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The J Wave Syndromes and their Role in Sudden Cardiac Death

Dongqi Wang, MD, PhD¹, Gan-Xin Yan, MD, PhD^{1,2,3}, and Charles Antzelevitch, PhD⁴

¹ The First Affiliated Hospital, Medical School of Xi'an Jiaotong University, Xi'an, China

² Main Line Health Heart Center and Lankenau Institute for Medical Research, Wynnewood, PA, USA

³ Jefferson Medical College, Philadelphia, PA, USA

⁴ Masonic Medical Research Laboratory, Utica, NY, USA

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The electrocardiographic J wave, also referred as the Osborn wave, is a deflection with a dome or hump morphology at the junction between the QRS complex and the ST segment on the body surface ECG. Earlier studies attributed the J wave to a variety of factors including hypoxia, injury current, acidosis, delayed ventricular depolarization, and early ventricular repolarization.¹ Clinical and arrhythmogenic significance of the J wave abnormalities had largely been ignored until 1996 when Yan and Antzelevitch published a study elucidating the ionic and cellular basis of the J wave, indicating that a prominent I_{to} -mediated action potential notch in ventricular epicardium but not endocardium may produce a transmural voltage gradient during early ventricular repolarization that could register as a J wave or J point elevation in the ECG.² Growing evidence has since been advanced indicating that J wave abnormalities, which are often accompanied by early repolarization and ST segment elevation on the ECG, are in some cases associated with a risk of sudden cardiac death. The J wave syndromes, which represent a variable spectrum of phenotypic expression with accentuation of the J wave, can be inherited or acquired.^{3–6} This review attempts to summarize current knowledge about J-wave syndromes- linking bench work with the bedside.

Historical Perspective of J wave and J wave syndromes

Tomaszewski et al first described J wave as a slowly inscribed deflection between QRS complex and earliest part of ST segment on the ECG in an accidentally frozen man in 1938.⁷ Similar descriptions of hypothermic J waves followed in which the J wave was described as a widening secondary deflection of QRS complex. Osborn described what he called “current

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Address for correspondence: Charles Antzelevitch, PhD, FHRS, Executive Director and Director of Research, Gordon K. Moe Scholar, Masonic Medical Research Laboratory, 2150 Bleecker Street, Utica, NY 13501, Phone: (315)735-2217, FAX: (315)735-5648, ca@mmrl.edu.

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of injury” in hypothermic dogs that later fibrillated in 1953.⁸ This so called “current of injury” was in fact a J wave that was later named as Osborn-J wave.⁹

Appearance of the J wave or J point elevation is often associated with an early repolarization pattern and ST segment elevation. The early repolarization pattern and ST segment elevation was first reported by evaluating the four-lead electrocardiogram of two hundred healthy young men and women in 1936 by Shipley and Hallaran. This electrocardiographic phenomenon was ascribed to accelerated ventricular repolarization^{10,11} In subsequent years, several investigators attempted to characterize the clinical importance of early repolarization pattern and failed to find any immediate and long term consequences.^{12,13}

A shift away from a benign view of the J wave began in 1984 when Otto and coworkers presented three cases of ventricular fibrillation that occurred during sleep in young males of Southeast Asian refugees who had structurally normal hearts. In one of three patients, a prominent J wave with ST segment elevation appeared after termination of his ventricular fibrillation. More interestingly, inducible ventricular fibrillation in this patient was inhibited by quinidine, a drug that inhibits I_{to} , but not procainamide.¹⁴ This indicates that I_{to} -mediated J wave may play a role in the sudden unexpected nocturnal death. Sudden unexpected nocturnal death was reported in the literatures as early as in 1950s–1960s.¹⁵ In the Philippines capital city Malina, a total of 722 apparently healthy young males died during sleep between 1948 and 1982, a disease called “Bangungut” (to rise and moan during sleep) in their native language.¹⁶ Sudden unexpected nocturnal death is fairly popular in Southeast Asian and Pacific Rim countries and its etiology remained a mystery for many decades.^{17,18}

In 1992, Pedro and Josep Brugada published a landmark study describing eight similar sudden cardiac death patients in whom the ECG revealed “right bundle branch block” and ST segment elevation limited to the precordial leads V1 to V3 in the absence of ischemic or other structural disease.¹⁹ In 1994, Bjerregaard et al reported that a 47 year-old African American woman presented with recurrent syncope and a similar ECG pattern to that reported by the Brugada brothers. In this report, Bjerregaard et al. suggested that the so called “right bundle branch block” described by Brugada brothers in 1992 was in fact a prominent J wave.²⁰ This was the first report in which the contribution of J wave to ventricular fibrillation was discussed. This entity was later named as “Brugada syndrome”.^{2,21}

