: *Type I* is associated with an ER pattern predominantly in the lateral precordial leads, is very prevalent among healthy male

athletes and is rarely met in VF survivors. *Type 2* ER is mostly seen in the inferior or inferolateral leads, is also prevalent in healthy young males and is associated with a higher level of risk.^{58,59} Finally, *type 3* displays a global ER pattern (in the inferior, lateral, and right precordial leads) and carries the highest level of risk for development of life-threatening arrhythmias and VF storms.^{3,36}

Several investigators support the notion that ER might have a heritable basis, raising the question whether there are genetic similarities with other J-wave syndromes, although methodological limitations exist. In the Framingham Heart Study, siblings of individuals with ER had an ER prevalence of 11.6%, meaning a 1.89-fold risk compared to control group, but this was significantly attenuated after adjustment for age and sex.⁴⁴ Similarly, in a representative sample of the British general population comprised of 1877 individuals, Reinhard et al reported that offspring of ER-positive parents have a 2.5-fold increased risk of presenting with ER on their ECG.⁴⁵ However, whether these individuals carry an increased risk of presenting serious arrhythmias remains unknown. Recently published studies indicate that mutations in *KCNJ8*, a gene encoding the pore-forming subunit of the I_{K-ATP} channel^{46,47} and in several genes encoding the $\alpha 1$ (*CACNA1C*), $\beta 2$ (*CACNB2*) and $\alpha 2\delta$ (*CACNA2D*) subunits of the L-type calcium channel,⁴⁸ are more likely to be associated with ERS, with the first two of them implying a genetic connection with BrS, as subsequently described.

2. BRUGADA SYNDROME

Brugada syndrome is a clinical entity first described in 1992 by Josep and Pedro Brugada⁴⁹ characterized by a 40–60% incidence of life-threatening ventricular arrhythmias, predominantly polymorphic ventricular tachycardia that evolves into ventricular fibrillation.⁵⁰ The ECG features of BrS include a prominent J wave causing a pattern of incomplete right branch bundle block and ST-segment elevation in the right precordial leads (V1–V3) in the absence of myocardial ischemia or defined structural heart disease.^{10,50,51} More particularly, three types of Brugada waves have been identified (Fig. 3): *type I* is characterized by a triangular ST-segment elevation (coved type) followed by T-wave inversion in leads V1–V3; a downward displacement of the ST-segment lying between two elevations of the segment (saddle-type) in leads V1 through V3 without touching isoelectric line is typical of BrS *type II*; in *type III* the middle part of the ST-segment reaches the baseline. The T-waves in types II and III may not be inverted.²⁷

Brugada syndrome is particularly prevalent among Asian males and its characteristic ECG pattern is significantly influenced by changes in heart rate and autonomic tone, as seen in ERS.^{10,51} The underlying mechanism responsible for ST-segment elevation encountered in the BrS is a net out-



FIGURE 3. Characteristic electrocardiograms (ECGs) of Brugada type I (A) and type II (B).

ward current shift at phases 1 and 2 of the right ventricular epicardial action potential, causing a marked depression or complete loss of its dome.¹³ The extent of the loss of the phase-2 dome (partial or complete) is largely dependent on the size of intrinsic I_{to} .⁴⁰ I_{to} activity shows regional variability and is quite prominent in the right ventricular epicardium thus explaining the dynamic J wave activity limited to the right precordial leads.^{37,52,53} However, case reports have occasionally described variants of BrS with ECG changes in the inferior or lateral leads, suggesting that the pathophysiological changes responsible for BrS may not always be confined to the right ventricle.⁵⁴ Prominent right epicardial I_{to} activity results in a net outward current shift, which accentuates the I_{to} -mediated action potential notch in the epicardium to a more negative potential. As a consequence I_{Ca} fails to activate and the action potential dome fails to develop, leading to all-or-none repolarization and action potential abbreviation by 40% to 70%.^{13,52} In contrast, in the left ventricular epicardium where I_{to} is weaker, the outward current shift may only cause partial loss of action potential dome resulting in a minimal change in action potential duration. ECG morphology reflects the magnitude of action potential dome loss; when there is complete loss of the epicardial action potential dome, ST-segment elevation is covered on the ECG, a characteristic of type 1 BrS.^{13,43} When only depression of epicardial action potential dome occurs,

transmural voltage gradient is smaller, action potential is only minimally shortened and ST-segment elevation is usually upward concave- or saddleback-like, as observed in the ERS. Between these two categories, only the former carries a significant risk of severe phase-2 reentry-mediated ventricular arrhythmia.

