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J Wave syndromes: Brugada and Early Repolarization Syndromes

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Abstract

A prominent J wave is encountered in a number of life-threatening cardiac arrhythmia syndromes, including the Brugada (BrS) and early repolarization (ERS) syndromes. BrS and ERS differ with respect to the magnitude and lead location of abnormal J waves and are thought to represent a continuous spectrum of phenotypic expression termed J wave syndromes. Despite two decades of intensive research, risk stratification and the approach to therapy of these two inherited cardiac arrhythmia syndromes are still undergoing rapid evolution. Our objective in this review is to provide an integrated synopsis of the clinical characteristics, risk stratifiers, as well as the molecular, ionic, cellular and genetic mechanisms underlying these two fascinating syndromes that have captured the interest and attention of the cardiology community in recent years.

Keywords

Sudden cardiac death; J wave; Early repolarization; ST segment elevation; Cardiac arrhythmias; ventricular tachycardia; ventricular fibrillation; inherited cardiac arrhythmias syndromes

Introduction

A prominent J wave in humans has long been observed in the ECG in cases of hypothermia[1-3] and hypercalcemia.[4, 5] More recently, the presence of prominent J waves has been identified as a marker for a substrate capable of generating life-threatening ventricular arrhythmias.[6] In humans, the J wave more commonly appears as a J point elevation, with part of the J wave buried inside the QRS. When greatly amplified, it can appear as an ST segment elevation, as in cases of Brugada syndrome.

An early repolarization (ER) pattern in the electrocardiogram (ECG), consisting of a distinct J wave or J point elevation, a notch or slur of the terminal part of the QRS and an ST

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segment elevation (**Figure 1**), is generally found in healthy young males and has traditionally been viewed as benign.[7, 8] This view was challenged by us in the late 1990s and early 2000s on the basis of experimental data showing that an ER pattern in the canine coronary-perfused wedge preparation predisposes to the development of polymorphic ventricular tachycardia and fibrillation (VT/VF).[6, 9-11] Validation of this hypothesis was provided eight years later by Haïssaguerre et al.[12] and Nam et al.[13] These reports together with numerous additional case control and population-based studies provided clinical evidence of an increased prevalence of ER pattern, particularly in inferior and infero-lateral leads, among patients with a history of idiopathic ventricular fibrillation, thus confirming a link between ER pattern in the ECG and life-threatening cardiac arrhythmias. Terminology relative to ER has been a matter of confusion and contention. [14-16] A recent expert consensus report recommends that peak of an end QRS notch and/or the onset of an end QRS slur be designated as J(p) and that J(p) should exceed 0.1mV in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG for early repolarization to be present.[17]

The two principal forms of J wave syndrome

Two distinct forms of inherited J wave syndromes are recognized: Early repolarization syndrome (ERS) and Brugada syndrome (BrS). Both are associated with vulnerability to polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF) leading to sudden cardiac death[6, 12, 13, 18] in young adults without apparent structural heart disease. J wave syndromes are characterized by J-point and ST-elevation in distinct ECG-leads. The J wave syndromes have also, although far less often, been associated with sudden infant death syndrome (SIDS).[19-21] BrS is the right ventricular variant of hereditary J wave syndromes. The region most affected by the disease is the anterior right ventricular outflow tract. BrS patients display J-point and ST-segment elevation in the right precordial leads.[22, 23]

An early repolarization ECG-pattern (ERP) is characterized by a distinct J wave or J-point-elevation, notch or slur of the terminal part of the QRS and ST-elevation in the lateral (type I), infero-lateral (type II) or in infero-lateral + anterior or right ventricular leads (type III). ERP can be observed in acquired conditions such as hypothermia or ischemia.[6, 24, 25] When associated with VT/VF, it is referred to as early repolarization syndrome (ERS). Despite the different regional localization within the heart, BrS and ERS display several clinical similarities, suggesting similar pathophysiology (**Table 1**).[10, 14, 26-28] Previous studies have pointed to different pathophysiological basis based on the observation that sodium channel blockers unmask or accentuate J wave manifestation in BrS, but reduces the amplitude in ERS.[29] The recent study by Nakagawa et al., however, showed that J waves recorded using unipolar LV epicardial leads introduced into the left lateral coronary vein in ERS patients were indeed augmented, even though J waves recorded in the lateral precordial leads were diminished, due principally to engulfment of the surface J wave by the widened QRS.[30] Interestingly, the study of Kawata et al. showing an effect of pilsicainide to augment J waves and ST segment elevation in the right precordial leads, while reducing ER in the lateral leads in the same patient, actually provides support for a similar mechanism of ERS and BrS in light of the results advanced by Nakagawa and co-workers.[29] Also in support of the notion that these ECG patterns and syndromes are closely related are reports of cases of ERS that at times transition to ERS plus BrS.[31, 32]

