Idiopathic Ventricular Fibrillation, Early Repolarization and Other J Wave-Related Ventricular Fibrillation Syndromes

– From an Electrocardiographic Enigma to an Electrophysiologic Dogma –

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Current clinical and experimental data demonstrate that the electrocardiographic J wave plays a critical role in the pathogenesis of ventricular fibrillation (VF) in patients with Brugada syndrome (BS) and early repolarization (ER) syndrome (ERS). This has generated renewed interest in the presence of J waves and ERS in the general population, yet the identification of high-risk ECG markers and the risk stratification of subjects with ERS remain to be established. More recently, this concept has been expanded to VF mechanisms in patients with structural heart diseases. Some of the fatal arrhythmias in the setting of acute myocardial ischemia or infarction may share a similar, J wave-related electrophysiologic process. In canine arterially perfused wedge preparations, the occurrence of J wave-related arrhythmias is mediated by phase 2 reentry. The stability of the action potential (AP) dome in the ventricular epicardium is dependent on the prominence of the AP phase 1 notch. The ability to maintain the AP dome depends on a delicate balance between inward and outward ionic currents during depolarization and the early phase of repolarization. Outward shifts of the balance and inability to maintain the AP dome result in marked dispersion of repolarization and vulnerability to VF. This review describes the electrocardiographic and clinical features of the J waves in idiopathic VF and other structural heart diseases. (Circ J 2012; 76: 2723–2731)

Key Words: Electrocardiography; J waves; Sudden cardiac death; Ventricular fibrillation

Sudden cardiac death (SCD) occurs predominantly in patients with structural heart diseases. Data on SCD survivors indicate that 5–10% of cases occur in the absence of any apparent cardiac disease.1–2 Primary electrical disorders resulting from ion-channel mutations are believed to play a crucial role. Electrocardiography (ECG) provides important clues to the differential diagnosis of these primary electrical diseases. New clinical entities such as Brugada syndrome (BS), catecholaminergic polymorphic ventricular tachycardia, or short QT syndrome have been introduced.3–5 The recent introduction of a new clinical entity, early repolarization syndrome (ERS), and subsequent demonstration of the importance of the J wave in survivors of SCD have generated renewed interest in the ECG J waves.6–8 BS and ERS share many electrocardiographic and clinical features, and have been collectively grouped as J wave syndrome (JWS). The concept has now expanded to include other structural heart diseases such as acute myocardial infarction, variant angina and even some forms of cardiomyopathy.9–14 This highlights the possibility that J waves may be even more important than previously recognized and may serve as a common mechanism of ventricular fibrillation (VF) in various clinical settings. This review describes the electrocardiographic features and basic electrophysiologic mechanisms underlying these J wave-related VF syndromes.

VF in the Absence of Structural Heart Disease

The clinical evaluation of survivors of SCD needs to be comprehensive because the identification of a correctable cardiac condition is critically important. A proposed systematic approach to survivors of SCD includes ECG, telemetry, transthoracic echocardiography, coronary angiography, ergonovine provocation test, signal-averaged ECG, exercise treadmill test, and intravenous epinephrine and flecainide challenge. In selected patients, cardiac magnetic resonance imaging, voltage mapping, right ventricular angiography and biopsy, and electrophysiological tests are required. As the sensitivity of any diagnostic test is not 100%, and disease manifestation may fluctuate spontaneously, repeat testing at certain intervals may be sometimes required.15

Figure 1 summarizes the distribution of underlying cardiac diseases in SCD survivors who underwent an implantable
cardioverter defibrillator (ICD) implantation at the Asan Medical Center, Korea. Structural diseases were present in 209 (68%) of 309 ICD recipients. Coronary artery disease, hypertrophic or dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy were the most common structural abnormalities in this cohort. Among the 100 patients without structural cardiac diseases, LQTS, BS and ERS were identified in 10 (3.2%), 29 (9.4%) and 16 (5.2%) of the patients, respectively. After extensive search for an underlying etiology, the diagnosis remained idiopathic in 45 patients (14.5%). LQTS, long QT syndrome; BS, Brugada syndrome; ERS, early repolarization syndrome.