Although approximately 60% to 70% of BrS probands remain genotype negative, BrS seems to have a genetic basis, since several genes have been incriminated for its occurrence. BrS has been classified into seven categories (BrS 1-7) according to the specific gene mutation recognized so far. Genetic defects in *SCN5A* (BrS1) have been reported in 11% to 28% of Brugada syndrome probands and are the ones most frequently encountered. *CACNA1C* (BrS3), *CACNB2b* (BrS4), *GPD1L* (BrS2), *SCN1B* (BrS5), *KCNE3* (BrS6), and *SCN3B* (BrS7) are more rarely seen.⁵⁵ These mutations lead to either a loss of function of sodium (I_{Na}) or I_{CaL} channel current or a gain of function of I_{to} . Mutations in *SCN5A* cause a defect in the sodium channel, thus justifying the use of sodium channel blockers to unmask the concealed form of BrS.⁵⁶ Propagation of the action potential dome from sites at which it is maintained to sites at which it is lost causes local re-excitation, a situation in which an R-on-T extrasystole mediated by phase 2 reentry may propagate transmurally leading to the development of polymorphic ventricular tachycardia and ventricular fibril-

lation (VF). This sequence of events is further facilitated by an increase in transmural dispersion of repolarization, also present under this condition.¹³

The degree to which ERS and BrS overlap still remains unknown. Coexistence of both inferior or infero-lateral ER and typical right precordial BrS pattern in the same patient has been reported, further strengthening the opinion that ER may not be as benign as previously believed.⁵⁷ Moreover, experimental models have demonstrated that, under specific cellular conditions (e.g., ischemia–reperfusion), the ERS electrocardiographic pattern can be converted to a Brugada-like electrocardiographic pattern and that both electrocardiographic features may be present in the same patient.¹³ As already mentioned, despite the fact that these two syndromes show discrete differences, regarding lead localization of ECG abnormalities, opposite response to sodium channel blockers and body temperature (hypothermia induces or accentuates J-point elevation, whereas hyperthermia is a trigger for BrS associated arrhythmic episodes), they share several characteristics. They are both observed predominately in young, otherwise healthy men; they seem to show a familial predisposition and tend to respond in a similar way to heart rate changes, pharmacologic agents and autonomic modulation, exhibiting thus a dynamic pattern.⁵⁸ However, the clinical importance of these similarities needs to be determined.

IDIOPATHIC VF AND ER

Sudden cardiac death (SCD) remains a major public health problem responsible for approximately 350,000 deaths annually in the United States. Only 3–10% of patients who experience an out-of-hospital cardiac arrest are successfully resuscitated and the majority of these episodes are caused by ventricular tachyarrhythmias, predominantly in patients with ischemic heart disease and other cardiomyopathies. However, 6–14% of SCDs still occur in otherwise healthy young persons in whom no structural heart disease is detected, even after an extensive work-up.^{59,60} While a significant number of these cases are attributed to currently well-recognized channelopathies (LQTS, SQTS or BrS), others show no typical ECG signs during sinus rhythm. These individuals experience syncope or SCD usually caused by ventricular extrasystoles with a very short coupling interval, which have been successfully mapped to the Purkinje-fiber network^{61,62} and typically portray a superior axis, implicating an inferior origin.^{61–63} These extrasystoles lead to spontaneous polymorphic ventricular tachycardia or VF by falling on the peak or on the descending limb of the preceding T wave (R-on-T). All these cases are grouped under the term idiopathic VF (IVF).^{64–68} Patients with IVF and prominent J waves tend to develop arrhythmic storms with numerous episodes of VF that fail to respond to conventional antiarrhythmic therapy but respond exquisitely