In 2000 Gussak and Antzelevitch suggested that in some cases ER may be malignant, based on observations that an ER pattern in arterially-perfused wedge preparations can easily convert to one in which phase 2 reentry gives rise to polymorphic VT/VF.²² Evidence in support of this hypothesis was provided by Kalla et al.,²³ and Takagi et al.²⁴ in 2000. Kalla et al reported a case of idiopathic ventricular fibrillation in a 29 year old Vietnamese man whose ECG showed prominent J wave with ST segment elevation in the inferior ECG leads and first postulated that it may represent a variant of the Brugada syndrome.²³ Shortly thereafter, Takagi et al. provided additional evidence in support of this hypothesis.²⁴ In 2004, Qi et al reported that a young Chinese man with structurally normal heart survived from recurrent ventricular fibrillation and his ECG exhibited prominent J waves, early repolarization and ST segment elevation in all of 12 ECG leads.²⁵ This interesting case triggered a debate in China whether “J wave syndromes” should be used to cover all of clinical entities derived from accentuated J waves.³ Additional supporting evidence was provided by two reports in the New England Journal of Medicine in 2008. Both Haissaguerre and coworkers,²⁶ and Nam and coworkers²⁷ demonstrated a clear association between J waves with early repolarization pattern and ventricular fibrillation.

In 2010, Antzelevitch and Yan further defined J wave syndromes and divided them into four subtypes based on their ECG features and relative risk potentials of sudden cardiac death (Table 1).⁶

Ionic and Cellular Basis of J wave and Its Arrhythmogenesis

The fact that the J wave immediately follows the completion of ventricular activation (QRS complex) indicates the presence of a transient transmural voltage gradient during early ventricular repolarization. In the late 1980's, Antzelevitch and colleagues first proposed that a difference in repolarization phases 1 and 2 of the action potential between canine ventricular epicardium and endocardium form the basis for the ECG J wave.^{28,29} Ventricular epicardium commonly displays action potentials with a prominent notch (spike and dome) largely mediated by a 4-aminopyridine-sensitive transient outward current (I_{to}). The absence of a prominent notch in the endocardium is the consequence of a much smaller I_{to} . A prominent 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 in the ECG. Direct evidence in support of this hypothesis was obtained in the arterially-perfused canine ventricular wedge preparation.² The data obtained from the wedge preparation have demonstrated a linear correlation between the J wave size and I_{to} -mediated action potential notch in epicardium (Figure 1). Factors that influence I_{to} kinetics and ventricular activation sequence can modify the J wave on the ECG. With a normal ventricular activation sequence from endocardium to epicardium, an acceleration of heart rate reduces I_{to} due to its slow recovery from inactivation, resulting in a decrease in the J wave size.^{23,30} This property of the J wave is particularly useful in distinguishing the J wave from the terminal part of a notched QRS complex. Since a notched QRS is the consequence of altered ventricular activation, an increase in heart rate generally exaggerates its manifestation. Similarly, sodium channel blockers like quinidine, which inhibit I_{to} , act to reduce the size of the J wave^{31,32} but do not reduce the magnitude of QRS notching. The prominent J wave induced by hypothermia is the result of a marked accentuation of the spike and dome morphology of epicardial action potentials probably, due to the effect of cold temperatures to slow the activation kinetic of I_{to} less than that of the L-type Ca^{2+} current.²

The I_{to} -mediated epicardial action potential notch including spike and dome is sensitive to changes in net repolarizing current. An increase in net repolarizing current, due to either a decrease of inward current or augmentation of outward current, accentuates the notch leading to augmentation of the J wave. A further increase in net repolarizing current can further enhance the epicardial action potential notch, so that $I_{Ca,L}$ activation is influenced, resulting in partial or complete loss of the action potential dome at phase 2 that can manifest as early repolarization and ST segment elevation on the ECG.^{30,31,33}