### Table: Underlying diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long QT syndrome (LQTS)</td>
<td>10</td>
<td>3.2%</td>
</tr>
<tr>
<td>Brugada syndrome (BS)</td>
<td>29</td>
<td>9.4%</td>
</tr>
<tr>
<td>Early repolarization syndrome (ERS)</td>
<td>16</td>
<td>5.2%</td>
</tr>
<tr>
<td>J wave-related VF in the absence of structural heart diseases (IVF-J)</td>
<td>19</td>
<td>6.1%</td>
</tr>
<tr>
<td>Idiopathic ventricular fibrillation (IVF)</td>
<td>26</td>
<td>8.4%</td>
</tr>
<tr>
<td>Myocardial infarction or coronary artery disease</td>
<td>79</td>
<td>25.6%</td>
</tr>
<tr>
<td>Variant angina</td>
<td>10</td>
<td>3.2%</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>33</td>
<td>10.7%</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>45</td>
<td>14.6%</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>13</td>
<td>4.2%</td>
</tr>
<tr>
<td>Others (Sarcoidosis, valve, congenital diseases, etc.)</td>
<td>29</td>
<td>9.4%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>309</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

**Figure 1.** Summary of the distribution of underlying cardiac diseases in survivors of sudden cardiac death (SCD) who received an implantable cardioverter defibrillator (ICD) at the Asan Medical Center, Seoul, Korea. Structural diseases were present in 209 (68%) of 309 ICD recipients. Coronary artery disease, hypertrophic or dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy were the most common structural abnormalities in this cohort. Among the 100 patients without structural cardiac diseases, LQTS, BS and ERS were identified in 10 (3.2%), 29 (9.4%) and 16 (5.2%) of the patients, respectively. After extensive search for an underlying etiology, the diagnosis remained idiopathic in 45 patients (14.5%). LQTS, long QT syndrome; BS, Brugada syndrome; ERS, early repolarization syndrome.

Interestingly, after careful review of all the ECGs taken during peri-event periods, provocation, and at the outpatient clinic, a significant proportion (19/45, 42.2%) of the patients whose diagnosis was presumed to be idiopathic showed a J wave fluctuation, which did not satisfy the diagnostic criteria of either BS or ERS. These patients are described later in the section about J wave-related VF syndrome in the absence of structural heart disease (IVF-J). In 26 patients, abnormal findings were not identified in any of the ECGs, and these cases were termed true “idiopathic VF (IVF)”.

**BS**

BS is the prototype of cardiac ion-channel diseases, and has opened a new era in translational electrophysiology. It is characterized by unique ECG changes of coved-type J/ST/T waves, and a high risk of developing VF. The prevalence of the typical coved-type BS ECG is approximately 0.1% in the general population. The odds ratio of mortality was previously reported to be 52.63 in patients with a BS ECG pattern compared with that of control subjects. The risk stratification of subjects who display a BS-type ECG remains a subject of some debate. A history of syncope is unanimously accepted as the most important prognostic marker, but controversy exists on the role of an electrophysiologic study (EPS). The initial report by Brugada et al emphasized an important prognostic implication of EPS results. However, subsequent investigations have failed to verify this. Other factors such as family history and SCN5A mutations are of little prognostic importance. ECG parameters, including PQ interval, T wave amplitude, fragmented QRS, and post-exercise ST-segment augmentation, have been reported as significantly associated with the prognosis of BS, but this needs further investiga-
The annual cardiac event rate was reported to be 7.7% in patients with aborted SCD, 1.9% in patients with syncope, and 0.5% in asymptomatic patients. Because of this low risk of events and the uncertain predictive role of EPS, the 2006 ACC/AHA/ESC guideline indicates a simpler approach based largely on fatal ventricular arrhythmia or symptoms (syncope). An EPS in asymptomatic subjects was designated a Class IIb indication.