to quinidine therapy.^{66,69}

As previously stated, ERS, BrS and IVF are identical in terms of their ionic and cellular basis and may be referred to as I_{to} -mediated J-wave syndromes. The only difference among these clinical entities determining their clinical significance is the difference in I_{to} activity, its spatial distribution and the resultant J wave size.¹ When observed in leads V1–V3 (i.e. BrS), J waves and ST segment elevation are traditionally considered malignant, indicating a high risk of developing VF. In contrast, when demonstrated in V4–V6 (i.e. ERS type 1) it is believed that they are benign. While pathophysiological alterations of J wave involving the right ventricle are arrhythmogenic, those related to the left ventricular anterolateral regions are probably benign. The role of the I_{to} channels in arrhythmogenesis is also supported by the higher incidence of VF in patients with acute inferior myocardial infarction and involvement of the right ventricle (8.4%) than in those without right ventricular involvement (2.7%).^{70,71}

Since 1953, when Osborn first implied a possible connection between hypothermia-induced J-waves and occurrence of VF in a canine model, much knowledge has been added concerning the arrhythmogenic potential of J-waves. During the last decade, several case reports, mostly from Asia, highlighted the fact that patients with IVF not only demonstrate distinct J waves on the baseline ECG but also show accentuation of J-wave amplitude immediately prior to the onset of the arrhythmia.^{10,11,41,46,63,72–77} Moreover, experimental studies, demonstrating that the J wave is a marker of increased dispersion of repolarization rendering the subject vulnerable to phase-2 reentry, further supported the notion that ER pattern is a predisposing factor to more malignant arrhythmias.^{1,3,12,15,78} In addition, ECG imaging data support the presence of areas with short action potential and ER and suggest that abnormally steep spatial repolarization gradients provide the ideal substrate for unidirectional block and reentry, leading to proarrhythmia.⁷⁹ However, more robust clinical evidence was derived from 6 case control series involving 331 IVF patients^{5,19,20,32,80,81} and 3 population-based studies with almost 19,000 adults^{6,8,82} conducted during the last 5 years. All except one⁷ defined ER as QRS-ST junction elevation ≥ 0.1 mV (with notching or slurring) in two consecutive inferior-lateral leads.

Although case – control studies do not establish a cause-effect relationship, strong evidence in favor of an association between ER and VF-related SCD has emerged.^{82,83} In 2008, Haissaguerre et al presented the largest series of successfully resuscitated IVF patients so far.¹⁹ A total of 206 patients presenting with IVF in 9 different countries were included; not only was ER observed in significantly more patients with IVF than well-matched healthy subjects (31% vs. 5%, $P < 0.001$), but also data derived from implantable cardioverter-defibrillators (ICD) showed a higher possibility of VF recurrence in survivors with ER than in those without ER (41% vs. 23%, $P = 0.008$), during a five-year follow-up period. In addition, researchers