ERS and BrS share a number of common clinical features (**Table 1**): Males are dominant in both syndromes: in the Brugada syndrome, the percentage of males involved ranges from 71 to 80 % in Caucasians but as high as 94%-96% in Japanese.[33, 34] Similarly, in the setting of ER pattern, males develop ventricular fibrillation in 60% of cases in the study of Haïssaguerre et al [12] but in a much higher percentage reported by Japanese investigators.[29] The patients with BrS or ERS may be totally asymptomatic until presenting with syncope and sudden cardiac arrest often due to ventricular fibrillation. The risk for development of VT/VF is dictated in large part by the ER subtype (Type I, II or III), as previously discussed.[6] In both syndromes, the highest incidence of ventricular fibrillation or sudden cardiac death occurs in the third decade of life when testosterone levels peak in males.[35] Another important clinical feature of both syndromes is that J wave and associated ST segment elevation are accentuated during bradycardia or after pauses.[36, 37] This may explain why ventricular fibrillation in both syndromes often occurs during sleep or at a low level of physical activities.[29, 38]

In addition to reports of SCD in otherwise healthy patients displaying an ER pattern, this ECG pattern has been associated with an increased arrhythmogenic risk and SCD in patients with acute myocardial infarction[39], chronic coronary disease[40], heart failure[41] and hypothermia [24, 42]

Genetics

BrS has been associated with mutations in 19 different genes (**Table 2**). To date more than 300 BrS-related mutations in *SCN5A* have been described [14, 43, 44] Mutations in *CACNA1C* (Cav1.2), *CACNB2b* (Cavß2b) and *CACNA2D1* (Cavα2δ) are found in approximately 13% of probands.[45-48] Mutations in glycerol-3-phophate dehydrogenase 1-like enzyme gene (*GPD1L*), *SCN1B* (β_1-subunit of Na channel), *KCNE3* (MiRP2), *SCN3B* (β3-subunit of Na channel), *KCNJ8* (Kir 6.1), *KCND3* (Kv4.3), *RANGRF* (MOG1), *SLMAP*, *ABCC9* (SUR2A), (Navß2), *PKP2* (Plakophillin-2), *FGF12* (FHAF1), *HEY*2, and *SEMA3A* (Semaphorin) are more rare.[49-5354-6153, 62-69] We recently reported an association of BrS with *SCN10A*, a neuronal sodium channel that co-associates with *SCN5A*, with a yield of 16.7%.[70] Mutations in these genes lead to loss of function in sodium channel current (I_{Na}) and calcium channel current (I_{Ca}), as well as to a gain of function in transient outward potassium current (I_{to}) or ATP-sensitive potassium current ($I_{K\text{-}ATP}$). Mutations in *KCNH2* and *KCNE5*, although not causative, have been identified as capable of modulating the substrate for the development of BrS. Loss-of-function mutations in *HCN4* causing a reduction in pacemaker current, I_f, can unmask BrS by reducing heart rate.[71]

The familial nature of the ER pattern has been demonstrated in a number of studies.[72-74] The ER pattern and ERS have been associated with mutations in 7 genes. Consistent with the findings that $I_{K\text{-}ATP}$ activation can generate an ER pattern in canine ventricular wedge preparations, mutations in *KCNJ8 and ABCC9*, responsible for the pore forming and ATP-sensing subunits of the $I_{K\text{-}ATP}$ channel, has been reported in a patients with ERS as well.[49, 51, 75] Loss of function mutations in the α1, α2 and α2δ subunits of the cardiac L-type calcium channel (*CACNA1C, CACNB2, and CACNA2D1*) have been uncovered in

patients with ERS[45] as have mutations in *SCN5A*.[76] We have also recently reported an association of *SCN10A* with ERS.[70]

A word of caution is appropriate here. It is important to recognize that a small fraction of identified genetic variants in the numerous genes associated with BrS and ERS have been examined using functional expression studies to establish causality or to establish a plausible contribution to pathogenesis. Only a handful have been studied in genetically engineered animal model and very few have been studied in native cardiac cells or in induced pluripotent stem cell-derived cardiac myocytes isolated from ERS and BrS patients. Computational strategies developed to predict the functional consequences of mutations are helpful, but these methods have not been rigorously tested. The lack of functional or biological validation of mutation effects remains the most severe limitation of genetic test interpretation as recently highlighted by Schwartz et al.[77] This limitation is still more concerning in cases in which a susceptibility gene is identified on the basis of a single proband and with the absence of familial segregation data. Recent studies have suggested a more complex genetic background for BrS. Bezzina et al[60] provided evidence that BrS is associated with common genetic variants suggesting a multigenic origin of the syndrome. Other authors, including Le Scouarnec et al [78] and Behr et al[79], have questioned the impact of rare gene-variants, with the exception of SCN5A, in the pathogenesis of the synmdrome. These studies once again call for caution in the interpretation of genetic resutls as well as the need for genotype-phenotype correlation data and functional expression data before designating a rare variants as causative of the disease.