In addition to risk stratification, the ECG diagnosis of BS needs to be redefined. Richter et al defined a subgroup of patients who demonstrate type I BS ECG only in 1 right precordial lead (V1 or V2). Although these cases did not satisfy the diagnostic criteria of BS, the overall clinical profile and arrhythmic risks were found to be similar to those with type I ECG in more than 1 precordial lead. The authors suggested from their analysis that the definition of BS needs to be revised. In addition, the classification of the BS ECG subtypes proposed in the second consensus meeting is not inclusive of all BS-type ECG variants. The diagnostic criteria of the BS type II/III ECG restricts this definition to cases in which the J wave is ≥2 mm, but it is not uncommon to find, among the survivors of SCD, J waves <2 mm even after pharmacologic provocation. This limitation has led to a proposal for new ECG criteria. For example, the Japanese IVF study group reclassified BS ECGs into 3 subtypes: type I, type II/III, and type S. Type S has been defined as a coved-type ST segment elevation with J wave amplitude 0.1–0.2 mV. The clinical features and long-term outcomes of these type II/III or type S subgroup patients have not yet been described.

Another pitfall in the ECG diagnosis of BS is the so-called “masked” BS. In patients with bundle branch block (BBB), the BS-type ST changes may be buried within the wide QRS complex, being unmasked only when the BBB is relieved. Therefore, in patients with cardiac arrest and right BBB, the possibility of masked BS should be considered in the differential diagnosis before concluding that the condition is idiopathic (Figure 2).

ERS The introduction of ERS has provoked widespread interest in the J wave phenomenon among clinicians and electrophysiologists. The history of this J wave-related VF dates back to decades ago when the importance of J waves and their dynamic changes before VF episodes was first described. Prompted by the similarity in the ECG features and the potential of converting to BS ECG patterns, the benign nature of the ER pattern was questioned, and the new term, “J wave syndrome” was coined. The possible association of the J wave with IVF was later confirmed in the landmark study by Haïssaguerre et al, which provided a comprehensive description on the clinical and electrocardiographic manifestations, and response to treatment. The spotlight shed on the J wave and ER pattern was followed by case-control and large population studies that searched for...
the ECG markers of ER patterns that would distinguish malignant from benign forms of ER. Tikkanen et al showed in their 30-year follow-up cohort that a J wave >2 mm in the inferior leads was a particularly important indicator of a subgroup of patients with a higher risk of arrhythmic death (relative risk, 2.92). Subsequent reports have also shown that the ERS pattern is associated with a significant increase in the risk of arrhythmic or cardiac mortality. The discrepancy between the traditional concept and recent studies seems to stem from the difference in the definition of ERS, as indicated previously by Derval et al. In contrast to the traditional definition of ERS, in which ECG characteristics are composites of ST segment elevation, J wave and symmetric tall T wave, the new definition of ERS proposed by Haissaguerre et al, and subsequently by others, centers more on the J wave notch or slur, irrespective of the ST-segment changes. This new definition drastically changed the concepts and attitudes towards this common ECG finding in clinical practice.