Depending on the extent of epicardial action potential phase 2 depression (partial versus complete loss of the dome), the ST segment may behave differently. Partial loss of the epicardial action potential dome manifests as early repolarization with or without ST segment elevation. ST segment elevation due to partial loss of the epicardial action potential is concave upward or saddleback like.^{30,34} Complete loss of the epicardial action potential dome in response to an increase in outward current (e.g., I_{to} or I_{K-ATP}) or a decrease in inward current (e.g., I_{Na} or I_{Ca}), particularly in the right ventricle where the I_{to} -mediated phase 1 is prominent, results in coved ST segment elevation as often seen in the Brugada syndrome (Figure 2).^{31,33}

Loss of the dome is usually heterogeneous, occurring at some sites but not others, leading to a marked dispersion of repolarization on the epicardial surface (Figure 3). The epicardial action potential dome³⁵ may then propagate from epicardial sites where it is maintained to

sites at which it was lost, thus producing local re-excitation, termed phase 2 reentry. The closely-coupled extrasystole produced via phase 2 reentry always occurs on the descending limb of T wave producing an R-on-T phenomenon which can initiate polymorphic ventricular tachycardia (VT) or fibrillation (VF) (Figure 3).

Subtypes of J wave Syndromes and Their Clinical Features

Inherited J wave syndromes can be divided into four subtypes based on their ECG features and relative risk for contributing to sudden cardiac death. Gene mutations have been identified in all four subtypes (Table 1).⁶

Type 1 is a distinct J wave or J point elevation accompanied by early repolarization pattern with or without concave upward ST segment elevation that is limited to the left precordial leads V4 to V6. This pattern has previously been referred to as “early repolarization syndrome”, and generally considered to be a benign ECG phenomenon seen in healthy individuals particularly athletes. Its prevalence is estimated at 5.8% in adults.³⁶ Type 1 ER pattern is rarely associated with VT/VF and SCD.

Type 2 is a prominent J wave or J point elevation with an ER pattern occurring predominantly in inferior leads II, III and aVF. The prevalence of Type 2 is estimated to be 3.5% in adults,³⁶ but it is probably more prevalent in Asian males. There is mounting evidence that Type 2 is associated with moderate risk for sudden cardiac death.^{14,23,24,26,27}

Type 3 is rare and its true prevalence is unknown. This type of ECG is characterized by global J waves or J point elevation with marked ST segment elevation, particularly in the period immediately preceding the development of VT/VF (Figure 4). Patients with Type 3 often present with recurrent ventricular fibrillation, often characterized as electrical storms.^{25,27}

Type 4 is the Brugada syndrome in which prominent J waves and ST segment elevation are limited to the right precordial leads V1 to V3. The initial publication in 1992 by Pedro and Josep Brugada described eight similar sudden cardiac death patients.¹⁹ Because the ECG pattern of the Brugada syndrome can be dynamic and is often concealed, it is difficult to estimate the true prevalence of the disease in the general population. In two Asian studies, Brugada type ECG (coved ST segment elevation) was observed in 12/10,000 inhabitants; type 2 and 3 ST segment elevation, which are not diagnostic of Brugada syndrome, were much more prevalent, appearing in 58/10 000 inhabitants.^{37,38}

The common clinical features of the J wave syndromes include: (1) modulation of J wave and associated ST segment elevation by heart rate and autonomic tone; tachycardia and/or increased sympathetic tone lead to reduction in the magnitude of the J wave and normalization of the ST segment, whereas bradycardia or increases vagal tone augment the magnitude of the J wave and cause ST segment elevation;^{21,23} (2) J wave syndromes predominate in males; (3) arrhythmic events are more likely to occur between the age of 20 and 40 with a median age of in the mid 30's.^{16–18,39}

Among the J wave syndromes, Brugada syndrome has been the most widely studied. Consensus reports published in 2002 and 2005 delineated diagnostic criteria, risk stratification schemes and approaches to therapy.^{40,41} The Brugada syndrome is definitively diagnosed when a spontaneous or drug-induced type 1 or coved ST segment elevation is observed in more than one right precordial lead (V1 to V3) in conjunction with one of the followings: documented VF, polymorphic ventricular tachycardia, a family history of sudden cardiac death at <45 years old, coved-type ECGs in family members, inducibility of VT with programmed electrical stimulation, syncope, or nocturnal agonal respiration.⁴¹

Diagnosis of the Brugada syndrome is also established when a type 2 or 3 ST-segment elevation in more than one right precordial leads under baseline conditions is converted to the diagnostic type 1 pattern upon exposure to a sodium channel blocker (ST-segment elevation should be ≥ 2 mm). One or more of the clinical criteria described above should also be present.