Ionic and Cellular Mechanisms

The J wave is inscribed as a consequence of a transmural voltage gradient caused by the presence of an action potential notch in epicardium but not endocardium, secondary to a transmural distribution of transient outward current (I_{to}).[27]

The cellular mechanisms underlying J wave syndromes have been mired in controversy.[80, 81] Two principal hypotheses have been advanced in the case of BrS (**Figure 2**): 1) The **repolarization hypothesis** maintains that an outward shift in the balance of currents in right ventricular epicardium leads to repolarization abnormalities resulting in the development of phase 2 reentry, which generates closely-coupled premature beats capable of precipitating VT/VF; 2) The **depolarization hypothesis** maintains that slow conduction in the right ventricular outflow tract plays a primary role in the development of the electrocardiographic and arrhythmic manifestations of the syndrome. Although these theories are not mutually exclusive and may indeed be synergistic, from the standpoint of appropriate therapy, correct assessment of the cellular pathophysiology is important.

The most compelling evidence in support of the depolarization hypothesis comes from a study by Nademanee et al.[82] showing that radiofrequency (RF) ablation of epicardial sites displaying late potentials and fractionated bipolar electrograms (EGs) in the right ventricular outflow tract (RVOT) of BrS patients significantly reduced the arrhythmia-vulnerability and ECG-manifestation of the disease. These authors concluded that the late potential (LP) and fractionated electrogram activity are due to conduction delays within the RVOT and elimination of the sites of slow conduction is the basis for the ameliorative effect of ablation

therapy.[82] In a direct test of this hypothesis, our group recently suggested an alternative cellular electrophysiological mechanism as the basis for late potentials and fractionated electrogram activity in the setting of BrS.[83] As illustrated in **Figure 3**, when the genetic defects associated with BrS are pharmacologically mimicked in the coronary-perfused canine right ventricular wedge model of BrS, high frequency late potentials develop in the right ventricular (RV) epicardium secondary to concealed phase 2 reentry. At other sites, low-voltage fractionated electrogram activity develops due to regional desynchronization in the appearance of the second action potential upstroke, secondary to accentuation of the epicardial action potential notch. In no case was delayed conduction of the primary beat observed.

If late potentials and fractionated electrogram activity recorded from the RVOT do not reflect depolarization and conduction abnormalities, what is the basis for the ameliorative effect of RVOT ablation? **Figure 4** illustrates that ablation of sites of phase 2 reentry in the canine ventricular wedge model of BrS markedly diminishes the manifestation of J waves and ST segment elevation and abolishes all arrhythmic activity. The data provide support for the hypothesis that ablation destroys the cells with the most prominent action potential notch, thus eliminating the cells responsible for the repolarization abnormalities that give rise to phase 2 reentry and VT/VF. These findings collectively lend strong support for the repolarization hypothesis. Also in support of this thesis is the congruence between BrS and ERS, which by virtue of its name is considered to be due to a repolarization defect.

Conduction delays are known to give rise to notching of the QRS complex. Although such notching often occurs on the rising phase of the QRS or during the middle of the descending phase, it can occur at the terminal portion of the QRS, thus masquerading as a J wave. [14, 84] How then can we differentiate an end of QRS notch from a J wave? One method that we and others have previously suggested is to gauge the response to prematurity or to an increase in rate. Delayed conduction invariably becomes worse at faster rates or during premature beats thus leading to an accentuation of the notch, whereas repolarization defects are usually mitigated resulting in a diminution of the J wave at faster rates. Although typical J waves are usually accentuated with bradycardia or long pauses, the opposite has been described.[85, 86] J waves are often seen in young males with no apparent structural heart diseases, whereas intra-ventricular conduction delay is often observed in older individuals or those with a history of myocardial infarction or cardiomyopathy. **Figure 5** illustrates examples of both. The tachycardia-augmented notches (**Figure 5D**) can result in apparent “J” waves that are as tall or taller than 50% of the R wave[85] and as such may be more reasonably characterized as an R’ due to intra-ventricular conduction delay.[84] The prognostic value of a fragmented QRS has been demonstrated in BrS, [87, 88] although fragmentation of the QRS is not associated with increased risk in the absence of cardiac disease. [89] Factors that may aid in the differential diagnosis of J wave vs IVCD-mediated syndromes are summarized in **Table 4**.