mapped the site of origin of ectopic activity in 8 patients and found that this was consistent with the location of the repolarization abnormality on the ECG. Subsequently, Rosso et al²⁰ compared the ECG of 45 IVF patients with a group of age- and sex-matched control subjects and found that J-point elevation in the inferior or lateral (I, aVL) leads was significantly more common among the IVF survivors (42% vs. 13%, $P=0.001$). Interestingly, J-point elevation in V4–V6 occurred with equal frequency among IVF subjects and control group (6.7% vs. 7.3%, $P=0.86$). IVF patients had J-point elevation mainly in the inferior leads, less commonly in I to aVL and least commonly in leads V4 to V6. However, the authors concluded that finding a J-wave in a young adult would only minimally increase the probability of IVF from 3.4:100,000 to 11:100,000, reflecting the overall low incidence of this clinical entity in the general population. In another study, Merchant et al⁸⁰ observed that left precordial ER was more prevalent in IVF survivors than in controls and QRS notching is the most prevalent pattern in the malignant variants of ER. Nam et al⁵ reported that ER is more common in IVF survivors than in controls representing the general population (58% vs. 3%), especially when it is depicted in multiple leads (73% vs. 15%, $P<0.05$). A short–long–short sequence and extrasystoles with short coupling intervals were found to precede the occurrence of VF storms. Derval et al⁸¹ evaluated the prevalence and characteristics of ER in 100 VF patients in CASPER (Cardiac Arrest Survivors With Preserved Ejection Fraction Registry). The authors reported that ER, although often intermittent, is more pronounced in IVF patients and that J-point elevation in IVF patients had higher amplitude and wider distribution than those with an established cause of cardiac arrest.

Concerning the population-based studies, in 2003 Klatsky et al⁶ first reported that only 1% of the general adult population has ER and that such individuals do not have any measurable increased risk for death or hospitalization for cardiac reasons. However, although it is the largest study to date, it has severe methodological limitations, mostly concerning the initial interpretation of the surface ECG; emphasis was given on the presence or absence of ST-segment elevation rather than the presence of J waves, whose arrhythmogenic potential versus ST-segment elevation is well-proven nowadays. Tikkanen et al⁸ systemically examined the long-term outcome of ER in the general population. They assessed the prevalence and prognostic significance of ER in a community-based population of 10,864 middle-aged subjects. Individuals were followed-up for a mean period of 30 ± 11 years. The primary endpoint was cardiac death and secondary endpoints were all-cause mortality and arrhythmic death. The prevalence of ER in the general population was 5.8%. J-point elevation ≥ 0.1 mV in the inferior leads was found to be associated with a 1.28-fold increased risk of cardiac death ($p=0.03$), whereas in the lateral leads it was of borderline significance in predicting cardiac death and all-cause death. J-point elevation ≥ 0.2 mV in inferior leads was

observed in 0.3% and increased the adjusted relative risk of death from cardiac causes to 2.98 ($P<0.001$). A total of 9.3% of individuals with ER died of a proven arrhythmic cause over the follow-up period, implying that almost 90% of the cases of ER on ECG were benign. Interestingly, the survival curves started to diverge 15 years after the first ECG recording and continued to diverge at a constant rate throughout the follow-up period, despite continued improvement in the treatment and prognosis of patients with cardiac disease during the past two decades. However, it is highly unlikely that this observation represents death from idiopathic VF because the latter is a relatively rare disease most prevalent at a younger age. On the contrary, in individuals with ER and underlying increased dispersion of repolarization, coronary heart disease, a common clinical situation in a population of middle-aged subjects, might be the trigger to provoke “ischemic VF”.⁸⁴ Sinner et al⁸² reported a 2- to 4-fold increased risk of cardiac mortality in relatively younger individuals (35–54 years old) with J-wave elevation ≥ 0.1 mV, particularly when it was present in inferior leads. However, similar to the previously mentioned study, their mortality curves began to diverge only by the age of 50 years on average.

To conclude, J-point elevation is more frequently observed among patients with IVF than matched control subjects. However, IVF is extremely rare in the general population and according to the Bayes’ law of conditional probabilities, the presence of J-waves on the ECG is likely to cause only a negligible increase in its prevalence and the overall risk for this disease would still be roughly 1:10,000. Hence, the incidental finding of a J-wave during ECG screening of otherwise healthy individuals should not be necessarily interpreted as a marker of increased risk and careful evaluation should be attempted.

ESTIMATING THE RISK

Data obtained from the aforementioned case control studies have enhanced our knowledge concerning the features that could distinguish malignant J waves from benign ERS cases. Investigators have analyzed several clinical (gender, personal history, positive family history of SCD) and ECG characteristics (e.g. morphology and localization of J-waves) of IVF patients and examined their possible connection with the occurrence of life-threatening arrhythmias. Given the data available, the following conclusions can be drawn (Table 2).

