Published in final edited form as:

J Electrocardiol. 2013 ; 46(2): . doi:10.1016/j.jelectrocard.2012.12.002.

Early repolarization syndrome: A decade of progress

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Stemming back to the days of Einthoven, ECG phenomena of “early ventricular repolarization” were often misinterpreted or dismissed without appropriate clinical consideration or detailed investigation. This ensued because of a prevailing opinion that the nature of these phenomena was largely “benign”. Early repolarization changes consistent with Brugada Syndrome (BrS) were interpreted as “innocent” and therefore, overlooked for decades until 1992.¹ The so-called “early repolarization syndrome” (ERS) was universally and unequivocally regarded as “normal,” a “normal variant,” or a “benign early repolarization” until 2000.²

A decade ago, we challenged the “benign” nature of ERS.² The available experimental data suggested that:

- a. Early repolarization pattern (ERP) should not be considered as either normal or benign a priori and that
- b. Under certain conditions known to predispose to ST-segment elevation, subjects with ERP may be at greater arrhythmogenic risk.

Validation of this hypothesis was provided in 2008 in a seminal study reported in the *New England Journal of Medicine* by Haïssaguerre et al.,³ accompanied by editorial comments by Wellens⁴ and a letter to the editor by Nam et al.⁵ These reports provided clinical evidence that there was indeed an increased prevalence of the ERP among patients with a history of idiopathic ventricular fibrillation. Numerous case-control and population based studies followed, confirming a link between ERP and fatal cardiac arrhythmias (see Antzelevitch⁶ for review). Arrhythmogenic forms of ERP are now listed among other primary electrical diseases of the heart.⁷ The past decade has witnessed a rapid surge of interest among clinicians in ERS. Steady progress over the past decade has advanced our understanding of the molecular, cellular, and genetic basis for this primary hereditary channelopathy and its arrhythmogenic potential.

The main focus of this editorial is to highlight the major achievements of clinical and experimental aspects of ERS with special emphases on ECG diagnosis, electrophysiological peculiarities, cellular, molecular, and genetic considerations, risk stratification, treatment, follow-up, and clinical recommendations.

ECG diagnosis

ERP is often diagnosed in young and otherwise healthy individuals (predominantly, males) during routine health check-ups. The “classical” ECG pattern of ERP generally consists of J-deflections with horizontal/upsloping ST-segment elevation, most prominent in mid-precordial leads (V2–V4). It is noteworthy that similar changes might appear in other leads but, to a lesser extent.²

An “atypical” ERP is characterized by the manifestation of the following in the absence of acute coronary insufficiency:

- a. Abnormal elevation of the J-point or ST-segment (>2 mm in right precordial leads and/or 1 mm in other leads);
- b. J-deflections or distinct J-waves with or without ST-segment elevation that are most prominent in the inferior and/or lateral; or
- c. Bradycardia-dependent “slurring or notching” of the downsloping portion of the QRS complex.

“Atypical” ERP, especially in inferior or infero-lateral leads, is commonly associated with the higher risk for life-threatening arrhythmias.^{8–15} Global ERP, manifesting ER in the inferior, lateral and right precordial leads (Type 3 ERS), is associated with the highest level of risk and the development of electrical storms.^{5,16} ECG indices that may be helpful in assessment of arrhythmogenic risk for ERS include:

- a. Localization and number of leads in which ERP is present¹⁷
- b. Horizontal or descending ST-segment following the J-wave or J-point elevation¹¹
- c. Magnitude of J-point elevation¹⁰
- d. Magnitude and duration of J-wave
- e. Association of ERP with abbreviated QT intervals
- f. Short-coupled extrasystoles
- g. Transient J-wave augmentation

It is important to emphasize that abnormal (e.g. inverted) T-waves are not an integral part of ERP and should be considered as an independent ECG abnormality. Also, ECG patterns consistent with ERP and inverted T-waves are not uncommon ECG findings in athletes of West-Asian and African origin,^{18–20} who are also known for high prevalence of hypertrophic cardiomyopathy and sudden cardiac death.