The ionic and cellular mechanisms underlying ERS were recently advanced in a report by Koncz and co-workers.[90] The authors provided evidence in support of the hypothesis that, similar to the mechanism operative in BrS, an accentuation of transmural gradients, in this case across the LV wall, underlies the repolarization abnormalities responsible for ERS,

giving rise to J point elevation, distinct J waves, or slurring of the terminal part of the QRS (**Figure 1**). The repolarization defect is accentuated by cholinergic agonists and reduced by quinidine, isoproterenol, cilostazol and milrinone, accounting for the ability of these agents to reverse the repolarization abnormalities responsible for ERS. [90, 91] These authors also showed significantly higher intrinsic levels of I_{to} in the inferior LV, providing an explanation for the greater vulnerability of the inferior LV wall to VT/VF.[90] The clinical translation of these experimental findings has been facilitated by the advent and implementation of electrocardiographic imaging (ECGI) by Rudy and co-workers. Using ECGI mapping, Ghosh et al. identified abnormally short activation-recovery intervals (ARI) in the inferior and lateral regions of LV and a marked dispersion of repolarization in support of regional accelerated repolarization.[92] More recent studies involving ECGI mapping in an ERS patient during VF have demonstrated VF rotors anchored in the inferior-lateral left ventricular wall.[15]

Risk stratification

A great deal of effort has been devoted to assessment of risk for the development of life-threatening arrhythmias. The incidental discovery of a J wave on routine screening should not be interpreted as a marker of "high risk" for SCD since the odds for this fatal disease is approximately 1:10,000.[93] Rosso et al. indicated that the presence of a J wave on the ECG increases the probability of VF from 3.4:100,000 to 11:100,000.[94, 95] However, careful attention should be paid to subjects with "high risk" ER or J waves. **Table 3** presents the available data of studies designed to identify patients at high risk. Among these risk stratifiers, some are highly predictive, including: 1) history of cardiac events or syncope likely due to VT/VF, 2) pause-dependent augmentation of J waves, especially when accompanied by T wave inversion, and 3) prominent J waves in global leads including Type 1 ST segment elevation in the right precordial leads. Fragmentation of the QRS, although predictive of cardiac events in the J wave syndromes, is non-specific in that it is associated with a high risk of sudden death in other cardiac arrhythmia syndromes.

In the case of ERS, the morphology of the ST segment is reported to be associated with increased arrhythmic risk. Tikkanen *et al* were the first to suggest that a horizontal or descending ST segments portends a higher risk for arrhythmic events and SCD.[96] In contrast, an ER pattern with a rapidly ascending pattern, typically observed in healthy athletes, was associated with a relatively benign prognosis. Rosso *et al.* and Rollin *et al.* reported additional evidence linking a horizontal ST segment to an increased risk for SCD soon thereafter. [97, 98]

In a recent review, Mahida and coworkers concluded that the presence of inferior or widespread J point elevation, a markedly elevated J point, a horizontal or descending ST segment, pause-dependent augmentation of the J wave amplitude, short coupled extrasystoles, and QRS notching predict progressively greater risk for SCD in patients presenting with syncope. [15]

Approaches to therapy

Implantation of an ICD is the mainstay of therapy for J wave syndrome patients presenting with aborted SCD or documented VT/VF with or without syncope (Class I recommendation). [99, 100] According to the 2013 HRS/EHRA/APHRS consensus statement, ICDs can be useful (Class IIa) in symptomatic BrS patients with Type I pattern, in whom syncope was likely caused by VT/VF and may be considered (Class IIb) in asymptomatic patients inducible by programmed electrical stimulation (PES).[101] ICDs are not indicated in asymptomatic patients. There is no clear role for PES in patients with ERS.

Pacemaker therapy—Although arrhythmias and sudden cardiac death generally occur during sleep or at rest and have been associated with slow heart rates, a potential therapeutic role for cardiac pacing remains largely unexplored.[102]

Only a few case reports are available in the literature.[103, 104]

Radiofrequency Ablation Therapy—Nademanee et al.[82] showed that radiofrequency (RF) ablation of **epicardial** sites displaying late potentials and fractionated bipolar electrograms (EGs) in the right ventricular outflow tract (RVOT) of BrS patients can significantly reduce arrhythmia-vulnerability and the ECG-manifestation of the disease. Ablation at these sites was reported to render VT/VF non-inducible and to normalize the Brugada ECG pattern in the majority of patients over a period of weeks or months. Long-term follow-up (20±6months) showed no recurrent VT/VF with only 1 patient on medical therapy with amiodarone. Since then, case reports have been published in support of these effects.[105] Ablation therapy can be life-saving in otherwise uncontrollable cases or cases in which ICD therapy is contraindicated. In the HRS/EHRA/APHRS expert consensus guideline, radiofrequency ablation is a **Class IIb** recommendation in BrS-patient with frequent appropriate ICD-shocks due to recurrent electrical storms.[101] There are no clinical reports of ablation of the LV substrate in patients with ERS.