Implantable cardioverter defibrillator (ICD) implantation is the only proven effective treatment for the Brugada syndrome. Survivors of cardiac arrest with Brugada syndrome and other types of J wave syndromes are at a high risk for recurrence and should be protected by an ICD.

Other treatment options involve the use of pharmacologic agents, including I_{to} blockers such as quinidine.^{42–44} Antiarrhythmic agents such as amiodarone and β -blockers have been shown to be ineffective. The presence of a prominent I_{to} is critical to the mechanism underlying the Brugada syndrome. Consequently, the most prudent approach to therapy, regardless of the ionic or genetic basis for the disease, is to inhibit I_{to} . Cardioselective and I_{to} -specific blockers are currently not available. An agent currently on the market in the United States and other regions of the world with significant I_{to} blocking properties is quinidine, and this agent was proposed for the treatment of BrS in 1999.⁴² Belhassen et al.⁴³ reported on the efficacy of quinidine in a prospective study of 25 patients. After a follow-up period of 6 months to 22.2 years, of 19 patients treated with oral quinidine for 6 to 219 months (56 ± 67 months) none developed arrhythmic events. The effectiveness of quinidine has been demonstrated in a number of studies⁴⁵ (for references), the most recent of which involves its use in children with BrS⁴⁶. Oral quinidine therapy is also a reasonable “bridge therapy” or adjunct to ICD therapy⁴⁷. A prospective Registry for asymptomatic Brugada patients has been created with the aim of tracking the effectiveness of empiric therapy with quinidine.⁴⁸ There is a clear need for development of a more cardioselective and I_{to} -specific blocker.

ST Segment Elevation and Phase 2 Reentry in Acute Myocardial Ischemia—

Whether I_{to} -mediated phase 2 reentry plays an important role in initiating ventricular fibrillation (VF) during early acute myocardial ischemia is not clear, but clinical observations suggest some association of risk of primary VF during acute myocardial infarction with increased I_{to} density. For example, women with coronary heart disease have only a quarter of the risk for sudden cardiac death as compared to men.⁴⁹ This may be due, in part, to a more prominent I_{to} in males versus females, which has been thought to be responsible for the predominance of J-wave syndromes in men.⁵⁰ Similarly, the incidence of primary VF is higher in patients with acute inferior MI who have right ventricle involvement (8.4%) than those without (2.7%), or anterior MI (5.0%)⁵¹ This is because I_{to} in the epicardium is much more prominent in the right ventricle vs. the left.^{52,53}

All of these indicate that the fundamental mechanisms responsible for ST segment elevation and the initiation of VF are similar in the early phase of acute myocardial ischemia and the J wave syndromes.^{31,34} In 2004, Yan et al first demonstrated that R-on-T extrasystoles capable of initiating VF can develop via the mechanism of phase 2 reentry during the early acute myocardial ischemia in an animal model (Figure 5).³ This is supported by more recent emerging clinical data that J wave plays an important role in the development of VF in acute coronary syndrome.^{54–56}

Summary

Advances in modern laboratory technologies and techniques over the past decade, including electrophysiological and genetic analyses, have uncovered many novel mechanisms

underlying sudden cardiac death, the J wave being one example. J wave syndromes include a spectrum of disorders that involve accentuation of the I_{to} -mediated epicardial action potential notch in different regions of heart, leading to the development of prominent J waves, early repolarization, and ST segment elevation on the ECG. Phase 2 reentry has been identified as the trigger in the J wave syndromes, and enhanced dispersion of repolarization as the substrate, giving rise to polymorphic ventricular tachycardia and fibrillation and sudden death.

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A. J Wave in a Young Asian Male Who had Recurrent VF

B. Canine Ventricular Action Potentials and ECG

Figure 1.

Cellular basis for the J wave. **A:** Prominent J waves in lead II, III were recorded from a young Asian male who had recurrent ventricular fibrillation (VF). **B:** Simultaneous recording of transmembrane action potentials from epicardial (Epi) and endocardial (Endo) regions and a transmural ECG in a coronary-perfused canine ventricular wedge preparation. An I_{to} -mediated action potential notch in the epicardium but not endocardium is associated with a J wave. A premature stimulus (S_1 - S_2 =300 ms) caused a parallel decrease in the amplitude of the epicardial action potential notch and of the J wave (modified from ref.² with permission).