The ECG pattern of ERP is often associated with shorter-than-normal QT interval and, similar to BrS, is more pronounced at slower heart rates or following long pauses (e.g. post-extrasystolic pause). In many cases, a clear distinction between ERS, BrS, and Short QT syndrome cannot always be made on the basis of an ECG alone. In these cases, genetic tests are sometimes helpful in identifying the primary channelopathy and, hence, the most appropriate treatment.

Electrophysiological peculiarities

“Switching” of ECG localization between different ECG leads and ST-T pattern in the same patient is not uncommon among patients with J-wave syndrome.^{5,16} Similarly to other J-wave syndromes (e.g. Brugada syndrome [BrS], hypothermic (Osborn) J-wave), ECG manifestation of ERP can display high dynamicity, changing hour to hour, day to day and year to year. Phenotypic expression is greatly dependent on or modulated by:

- Heart rate and pauses (i.e. ERP is more prominent at slower heart rates). The accentuated ERP can be suppressed at fast pacing rates or in association with premature atrial beats,
- Mediators of autonomic nervous system. Acetylcholine or high parasympathetic tone accentuates the manifestation of ERP. Of note, ERP-like ECG changes are often associated with high spinal cord injury that, in its own turn, is associated with

deterioration or disruption of the cardiac sympathetic activity, leaving parasympathetic activity unopposed.²¹ ECG patterns “wax and wane” in ERS and BrS due in large part to variations of autonomic tone.²²

- Drugs, such as sodium-channel blockers, beta-blockers, quinidine or isoproterenol. Sodium-channel blockers can be used to unmask latent forms of BrS as well as some, but not all cases, of ERS. The accentuated ERS could then be suppressed with quinidine and isoproterenol.^{23,24}
- Androgen hormones. Since ERS is diagnosed predominantly in young males, it is anticipated that testosterone might play an important role in age-related appearance of ERS. Indeed, after puberty, ST-segment elevation in the precordial leads, particularly in the right precordial leads, becomes more prominent in males, but not in females, and decreases gradually with advancing age.²⁵ Androgen-deprivation therapy significantly decreased ST-segment elevation, and arrhythmogenic events in BrS. Similar changes might be relevant in ERS.

Cellular, molecular, and genetic considerations

Much of the experimental data relative to J-wave syndromes derive from studies involving the coronary-perfused wedge preparation. These studies have demonstrated a common cellular mechanism for the electrocardiographic and arrhythmic manifestations of the J-wave syndromes (ERS and BrS), their response to various drugs and neurohormones, including the pro-arrhythmic risk of sodium-channel blockers in BrS (see Antzelevitch and Yan¹⁷ for more detailed information). A transmural voltage gradient caused by differences in the magnitude of I_{to} -mediated action potential (AP) notch between ventricular epicardium and endocardium is thought to be responsible for inscription of the electrocardiographic J-wave.²⁶ Fig. 1 illustrates the diversity of ECG phenotypes generated by different configurations of the epicardial action potential notch and varying degrees of transmural conduction in coronary-perfused canine left ventricular wedge preparations. These range from a J point elevation to slurring of the terminal part of the QRS, distinct J waves with and without ST segment elevation as well as gigantic J waves, appearing as an ST segment elevation, which often give rise to polymorphic VT. The distinctive ERP patterns all result from “early repolarization” of the epicardial action potential and reflect the dynamicity that can be observed clinically in select patients with ERP or ERS. These findings provide justification for the long-standing use of the nomenclature and question the need for narrow or overly restrictive definitions of ERP.^{28–30}

Whether reduced by I_{to} blockers, such as 4-aminopyridine or quinidine, increased heart rates or premature activation or augmented by exposure to hypothermia, I_{Ca} and I_{Na} blockers or I_{to} agonists such as NS5806, changes in the magnitude of the epicardial AP notch parallel those of the J-waves.²⁶ Augmentation of the net repolarizing current, whether secondary to a decrease of inward current or an increase of outward current, accentuates the notch, leading to augmentation of the J-waves or the appearance of ST-segment elevation. A further increase in net repolarizing current results in accentuation of the AP notch and loss of the AP dome and plateau, leading to a transmural voltage gradient that manifests as an accentuated J-waves or an ST-segment elevation, leading to the development of phase 2 reentry and polymorphic ventricular tachycardia.¹⁷