Pharmacologic approach to therapy

Approach to therapy of BrS—ICD implantation may not be a practical solution for infants and young children due to a high complication rate or for patients residing in regions of the world where an ICD is out of reach because of economic factors. A pharmacologic approach to therapy, based on a rebalancing of currents active during the early phases of the epicardial action potential in the right ventricle so as to reduce the magnitude of the action potential notch and/or restore the action potential dome, has been a focus of basic and clinical research in recent years. **Table 5** lists the various pharmacologic agents thus far investigated. Antiarrhythmic agents such as amiodarone and β blockers have been shown to be ineffective. [106] Class IC antiarrhythmic drugs (such as flecainide and propafenone) and class IA agents, such as procainamide, are contraindicated because of their effects to unmask the Brugada syndrome and induce arrhythmogenesis. Disopyramide is a class IA antiarrhythmic that has been demonstrated to normalize ST segment elevation in some Brugada patients but to unmask the syndrome in others. [107]

Because the presence of a prominent transient outward current, I_{to}, is central to the mechanism underlying BrS and ERS, the most rationale approach to therapy, regardless of the ionic or genetic basis for the disease, is to partially inhibit I_{to}. Cardio-selective and I_{to}-specific blockers are not currently available. 4-aminopyridine (4-AP) is an agent that is ion-channel specific at low concentrations, but is not cardio-selective in that it inhibits I_{to} in the nervous system. Although it is effective in suppressing arrhythmogenesis in wedge models of the Brugada syndrome, [10] it is unlikely to be of clinical benefit because of neurally-mediated and other side effects.

The only agent on the market in the United States and around the world with significant I_{to} blocking properties is quinidine. It is for this reason that we suggested in 1999 that this agent may be of therapeutic value in BrS.[10, 108] Experimental studies have since shown quinidine to be effective in restoring the epicardial action potential dome, thus normalizing the ST segment and preventing phase 2 reentry and polymorphic VT in different experimental models of the Brugada syndrome, regardless of which pharmacologic agents were used to mimic BrS-phenotype. [10, 83, 109-111] Additionally, a recent experimental study suggests that quinidine, owing to its effect to block I_{to}, can exert a protective effect against hypothermia-induced VT/VF in a J wave syndrome model.[42] It is noteworthy that historically, quinidine was used to prevent ventricular fibrillation in patients who required hypothermia for surgical procedures. [111]

Clinical evidence of the effectiveness of quinidine in normalizing ST segment elevation and or preventing arrhythmic events in patients with the BrS has been reported in numerous studies and case reports [112-126] The first prospective study describing the effects of quinidine to prevent inducible and spontaneous ventricular fibrillation (VF) was reported by Belhassen and coworkers.[115] The results were consistent with those reported the same group in prior years [113, 127] and later by other investigators [128, 129]. The data highlight the need for randomized clinical trials to assess the effectiveness of quinidine, preferably in patients with frequent events who have already received an ICD. Hermida et al. reported 76 % efficacy in prevention of VF induced by PES.[128]

Because of the GI side effects of high dose quinidine, low-dose quinidine (<600mg) has been suggested to be as a therapeutic option. Marquez et al. evaluated the clinical history of symptomatic patients with recurrent arrhythmias and frequent ICD discharges and reported that relatively low dose quinidine, as adjunctive therapy, completely prevented arrhythmias in 85 % of the patients (median follow-up of 4years).[118].

In a more recent trial conducted at two French centers, 44 asymptomatic BrS patients with inducible VT/VF were enrolled (47 ± 10 years, 95% male).[130] Of these, 34 (77%) were no longer inducible while treated with 600 mg/day hydroquinidine (HQ) for 6.2 ± 3 years. Among the 10 other patients (22%), who remained inducible and received ICD (Group PVS +), none received appropriate therapy during a mean follow-up of 7.7 ± 2 years. The overall annual rate of arrhythmic events was 1.04%, without significant difference between inducibility under HQ. One-third of patients experienced device-related complications.

A prospective registry of empiric quinidine for asymptomatic Brugada syndrome has been established. The study appears at the National Institutes of Health website (ClinicalTrials.gov) and can be accessed at http://clinicaltrials.gov/ct2/show/NCT00789165?term_brugada&rank_2. Doses between 600 and 900 mg were recommended, if tolerated. [116]

In the latest_HRS/EHRA/APHRS expert consensus statement, quinidine was given a class IIa recommendation in BrS patients who are qualified for an ICD but in whom hindering factors are present, IIa in ICD-patients with electrical storms, and IIb recommendation in asymptomatic BrS-patients displaying a spontaneous Type I ECG. [101]

The development of a more cardio-selective and I_{to}-specific blocker would be a most welcome addition to the limited therapeutic armamentarium currently available to combat this disease. Agents that augment the L-type calcium channel current, such as β adrenergic agents like isoproterenol, denopamine or orciprenaline, are useful as well. [10, 121, 125, 131-133] Isoproterenol, sometimes in combination with quinidine, has been utilized successfully to control VF storms and normalizing ST elevation particularly in children [113, 114, 125, 129, 134-141. 119, 142-146]. The occurrence of spontaneous VF in patients with Brugada syndrome is often related to increases in vagal tone and correspondingly electrical storm is sometimes treatable by the increase of sympathetic tone via isoproterenol administration. In the latest HRS/EHRA/APHRS guideline, Isoprotereonol has a Class IIa recommendation for BrS patients presenting with electrical storms.[101]