The concerns posed by the association of the J wave and the increased risk of arrhythmic mortality spurred investigations of new methods for risk stratification of subjects with ER patterns. Tikkanen et al again identified a subgroup of patients with ER who show a benign long-term prognosis. If the ST-segment after the J wave is ascending, the long-term mortality is not significantly different from that of the general population, whereas subjects with a J wave and horizontal or descending ST-segment changes are at higher risk of arrhythmic death. This idea was confirmed in subsequent studies. Viskin et al tested this result in a cohort of IVF patients and found that the presence of J wave is associated with idiopathic VF with an odds ratio of 4.0, but that having both a J wave and horizontal/descending ST-segment changes yielded an odds ratio of 13.8. Because of the high prevalence of ER pattern, this risk stratification has profound clinical importance. However, the current risk stratification scheme is still in its infancy. The reported odds ratio for the occurrence of VF in the high-risk group (J wave and horizontal or descending ST-segment) is still too low. The estimated odds (≈34/100,000) for developing VF in patients with both a J wave and horizontal/descending ST-segment are not sufficient to forecast future arrhythmic risk among subjects with an ER pattern. In addition, this risk marker does not have immediate prognostic implications. For example, in a previous Finnish population study, mortality differences emerged more than 10 years after diagnosis. In an Israeli cohort of IVF patients and matched controls, J waves with horizontal/descending ST-segments were observed in 13 (68.4%) of 19 IVF patients, whereas 4 (25%) of the 16 age-matched controls had a horizontal/descending ST-segment morphology (Figure 3 of reference 48). The high prevalence of ascending ST-segment changes in the IVF group, and significant proportion of horizontal/descending ST-segments in the control group makes a differential diagnosis dif-

![Figure 3. Initiation of ventricular fibrillation (VF) in patients with early repolarization syndrome (ERS). (A) 12-lead ECG obtained during an electrophysiologic study in a 53-year-old female. The patient presented with recurrent syncope, VF and aborted sudden death. Five days after this electrical storm, the patient underwent an electrophysiologic study. The ECG shows 1 of the 5 spontaneous VF episodes that occurred during the study. The J waves in the lateral precordial leads were greatly augmented after a long pause before the precipitation of VF. A premature ventricular beat with a short coupling interval of 280 ms initiates VF. (B) RR interval histogram obtained during ICD interrogation in a 43-year-old male patient with ERS. A short-long-short alternation of the cycle length initiating 20 beats prior to the VF onset was recorded. Patients with ERS typically showed bigeminy PVCs with short coupling intervals. PVC, premature ventricular contraction.](attachment:image)
J Wave-Related VF Syndromes

The proposed JWS in structurally normal hearts refers to BS and ERS. However, analysis of ECGs from SCD survivors...
suggests that the J wave may be responsible in a significant proportion of those patients with IVF. Figure 5 shows an example of ambiguous ECG features that are commonly recorded in survivors of SCD. ECGs were recorded in a 33 year-old male SCD survivor during a flecainide provocation test (Figures 5A,B). The patient presented with agonal respiration and seizure-like activity during sleep. VF was documented and an ICD was implanted. The coved-type ST-segment elevation is close to that of type I BS ECG, but the amplitude of the J wave is <2 mm (arrow) and localized in V1 only. This, by definition, does not satisfy the diagnostic criteria of BS but in practice is generally referred to as BS. (C,D) ECGs recorded during outpatient clinic follow-up of a 32 year-old male patient who was found unconscious at home and was resuscitated from VF. A fluctuating J wave and ST-segment can be seen in the right precordial leads. This type II/III BS ECG pattern (arrow) was recorded during a flecainide test, but a typical type I pattern was not provoked. VF, ventricular fibrillation.

The definition of ERS is limited to J waves in the inferior or lateral precordial leads to avoid overlap with BS. However, the ECG features in this patient conform to the classic definition of an ER pattern. Based on current diagnostic criteria, these features do not belong to ERS because of the J waves in the right precordial leads, but at the same time, they do not satisfy the diagnostic criteria of BS because the ST/T wave morphology is not coved and the amplitudes of the J waves are <2 mm even after pharmacologic provocation.