GENDER

Although the majority of IVF survivors depicting J-waves on the surface ECG are male, the same observation also exists for controls. Therefore, a logical assumption is that we cannot use gender to distinguish benign from potentially malignant J-waves.

TABLE 2. High-risk criteria from clinical and laboratory evaluation

| |
|--|
| Probable |
| Male gender |
| History of syncope |
| History of familial SCD |
| ER in inferior leads or global ER pattern |
| Terminal notching of QRS complex |
| J-wave amplitude >0.2 mV |
| Horizontal or downward direction of the ST segment |
| Possible |
| EPS |
| Genetic Testing |
| ECG markers of TDR |

ECG = electrocardiogram; EPS = electrophysiology study; ER = early repolarization; SCD = sudden cardiac death; TDR = transmural dispersion of repolarization

FAMILY HISTORY OF SUDDEN DEATH

Although data from Haissaguerre’s team showed that a family history of sudden death is significantly more frequent among J-wave-positive IVF survivors, existing evidence from recent studies denotes that actually only a small percentage of IVF patients reported the sudden death of a family member.^{19,20,69} Thus, it is proposed that apparently healthy young persons with a positive family history of SCD should be carefully evaluated for the presence of congenital channelopathies, regardless of the presence or absence of J waves on their ECG.

SYNCOPE

Abe et al⁸⁵ reported that patients with syncope and no structural heart disease show a 10-fold prevalence of ER compared to healthy controls (18.5%, vs. 2%). Therefore, the possibility of ER-associated syncopal episodes cannot be excluded in at least some of these patients and all ER patients reporting syncope should be offered careful evaluation.

ATHLETES

Probably reflecting alterations in autonomic balance resulting in parasympathetic dominance, athletic activity and high-level training strongly predispose to ER⁸⁶; yet, the incidence of IVF in trained athletes is fairly low.³⁴ Although an ER pattern has been found in 20-90% of routine ECGs conducted in young competitive athletes,⁸⁷⁻⁹⁰ the yield to risk stratification is approaching nil.^{87,91} Investigators concede that lateral ER is the most commonly encountered pattern

in athletes^{20,86,92} and should generally be considered a benign finding. Recently Cappato et al⁹³ reported that J wave and/or QRS slurring in the inferior leads, alone or associated with leads V4-V6, was found more frequently among athletes with SCD than in control athletes. Nevertheless, the presence of this ECG pattern did not confer a higher vulnerability for recurrent malignant ventricular arrhythmias and its incidental finding in a healthy athlete should be considered as a marker that minimally increases the arrhythmic risk.

J-WAVE AMPLITUDE

Case control studies have shown that the J-wave amplitude in IVF patients is significantly larger than that in the controls.^{19,20,81} However, although there was an obvious trend toward higher J-point elevation in IVF patients, a cut-off for J-point elevation capable of reliably distinguishing the malignant from the benign J-wave could not be determined. In the population-based study by Tikkanen et al,⁸ a J-point elevation >0.2 mV in inferior leads, not only contributed to a significantly increased risk of cardiac death as compared with a J-point elevation ≥ 0.1 mV (adjusted relative risk 2.98 vs. 1.28) but also had a marked impact on arrhythmic death (adjusted relative risk, 2.92). Although all these data imply that a higher magnitude of the J-point elevation could be a discriminator of risk, a J-point elevation ≥ 0.2 mV is extremely rare in the general population. Moreover, it should be underlined that the J-wave amplitude is not a static entity but commonly shows beat-to-beat fluctuation, even without drug provocation or exercise. More importantly, a dramatic accentuation of the J-wave amplitude immediately preceding the electrical storm is commonly observed, portending a higher risk for VF in patients with ER.^{5,19}

