

## Rationale for the Use of the Terms *J*-Wave Syndromes and Early Repolarization

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The J-wave is a deflection immediately following the QRS complex of the surface electrocardiogram (ECG) that has been linked to the development of a pronounced dispersion of repolarization within the ventricular myocardium leading to the development of cardiac arrhythmias. When partially buried in the R-wave, the J-wave appears as a J-point elevation and may be accompanied by an ST-segment elevation, an electrocardiographic feature that is often referred to as an early repolarization (ER) pattern. Several lines of evidence have been advanced pointing to the association of ER pattern with life-threatening arrhythmias, designated as early repolarization syndrome (ERS) or Brugada syndrome (BrS) based on the region of the heart responsible for the arrhythmogenic substrate. Although BrS and ERS differ with respect to the magnitude and lead location of abnormal J-wave manifestation, they are thought to represent a continuous spectrum of phenotypic expression termed *J-wave syndromes* (1).

Early repolarization, consisting of a distinct J-wave or J-point elevation, a notch or slur of the terminal part of the QRS and an ST-segment elevation, is predominantly found in healthy young males and has traditionally been viewed as totally benign (2,3). The observation in 2000 that an ER pattern in the coronary-perfused wedge preparation can easily convert to one in which phase 2 re-entry gives rise to polymorphic ventricular tachycardia/ventricular fibrillation (VT/VF) prompted the suggestion that ER may in some cases predispose to malignant arrhythmias in the clinic (1,4,5). Sporadic case reports and experimental studies have long suggested a critical role for the J-wave in the pathogenesis of idiopathic ventricular fibrillation (IVF) (6–14). A definitive association between ER and IVF has been presented in more recent reports (15–19).

We recently suggested a classification scheme based on the available data (1). An ER pattern manifest predominantly in the lateral precordial leads was designated as Type 1; this form is very prevalent among healthy male athletes and is thought

to be associated with a relatively low level of risk for arrhythmic events. ER pattern in the inferior or inferolateral leads was designated as Type 2; this form is associated with a moderate level of risk. Finally, an ER pattern appearing globally in the inferior, lateral, and right precordial leads was labeled Type 3 and is associated with the highest level of risk and, in some cases, is associated with electrical storms (1). BrS represents a fourth variant in which ER is limited to the right precordial leads.

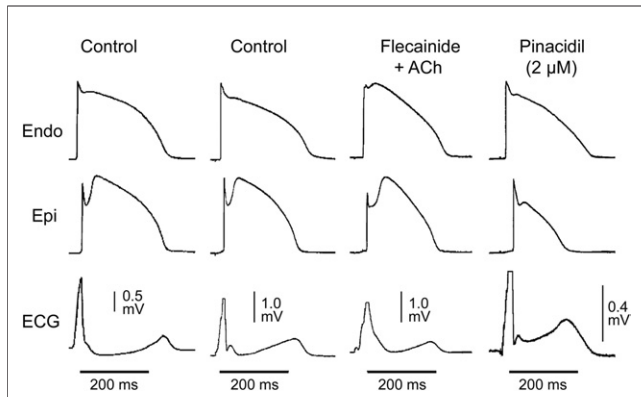
In both BrS and ERS, the manifestation of ER is dynamic (14,20,21), with the most prominent ECG changes appearing just before the onset of VT/VF (7–14, 20–22). The J-wave syndromes share other similarities as well, including a strong male predominance, clinical outcomes, risk factors, and a common arrhythmic platform related to amplification of the J-wave.

In this issue of the *Journal*, Surawicz and Macfarlane (23) question the appropriateness of the terms *J-wave syndromes* and *early repolarization*. The authors first question whether the low-frequency deflection at the end of the QRS that we refer to as a J-wave represents ventricular depolarization or early repolarization. Experimental data generated using the coronary-perfused wedge preparation have provided insights into the cellular basis for the J-wave (7,24,25). As illustrated in Figure 1, the presence of a transient outward current ( $I_{to}$ )-mediated action potential notch in ventricular epicardium, but not endocardium, produces a transmural voltage gradient during early ventricular repolarization that registers as a J-wave or J-point elevation on the ECG. Direct evidence in support of this hypothesis derives from the demonstration that factors that accentuate or diminish the action potential notch produce a corresponding change in the manifestation of the J-wave (7).  $I_{to}$  is largely responsible for phase 1 of the epicardial action potential; because it is slow to recover from inactivation, the current is reduced following an acceleration of heart rate or the introduction of a premature beat, resulting in a decrease in the magnitude of the J-wave (Fig. 2) (26,27). This feature is helpful in discriminating between a J-wave and a delayed depolarization interrupting the QRS, because the latter will become more accentuated with prematurity or acceleration of rate.