Another promising pharmacologic approach is the administration of phosphodiesterase III inhibitor cilostazol [125, 132, 147], which normalizes the ST segment, most likely by augmenting calcium current (I_{Ca}) as well as by reducing I_{to} secondary to an increase in cAMP and heart rate.[148] Other diverse effects of cilostazol in playing a role in its beneficial impact cannot be excluded. (e.g.: adenosine, NO, mitochondrial I_{KATP} [149]) Its efficacy in combination with bepridil in preventing VF-episodes was recently reported by Shinoharaet al.[150] A case report describing the failure of cilostazol in the treatment of a BrS-patient is also available in the literature.[151]

Milrinone is another phosphodiesterase III inhibitor recently identified as a more potent alternative to cilostazol in suppressing ST elevation and arrhythmogenesis in an experimental model of BrS.[83, 152] No clinical reports have appeared as yet.

Wenxin Keli, a traditional Chinese medicine (TCM), in addition to its actions to suppress atrial fibrillation by atrial-selective inhibition of I_{Na}-dependent parameters[153], has recently been shown to inhibit I_{to} and thus to suppress polymorphic VT in experimental models of BrS when combined with low concentrations of quinidine (5 μM). [110] A recent study has also reported the effect of Wenxin Keli to suppress ischemia-induced ventricular arrhythmias.[154]

Agents that augment sodium channel current active during the early phases of the action potential, including bepridil and dimethyl lithospermate B (dmLSB), have been suggested to be of value in BrS. Bepridil has been reported to suppress VT/VF in several studies of patients with BrS.[125, 155-157] The drug's action are thought to be mediated by: 1) inhibition of $I_{to;}$ 2) augmentation of I_{Na} via upregulation of the channels[158]; and 3) prolongation of QT

interval at slow rates thus increasing the QT/RR slope.[155, 157] Dimethyl lithospermate B, an extract of Danshen, a traditional Chinese herbal remedy, has been reported to slow inactivation of I_{Na} thus increasing I_{Na} during the early phases of the action potential (AP) and thus to suppress arrhythmogenesis in experimental models of BrS.[159]

Approach to therapy of ERS—It is not surprising that the approach to therapy of ERS is similar to that of BrS, since the mechanisms underlying the two syndromes are similar. Quinidine, phosphodiesterase III inhibitors and isoproterenol have all been shown to exert an ameliorative effect in preventing or quieting arrhythmias associated with ERS. Isoproterenol has been shown to be effective in quieting electrical storms developing in patients with either BrS[125, 134] or ERS[75]. Isoproterenol acts by increasing I_{Ca}, thus leading to a reversal of repolarization abnormalities secondary to restoration of the epicardial action potential dome in experimental models of BrS [10, 109] and ERS [90].

The phosphodiesterase (PDE) III inhibitor cilostazol has been reported to reduce the ECG and arrhythmic manifestations of ERS.[160] PDE inhibitors are known to activate I_{Ca} secondary to an increase in cAMP.[132, 148, 161-165] The augmentation of I_{Ca} is thought to prevent arrhythmias associated with the J wave syndromes by reversing the repolarization defects and restoring electrical homogeneity across the ventricular wall secondary to restoration of the epicardial action potential dome in both BrS[152] and ERS.[42] Cilostazol has been hypothesized to also block I_{to}. Augmentation of I_{Ca} together with inhibition of I_{to} are expected to produce an inward shift in the balance of currents active during the early phases of the epicardial action potential that should be especially effective in suppressing J wave activity.

The effectiveness of bepridil in ERS has been reported in a single patient thus far.[166]

No clinical data are available regarding the effectiveness of radiofrequency (RF) ablation in the setting of ERS, despite the fact that low voltage fractionated electrogram activity and high frequency late potentials are observed in the LV in patients with ERS[30] and in experimental models of ERS (Yoon and Antzelevitch, unpublished observation). Nakagawa et al.[30] reported the results of a study in which they recorded epicardial electrograms directly from the left ventricle of patients diagnosed with ERS by introducing a multipolar catheter into the left lateral (marginal) coronary vein, anterior interventricular vein (AIV), and middle cardiac vein (MCV) via the coronary sinus. The authors reported late potentials in the bipolar electrograms recorded from the left ventricular (LV) epicardium of the ERS patients.[30]