Figure 2. Pinacidil, a K_{ATP} channel opener, causes loss of action potential plateau in the canine right ventricular epicardium. Dynamic change in the epicardial action potential plateau is associated with different types of ST segment elevation (modified from ref.³¹ with permission).

Figure 3.

The mechanism responsible for J wave related arrhythmogenesis. **A:** Development of VF in a patient with the prominent J waves in lead II (reprinted from ref.⁵⁷ with permission). **B:** VF initiated by phase 2 reentry in a canine right ventricular wedge in the presence of 2.5 $\mu\text{mol/L}$ of pinacidil. Action potentials were simultaneously recorded from two epicardial sites (Epi₁ and Epi₂) and one Endo site. Loss of the AP dome in Epi₁ but not in Epi₂ led to phase 2 reentry capable of initiating VF (modified from ref.³⁰ with permission).

Figure 4.

ECG obtained from a 34-year-old Chinese man with a structurally normal heart who survived cardiac arrest displaying characteristics of the Type 3 early repolarization syndrome. Prominent J waves and ST segment elevation were observed in almost all ECG leads, including an early repolarization pattern in leads of I, II, aVL, aVF and V4 to V6 and a saddleback ST segment elevation suggestive of Brugada in V₂ to V₃ (thick arrows). R-on-T extrasystoles, likely due to phase 2 reentry (open arrows), were seen and the post-extrasystolic beat displayed a coved ST segment elevation characteristic of Brugada type 1 wave (thin arrows). Reprinted from Qi et al.²⁵ with permission.

Figure 5.

Acute regional myocardial ischemia resulting in complete loss of the action potential dome at Epi₂ within the ischemic zone but not at Epi₁ by perfused side of the ischemic border, leading to propagation of the dome at Epi₁ to Epi₂ (phase 2 reentry). Phase 2 reentry and probably its transmural propagation manifested as a closely-coupled R-on-T extrasystole on the ECG that was able to initiate VF. BCL=2000 ms. **B.** I_{to} traces recorded at step voltages from -20 to +30 mV in canine right ventricular epicardial myocytes isolated from the same ventricle from which the ventricular wedge in **Panel A** was isolated. I-V relationships (right): Averaged I_{to} density (30.3 pA/pF) was normalized by cell membrane capacitance in 4 myocytes. Reprinted from Yan et al.³ with permission.

J-wave Syndromes: Similarities and Differences

Table 1

	Inherited				Acquired	
	ER in lateral leads Type 1	ER in inferior or infero-lateral leads Type 2	Global ER Type 3	Brugada Syndrome Type 4	Ischemia-mediated	Hypothermia-mediated
Anatomic Location responsible for chief EP manifestations	Antero-lateral left ventricle	Inferior left ventricle	Left and right ventricles	Right ventricle	Left and right ventricles	Left and right ventricles
Leads Displaying J point/J-wave abnormalities	I, V4–V6	II, III, aVF	Global	V1–V3	Any of 12 leads	Any of the 12 leads
Response of J wave amplitude/ST Elevation to: Bradycardia Na ⁺ channel blockers	Increase Limited data	Increase Limited data	Increase Limited data	Increase Increase	N/A N/A	N/A N/A
Sex Dominance	Male	Male	Male	Male	Male	Either gender
VF	Rare	Yes	Yes, VF Storms	Yes	Yes	Yes
Response to Quinidine	Normalization of J point elevation and inhibition of VT/VF	Normalization of J point elevation and inhibition of VT/VF	Limited data; Normalization of J point elevation and inhibition of VT/VF	Normalization of J point elevation and inhibition of VT/VF	Limited data	Inhibition of VT/VF
Response to Isoproterenol	Normalization of J point elevation and inhibition of VT/VF	Normalization of J point elevation and inhibition of VT/VF	Limited data;	Normalization of J point elevation and inhibition of VT/VF	N/A	N/A
Gene Mutations	CACNA1C, CACNB2B	KCNJ8, CACNA1C, CACNB2B	CACNA1C	SCN5A, CACNA1C, CACNB2B, GPD1-L, SCN1B, KCNE3, SCN3B, KCNJ8	SCN5A	N/A

EP=electrophysiology; N/A=not available; ERS=early repolarization syndrome; VT=ventricular tachycardia; VF=ventricular fibrillation. Reprinted from ref. 6 with permission