Sodium-channel blockers such as procainamide, pilsicainide, propafenone, and flecainide cause a further outward shift of current flowing during the early phases of the AP and are therefore effective in inducing or unmasking concealed J-wave syndromes.^{31,32} In ERS, sodium channel blockers often appear to diminish the appearance of J-waves.³² This may be due in part to their effects to simultaneously slow transmural conduction, causing the J-wave to appear later on the downsloping segment of the R-wave.

The familial nature of ER patterns has been demonstrated in a number of studies,^{9,33,34} suggesting that genetic factors underlie some cases of ERS. Genetically-mediated, symptomatic ERS, like BrS, is a heterogeneous electrical disorder. Thus far, mutations in six genes have been identified in ERS patients. The gene/protein mutations associated with ERS include *CACNB2b/Cav 2b* (8.3%), *CACNA1C/Cav1.2* (4.1%), *CACNA2D1/Cav 2d* (4.1%), *SCN5A/Nav1.5*, *KCNJ8/Kir6.1* and *ABCC9/SUR2A*.⁶

Risk stratification

Although ERS and BrS share similar ECG, ionic and molecular characteristics, responses to changes in rate, neuromodulation and response to pharmacologic agents, most individuals exhibiting a “classic” ERP have minimal to no risk, while clinical outcomes in subjects with “atypical” forms of ERP are less benign. Therefore, identification of “high risk” patients is one of the most challenging tasks in clinical cardiology today. The following attributes should be considered in risk stratification of ERP:

1. Family history of ERS, unexplained syncope or family history of sudden (cardiac) death
2. Extension of ER pattern into a BrS pattern (Type 3 ERS)^{16,17}
3. Horizontal ST-segment following the J-wave^{11,13,13}
4. Localization of ERS in inferior or infero-lateral leads^{10,12}
5. Presence of closely-coupled ventricular premature complexes
6. Male gender¹⁷
7. Young age (13–45 years)
8. High parasympathetic tone (vagotonics)
9. Association of ERP with short QT intervals.³⁵

The available evidence suggests that ERP is associated with relatively low risk¹² except in the presence of the risk factors discussed above or when associated with other pathologies such as heart failure, severe hypokalemia or acute coronary syndrome.^{36–39}

Criteria for distinguishing benign from malignant variants of ERP remain poorly developed and there is a critical need for expanding our knowledge in this direction.

Treatment, follow-up, and clinical recommendations

The impressive progress of recent years notwithstanding, definitive recommendations regarding treatment and follow-up of subjects with ERS remain to be fully elucidated. Similar to BrS, implantable cardioverter–defibrillators (ICD) should be considered as a primary option for secondary prevention of fatal arrhythmias in symptomatic ERS patients. In ERS subjects with a strong family history of sudden cardiac death, drug treatment with quinidine and/or prophylactic implantation of an ICD should be considered. Cilostazol, a phosphodiesterase III inhibitor, has been shown to be effective in normalizing the ECG in cases of BrS, and is expected to do so in ERS.⁴⁰ In cases of ERS-mediated electrical storms, beta adrenergic agents such as isoproterenol are advisable.^{17,24}

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Fig. 1.

Different manifestations of early repolarization. Each panel shows transmembrane action potentials recorded from the epicardial and endocardial regions of arterially-perfused canine left ventricular wedge preparations and a transmural ECG simultaneously recorded. Under the conditions indicated, early repolarization of the epicardial action potential results in different configurations of the action potential notch giving rise to diverse electrocardiographic manifestations of ERP. The six panels illustrate the cellular basis for a J point elevation, a distinct J wave, slurring of the terminal part of the QRS, combined J wave, J point and ST segment elevation, and a gigantic J wave appearing as an ST segment elevation, which gives rise to polymorphic VT. Modified from Antzelevitch et al.²⁷ with permission.