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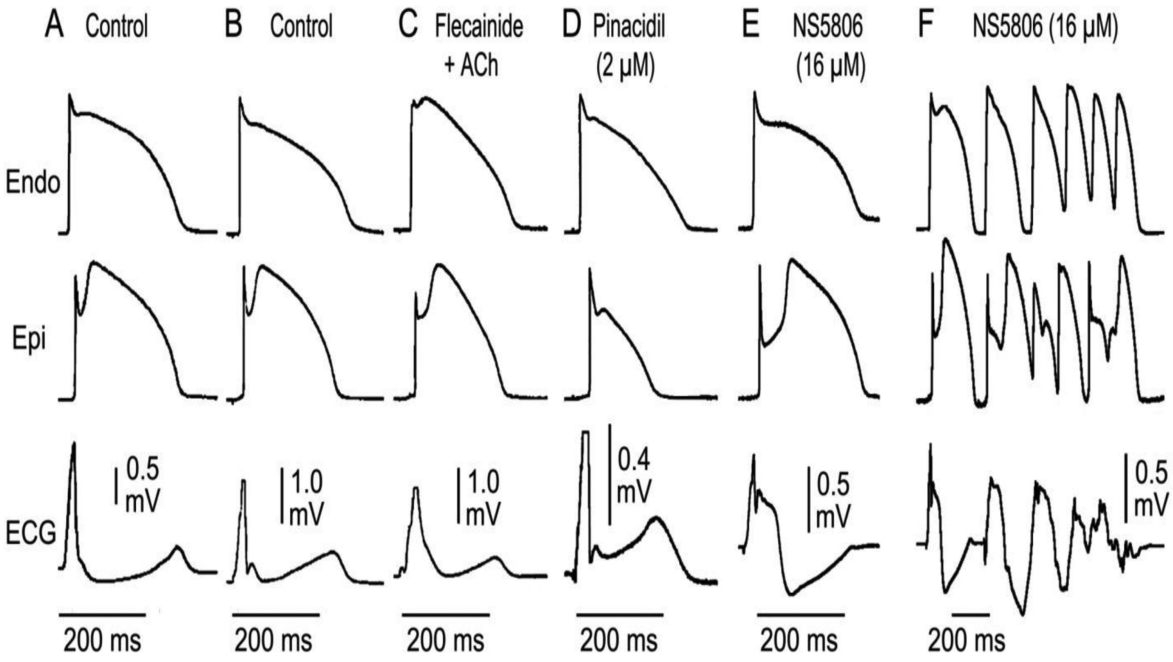

Figure 1.

Mechanisms underlying the different manifestations of the early repolarization pattern in the ECG. Each panel shows transmembrane action potentials simultaneously recorded from the epicardial and endocardial regions of an arterially-perfused canine left ventricular wedge preparation together with a transmural ECG. Under the conditions indicated, the transmural voltage gradients created by the appearance of an action potential notch in epicardium but not endocardium gives rise to an elevated J wave onset, J_O, (A),as distinct J wave (B), slurring to the terminal part of the QRS (C), a distinct J wave together with a ST elevation (D), a gigantic J wave appearing as an ST segment elevation (E). It is under these conditions that we see the development of polymorphic VT (F).Modified from [167], with permission.

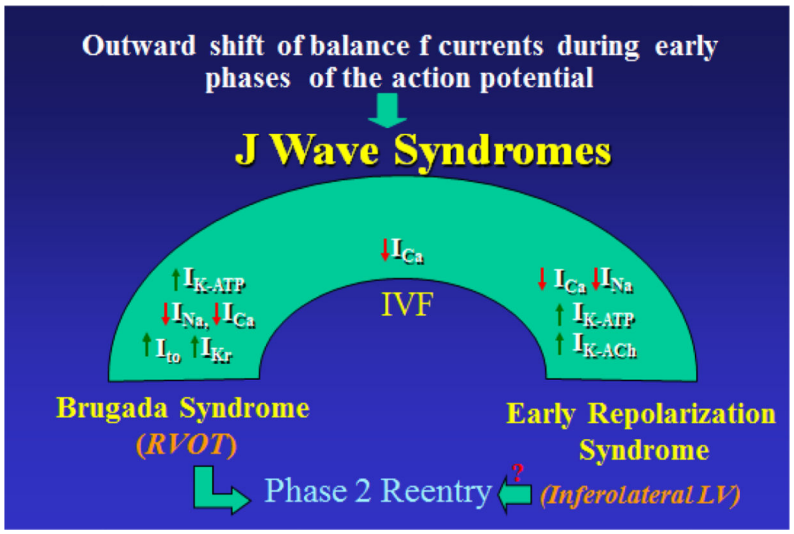

Figure 2.

J wave Syndromes. Schematic depicts our working hypothesis that an outward shift in repolarizing current due to a decrease in sodium or calcium channel currents or an increase in I_{to}, $I_{K\text{-}ATP}$, I_{Kr} or $I_{K\text{-}ACh}$, or other outward currents can give rise to accentuated J waves associated with the BrS, Early Repolarization Syndrome and some forms of IVF. The particular phenotype depends on what part of the heart is principally affected and which ion channels are involved. Accentuation of thee J waves in the right ventricular outflow tract (RVOT) gives rise to BrS, whereas accentuation in the infero-lateral left ventricle (LV) gives rise to ERS.