Surawicz and Macfarlane (23) highlight the importance of lead, sex, age, and race in evaluating the significance of

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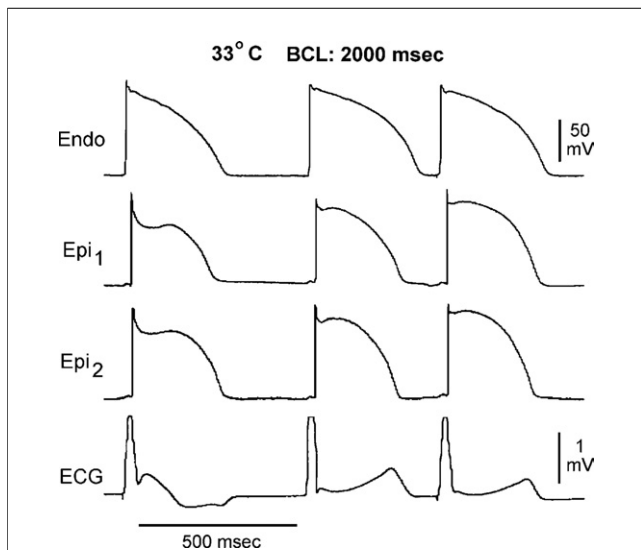
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**Figure 1** Different Manifestations of Early Repolarization

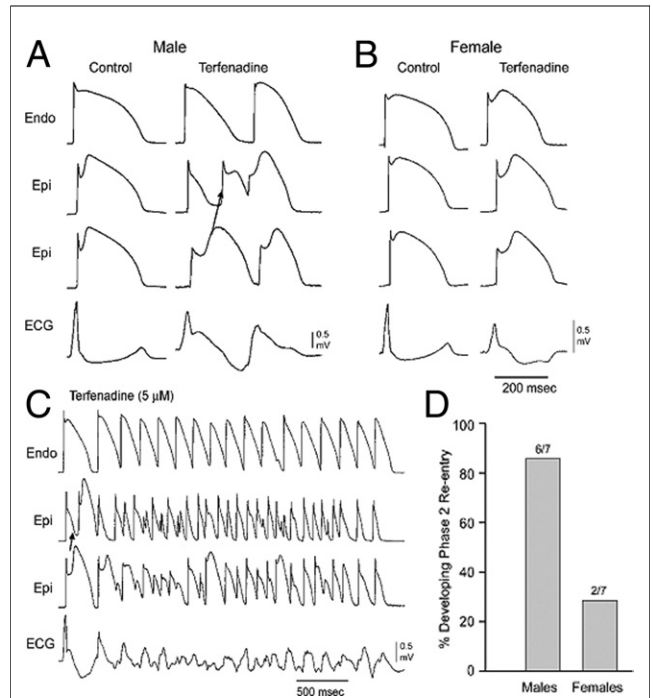
Each panel shows transmembrane action potentials recorded from the epicardial (Epi) and endocardial (Endo) regions of an arterially perfused canine left ventricular wedge and a transmural electrocardiogram (ECG) simultaneously recorded. Under the conditions indicated, the 4 panels illustrate the cellular basis for a J-point elevation, a distinct J-wave, slurring of the terminal part of the QRS, and combined J-wave, J-point, and ST-segment elevation. ACh = acetylcholine.

J-point elevation and early repolarization. Many of these distinctions are attributable to differences in the intensity of  $I_{to}$ , which have been shown to underlie the predisposition to the development of both BrS and ERS (28). Figure 3 illustrates the predominance of the BrS phenotype in coronary-perfused canine right ventricular (RV) wedge preparations isolated from males versus females. Myocytes isolated from the RV epicardium of males was shown in the same study to possess a higher density of  $I_{to}$  when compared with myocytes isolated from female hearts.



**Figure 2** Rate Dependence of the Epicardial Notch and J-Wave Under Hypothermic Conditions

Shown are action potential recordings from an endocardial and 2 epicardial sites of a coronary-perfused wedge preparation together with a pseudo-ECG. Abbreviations as in Figure 1.