In a cohort of ICD recipients at the Asan Medical Center, a significant proportion (19/309, 6.1%) of the recipients demonstrated J waves in their resting or peri-event ECGs. These 19 patients showed a BS type II/III pattern (J wave ≥2 mm, saddleback), or undefined (J wave amplitude, 1–2 mm) type ECGs that did not turn into typical type I ECG after intravenous flecainide provocation or during follow-up. In some of them, a type I BS ECG was mimicked when coved-type ST segment elevation occurred (Figure 5B), and in others ERS was mimicked when the J/ST/T waves had a saddleback morphology (Figure 5D). In fact, many of these patients were initially di-
agonsed with BS and managed accordingly. These patients showing variations in the J-ST-T waves, which are not defined by the current ECG criteria of BS or inferolateral ERS, should be called a subgroup of a broader JWS. This concept expands the territory of the JWS to some of the IVF patients (Figure 6). Most importantly, this is supported by the fact that these individuals show dynamic J wave behaviors in response to heart rate, pharmacologic treatment, autonomic response, and long-term outcome (appropriate ICD discharge), similar to BS or ERS patients.48–53

**J Wave-Related VF in Patients With Structural Heart Disease or Other Conditions**

The J wave phenomenon is observed not only in structurally normal hearts but in patients with structural heart diseases. The pathogenic role of the epicardial notch and phase 2 reentry in the early stages of acute myocardial ischemia was demonstrated by Yan et al54 who showed that acute regional myocardial ischemia results in heterogeneous loss of the epicardial action potential (AP) dome across the ischemic border zone, leading to phase 2 reentry and R-on-T extrasystoles inducing VFs. Although direct evidence is lacking, as the J wave is an electrocardiographic marker of vulnerability to phase 2 reentry, its presence in the setting of acute myocardial ischemia is presumed to portend a higher likelihood of VF and SCD. An unusual association of BS and vasopastic angina55 and occurrence of the J wave in acute ischemia supports these experimental results.56

This hypothesis was subsequently confirmed in patients with acute myocardial ischemia/infarction.8–11 The presence of ER pattern was found to increase the risk of VF occurrence within 48 h of AMI onset.9 A J-point elevation in the inferior leads, greater magnitude of the J-point elevation, and ER with a horizontal/ascending ST-segment are all significantly associated with VF occurrence. The importance of the J wave and its pathogenic role has also been demonstrated in patients with variant angina. ER pattern has been observed in one-fifth of variant angina patients, and is associated with an increased risk of cardiac events.13 The hazard ratio for cardiac events increases to 8.89 in patients with horizontal/ascending ST-segment elevation, whereas the relative risk for arrhythmic death is not significantly increased in subjects with ascending ST variants. These results argue that electrocardiographic ER patterns may indicate a more vulnerable milieu for the development of malignant arrhythmias in association with coronary artery spasm and myocardial ischemia. It is in line with a recent report suggesting that patients with BS might be more vulnerable to ischemia-related sudden death. Intracoronary infusion of acetylcholine results in BS-type marked ST-segment elevation in the absence of vasospasm, indicating that ischemia and vagal influences may act additively or synergistically with the substrate responsible for BS to elevate the ST-segment and precipitate VF.25

The high frequency of ER pattern in the inferior leads (22%) in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), a condition with mainly depolarization abnormalities, and in patients with noncompaction cardiomyopathy opens the possibility that various different mechanisms are involved in the genesis of the J wave.15,58–60 The prognosis diverges according to the presence of ER in patients with noncompaction cardiomyopathy, whereas arrhythmogenic events show no significant differences in ARVD/C patients.14,59 It remains to be resolved whether a similar electrophysiologic perturbation is responsible for malignant arrhythmias in these patients with structural cardiac abnormalities. An elegant suggestion by Boineau proposes another mechanism of the J wave and ER. Exaggerated left ventricular endocardial trabeculation and invagination of the Purkinje system deep into the mid-myocardial layer results in a more rapid activation of a thick left ventricular wall and premature completion of depolarization, finally exposing the J waves.60