J-WAVE DISTRIBUTION

In normal subjects, ER is usually confined to the inferior or lateral or left precordial leads. ER-positive patients presenting with IVF are more likely to demonstrate prominent J-waves in the inferior or in multiple leads.^{5,7,8,19,20,82} Although almost 50% of the patients with ER who developed VF depicted a global ER pattern on the ECG (type III ERS),^{5,19} the implications of a global J-wave are still undetermined; theoretically, this characteristic could imply a much more diffuse repolarization abnormality possibly carrying a higher risk. However, the relatively small number of IVF cases in the studies, the discrepancies of the data obtained and the overlap in the distribution of J waves present in IVF patients and controls precludes generalization of the results and prevent us from making safe clinical decisions based on the specific lead where the J waves are seen.

ER PATTERN

The prognostic impact of the three main types of early repolarization, namely, the presence of J waves, R-wave slur-

ring, and ST-segment elevation has been extensively examined. Most authors concede that J wave is the only reliable prognostic marker that distinguished patients with idiopathic VF from controls. Merchant et al⁸⁰ reported that QRS notching in leads V4-V6 was more prevalent among IVF cases than controls and concluded that left precordial terminal QRS notching could be used as a tool for risk stratification of subjects with ER. On the contrary, the presence of R-wave slurring and/or ST-segment elevation were of no prognostic value and provided no additional prognostic information.^{8,20,80,82} This probably explains why the population-based study by Klatsky et al,⁶ focusing mainly on ST-segment elevation, did not have a prognostic value. While a J wave followed by rapidly ascending ST elevation is the most common ER pattern among healthy athletes and does not appear to have any adverse prognostic significance, J waves followed by horizontal or descending ST segment seems to have a positive association with arrhythmic risk, possibly reflecting a myocardial area with extreme repolarization gradients.⁸⁴

ECG MARKERS

Abe et al reported that J-wave positive IVF patients had a higher incidence of late potentials, especially during the night when vagal tone dominates and the detection of late potentials using a 24-hour Holter ECG contributed to identification of those individuals at high risk for recurring arrhythmic events.³² Moreover, novel ECG markers reflecting transmural dispersion of repolarization have been successfully used and proposed to underlie arrhythmogenesis in J-wave syndromes;^{17,29,94} however, more studies are needed to confirm an association with proarrhythmia in ER patients.

ECHOCARDIOGRAPHY

A recently published study⁹⁵ supports the idea that specific types of false tendons found in echocardiographic studies may have a positive relationship with the presence of J-waves in the ECG. However these preliminary data need further evaluation and confirmation.

ELECTROPHYSIOLOGY STUDY (EPS)

IVF patients with ER did not show significantly higher inducibility than those without ER, even when induction of ventricular arrhythmia was attempted following a standard electrophysiological protocol.¹⁹ Moreover, only 34% of the patients with a clinical history of VF were inducible, rendering the electrophysiologic study a less sensitive method for risk stratification of symptomatic patients (syncope or IVF). Taking into account that healthy subjects with ERS resemble asymptomatic BrS in many features and the ongoing debate regarding the usefulness of EPS for risk stratification in asymptomatic BrS,⁹⁶⁻⁹⁸ the role of EPS in primary prevention of IVF in ERS is still obscure.

GENETIC TESTING

ER has been considered to be benign for many years and the importance of the genetic background in ER has recently been suggested, especially after the publication of several studies showing a higher prevalence of ER in siblings of IVF survivors with an ER pattern. However, although the scientific progress is overwhelming and as already stated, several genes involved in ERS, BrS and SQTs have been recognized, genetic markers to differentiate benign and arrhythmic forms of ER are still to be identified. Recently, Haisseguerre et al reported a rare variant in KCNJ8 gene as the first genetic abnormality associated with inferolateral ER and IVF⁴⁶ but more evidence is needed in order to incriminate specific genetic loci; current knowledge supports the idea that ER is probably polygenic and significantly influenced by environmental factors.⁸⁴