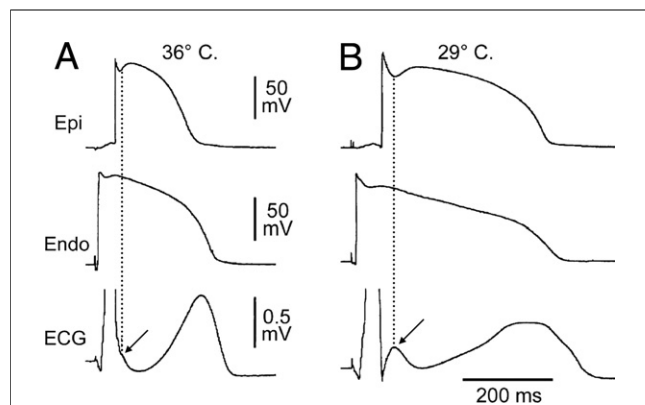


**Figure 3** Predominance of the Brugada Phenotype in Males

Each panel shows action potentials simultaneously recorded from 2 epicardial (Epi) sites and 1 endocardial (Endo) site of male or female right ventricular (RV) wedge preparations, together with a transmural electrocardiogram (ECG). (A) The addition of a potent sodium and calcium-channel blocking agent (terfenadine, 5  $\mu\text{mol/l}$ ) induces a heterogeneous loss of action potential dome, ST-segment elevation, and phase 2 re-entry (arrow) in a male RV wedge preparation. (B) The same concentration of terfenadine fails to induce as pronounced a Brugada phenotype in a female RV wedge preparation. (C) Development of polymorphic VT triggered by spontaneous phase 2 re-entry in a male preparation. (D) Incidence of phase 2 re-entry in male (6 of 7) versus female (2 of 7) RV wedge preparations when perfused with 5  $\mu\text{mol/l}$  terfenadine for up to 2 h. Modified, with permission, from Di Diego et al. (28).

The authors express curiosity as to why “the letter *J* in cardiac electrophysiology defines 2 unrelated and totally different events,” the J-point elevation seen in the normal ECG and the “long, slow deflection of uncertain origin at the end of the QRS complex, originally identified in hypothermia.” In previous studies designed to delineate the cellular basis for the J-wave, we demonstrated that the cellular basis for these 2 phenomenon is indeed similar (7,29). Figure 4 shows a marked accentuation of the J-wave in response to hypothermia in a canine left ventricular wedge preparation. Under normothermic conditions, much of the J-wave is buried inside the QRS. With hypothermia, the epicardial action potential notch is markedly accentuated and transmural conduction is slowed, giving rise to a distinct J-wave, reflecting the transmural voltage gradient created by accentuation of the notch in epicardium, but not endocardium. The 2 electrocardiographic morphologies represent 2 extremes of a continuous spectrum.

Asserting that “the letter *J* in cardiac electrophysiology defines 2 unrelated and totally different events” is tantamount to arguing that the normal T-wave of healthy



**Figure 4** Hypothermia-Induced J-Wave

Each panel shows transmembrane action potentials from the epicardial and endocardial regions of an arterially perfused canine left ventricular wedge and a transmural ECG simultaneously recorded. (A) At 36°C, the action potential notch in LV epicardium is relatively small and much of the J-wave is buried in the QRS, manifesting as a J-point elevation (arrow). (B) A decrease in the temperature of the coronary perfusate to 29°C results in a slowing of transmural conduction and a dramatic increase in the amplitude and width of the action potential notch in epicardium but not endocardium, leading to the development of a transmural voltage gradient that manifests as a prominent J-wave on the ECG (arrow). Modified, with permission, from Yan and Antzelevitch (7). Abbreviations as in Figure 1.

individuals and the bizarre notched T waves of patients with long QT syndrome type 2 are 2 totally different events when, in fact, they also are part of a continuous spectrum.

The authors also question the need for the term *early repolarization*. This term is one used by electrocardiographers for decades with very limited understanding of the mechanisms involved. Criticism of the term may have been justified in the early years, but no longer, for it is now clear that it is the early repolarization phase or phase 1 of the action potential, sometimes accompanied by a depression of phase 2, that is the basis for the ER pattern. Figure 1 illustrates how different manifestations of the early phases of the epicardial and endocardial action potential give rise to the various ECG morphologies associated with ER, including a J-point elevation, a distinct J-wave, slurring of the terminal part of the QRS, and combined J-wave, J-point, and ST-segment elevation.

The question is once again posed as to whether ER patterns may in some cases represent delayed activation. As previously discussed, this can be discerned on the basis of the ER response to prematurity and acceleration. It is noteworthy that a multitude of studies examining the rate dependence of ER have shown that this ECG manifestation normalizes at rapid heart rates, consistent with the repolarization hypothesis. It is also noteworthy that quinidine, via its action to inhibit  $I_{to}$ , normalizes the ER pattern and exerts an antiarrhythmic effect in this setting (29). If it was due to delayed activation, both acceleration and quinidine via its inhibition of the sodium channel current would be expected to accentuate the ER pattern.

We are truly indebted to Surawicz and Macfarlane (23) for their many valuable contributions to electrocardiography. Over a period of many decades, they have critically shaped our thinking with regard to diagnosis and treatment of cardiac arrhythmia and sudden death syndromes. On this particular issue, we respectfully disagree and make a plea for investigators to focus on diagnostic criteria and provocative measures that can be used to identify individuals at risk rather than on terminology. It is clear that the vast majority of individuals with ER are at no or minimal risk for arrhythmic events and sudden cardiac arrest. Our challenge moving forward is to develop better risk stratification strategies and more effective treatments for the J-wave syndromes (30).

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**Key Words** Brugada syndrome ■ cardiac arrhythmias ■ early repolarization syndrome ■ electrocardiogram ■ hypothermia ■ sudden cardiac death.