### Electrophysiologic Mechanism and the Concept of the “Dome Reserve”

The J wave has been shown to originate from the heterogeneous distribution of a transient outward current-mediated spike-and-dome morphology of the AP across the ventricular wall. The presence of a prominent AP notch in the epicardium, but not the endocardium, has been shown to provide a voltage gradient that manifests as a J (Osborn) wave or elevated J-point in the ECG.61,62 The unique features of the AP shape in the epicardium have rendered epicardial repolarization more susceptible to changes in response to drive cycle lengths, extrastimulation, drugs or ischemia.63–65 The heterogeneous loss of the AP dome by ischemia, the sodium channel blocker, flecainide, or acetylcholine results in the development of a large transmural dispersion of repolarization by abbreviation and marked prolongation of AP duration. This is followed by local re-excitation (phase 2 reentry) as a result of the AP dome propagating from sites where it was maintained to sites where it was abolished. Thus, the ECG J wave, a clinical marker of the AP notch, represents the vulnerability of the epicardial AP to an all-or-none repolarization, and susceptibility to fatal ventricular tachyarrhythmias. It is presumed that individuals with prominent J waves are thought to have the potential to lose their AP dome by extrinsic factors such as vagal stimula-

| Table. Risk Factors for Ventricular Arrhythmias in Long QT Syndrome and J Wave-Related Ventricular Fibrillation Syndromes |
|-------------------------------|---------------------------|
| Risk factors for torsades de pointes in LQTS (markers of reduced “repolarization reserve”) | Risk factors for polymorphic VT/VF in J-wave syndrome (markers of reduced “dome reserve”) |
| Female | Male |
| Congestive heart failure, acute ischemia | Acute ischemia |
| Hypokalemia, hypomagnesemia | Hypocalcemia |
| K channel blocker, psychotropic drugs, antibiotics, antifungals, antihistamine | Na channel blocker, Ca channel blocker, K channel opener, psychotropic drugs, cocaine intoxication |
| Fever | Hypothermia (ERS), fever (some patients with BS) |
| Bradycardia, pause | Bradycardia, pause |
| QT prolongation | Prominent J wave |

BS, Brugada syndrome; ERS, early repolarization syndrome; LQTS, long QT syndrome; VF, ventricular fibrillation; VT, ventricular tachycardia.
tion, sodium channel blocker or ischemia.

This ability of the ventricular myocardium to preserve its AP dome may be called “dome reserve”, and the lack of this reserve may simply be expressed by the electrocardiographic J waves. Roden et al proposed the concept of a “repolarization reserve” in which normal hearts have multiple, redundant mechanisms (multiple repolarization currents) during the physiologic repolarization process.\(^{66,67}\) Defects in 1 of these multiple mechanisms is insufficient to elicit the full-blown electrocardiographic features of LQTS. It is when multiple subclinical lesions are already present in the repolarization process that superimposition of an IV- blocking drug may produce marked AP prolongation, resulting in torsades de pointes (TdP). This concept of “physiological redundancy protecting against extreme perturbations” applies to both the drug-induced and the congenital forms of LQTS. As the decreased repolarization reserve is expressed by the risk factors for TdP (including female sex, bradycardia, congestive heart failure, subtle QT interval prolongation, and hypokalemia among others), a decreased dome reserve may be associated with male sex, bradycardia, acute ischemia, presence of a J wave, hypercalcaemia and other parameters (Table).

### Conclusions

Patients with BS and ERS share common electrocardiographic features and clinical manifestations. The J waves found in these patients are believed to play a key role in the genesis of VF. Identification of subjects with a high risk of SCD is still a matter of debate. The J wave is also found in a significant proportion of patients with IVF. Marked fluctuation of J waves in patients with IVF be incorporated into a broader definition of JWS. J waves found in patients with acute myocardial ischemia or infarction are negatively associated with clinical outcomes. The association of J waves in diverse structural heart diseases suggests that J wave-related phenomena may be a common electrophysiologic mechanism underlying VF in various clinical settings.

### Acknowledgments

The author thanks Jeong-hae Kwon and Ji-Hee Yoon for data collection.

### References