SHORT QT SYNDROME

Recently, Watanabe et al reported that ER was more prevalent in the short QT syndrome cohort (65%) than in the short QT control group free of arrhythmic events (30%) and the normal QT control group (10%).⁹⁹ The authors concluded that ER may be a useful marker for risk stratification of cardiac arrest in SQTs. Thus, it appears that it would be important to look for a short QT interval in patients with early repolarization and vice versa.¹⁰⁰

PATIENT MANAGEMENT

Early repolarization patients experiencing ventricular fibrillation (VF) are candidates for secondary prevention with an ICD.³⁴ However, electrical storms frequently recur; IVF survivors presenting ER showed a higher probability of VF recurrence than VF patients without ER (43% vs. 23%, $P < 0.001$) during 5 years of follow-up.¹⁹ In a multicenter study including 122 patients with ER and IVF, Haissaguerre et al⁶⁹ examined the effect of drug therapy on electrical storm. Authors reported that electrical storm was unresponsive to β -blockers, lidocaine, mexiletine and verapamil, whereas amiodarone was only partially effective. On the contrary, intravenous isoproterenol or deep sedation immediately suppressed electrical storm. Regarding long-term management, reports demonstrate that oral antiarrhythmic drugs are poorly effective in preventing VF recurrence, β -blockers, verapamil, mexiletine, amiodarone and class IC antiarrhythmic drugs included. Interestingly, quinidine not only was extremely effective suppressing all episodes of recurrent VF during the 25 ± 18 months of follow-up but also contributed to restoration of ER pattern of the ECG to normal.⁶⁹ Although the efficacy of quinidine has been attributed to I_{to} inhibition, its exact basis still remains unclear, taking into consideration its effect on other ion currents. Innovative drug research toward development of highly selective I_{to} blocking

agents that could be used to prevent J-wave-associated SCD (e.g., acute myocardial infarction, BrS, SQTS, and malignant ER) is currently in progress.¹⁰¹ While catheter ablation of the ectopic focus initiating the VF is another option for the management of drug-resistant VF patients with ER, only preliminary data showing positive short-term results exist and further studies are necessary to examine long-term efficacy.¹⁹

Regarding primary prevention, existing data are scarce and physicians should follow the general directions previously described. The prevention of ER-related SCD is closely related to accurate risk stratification. While SCD survivors should be aggressively treated, individuals at lower risk, based on clinical and laboratory characteristics, should be properly reassured, especially when ER is confined to left precordial leads. The role of autonomic tone needs to be further determined. As previously mentioned, bradycardia accentuates preexisting J waves and seems to be responsible not only for the more prominent ER pattern observed in athletes but also for the nocturnal occurrence of ER-associated SCD. Thus, some “at-risk” individuals could benefit from a pacemaker implantation to prevent bradycardia-dependent exaggeration of ER, especially during resting hours.³⁴

CONCLUSION

J wave syndromes include ERS, BrS and IVF. While the arrhythmogenic potential of BrS has been well established, little was known about the risk of ERS for many years. Current scientific knowledge derived from several case-control and population-based studies with long-term follow-up suggests that ER, particularly when observed in the inferior or inferolateral leads, is not always as benign as traditionally thought. However, although a high prevalence of ER in relatively young patients experiencing IVF has been recorded and SCD is a dramatic situation, IVF is extremely rare and the absolute additive risk attributed to ER is small. Nevertheless, it is imperative that all patients with ER presenting with unexplained syncope or reporting a family history of SCD or idiopathic ventricular arrhythmias be carefully evaluated. Toward this direction, more clinical and experimental studies are needed in order to establish commonly accepted recommendations by using reliable markers for risk stratification. Until then, clinicians should interpret data from the available studies with criticism and avoid inconsiderate generalization of their results; this will prevent them from adopting and then transmitting an exaggerated “fear of J-waves”.¹⁰² On the contrary, they should aim to closely monitor their ER patients in order to distinguish those who fulfill the criteria for further testing. At present, investigation of the asymptomatic individual with an isolated ER pattern and no other features to suggest arrhythmic risk is not indicated.¹⁰³

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