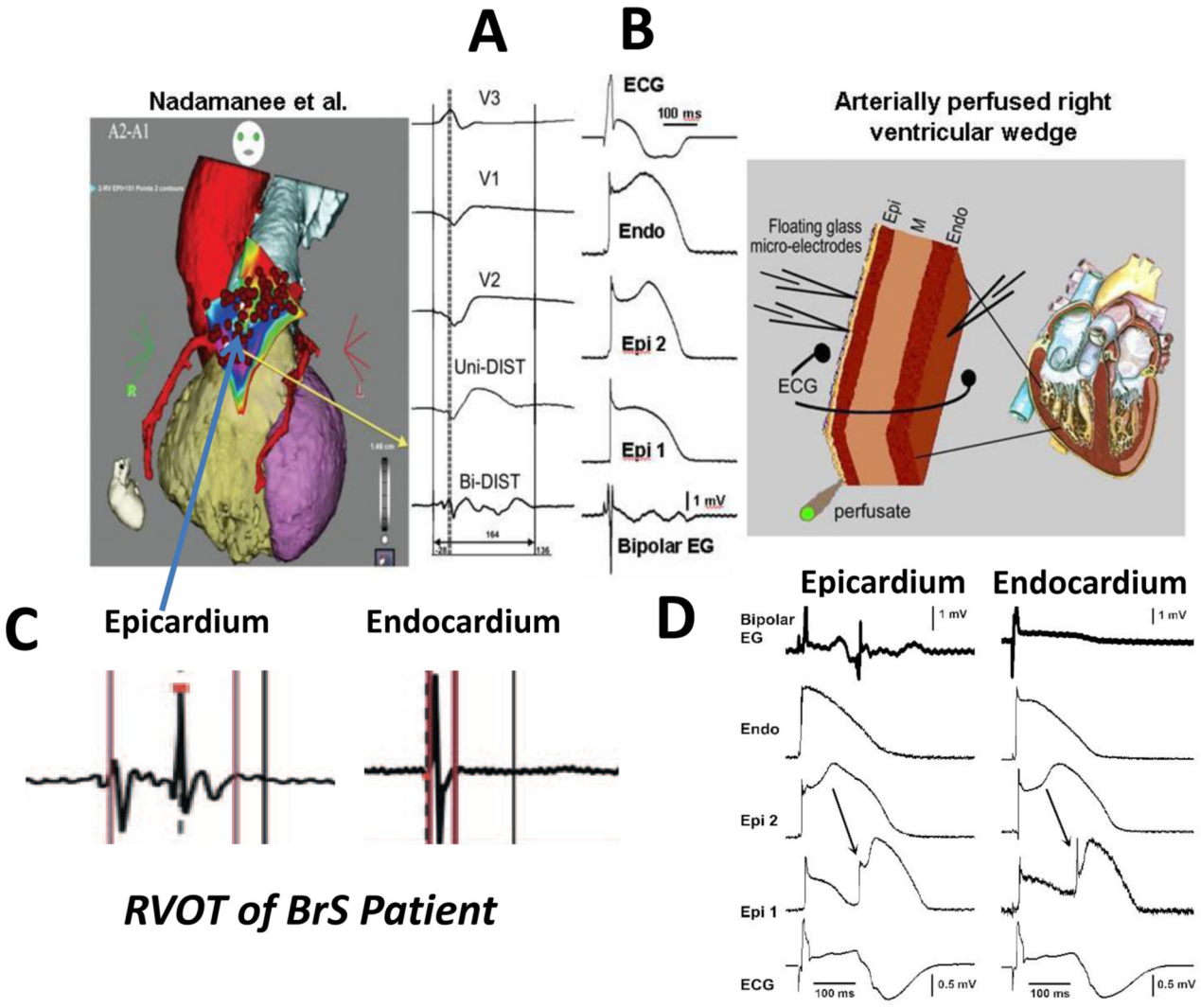

Figure 3.

Heterogeneities in the appearance of the epicardial action potential second upstroke gives rise to fractionated epicardial electrogram (EG) activity and concealed phase 2 reentry gives rise to high frequency late potentials in the setting of Brugada syndrome (BrS). **A:** Shown are right precordial lead recordings, unipolar and bipolar EGs from the right ventricular outflow tract of a BrS patient. **B:** ECG, action potentials from endocardium (Endo) and two epicardial (Epi) sites, and a bipolar epicardial EG (Bipolar EG) all simultaneously recorded from a coronary-perfused right ventricular wedge preparation treated with the I_{to} agonist NS5806 (5 μM) and the calcium channel blocker verapamil (2 μM) to induce the Brugada phenotype. Basic cycle length=1000 ms. **C**: Bipolar EGs recorded from the epicardial and endocardial surfaces of the RVOT in a patient with BrS. The epicardial EG displays fractionated electrogram activity as well as a high frequency late potential late potential (130 msec delay). **D**: Bipolar electrograms recorded from the epicardium and endocardium of a coronary-perfused wedge model of BrS, together with AP recordings from an endocardial and two epicardial sites and a transmural ECG. The clinical data are modified from

Nademanee et al.[82] and the experimental data are from Szel and co-workers [83], with permission).

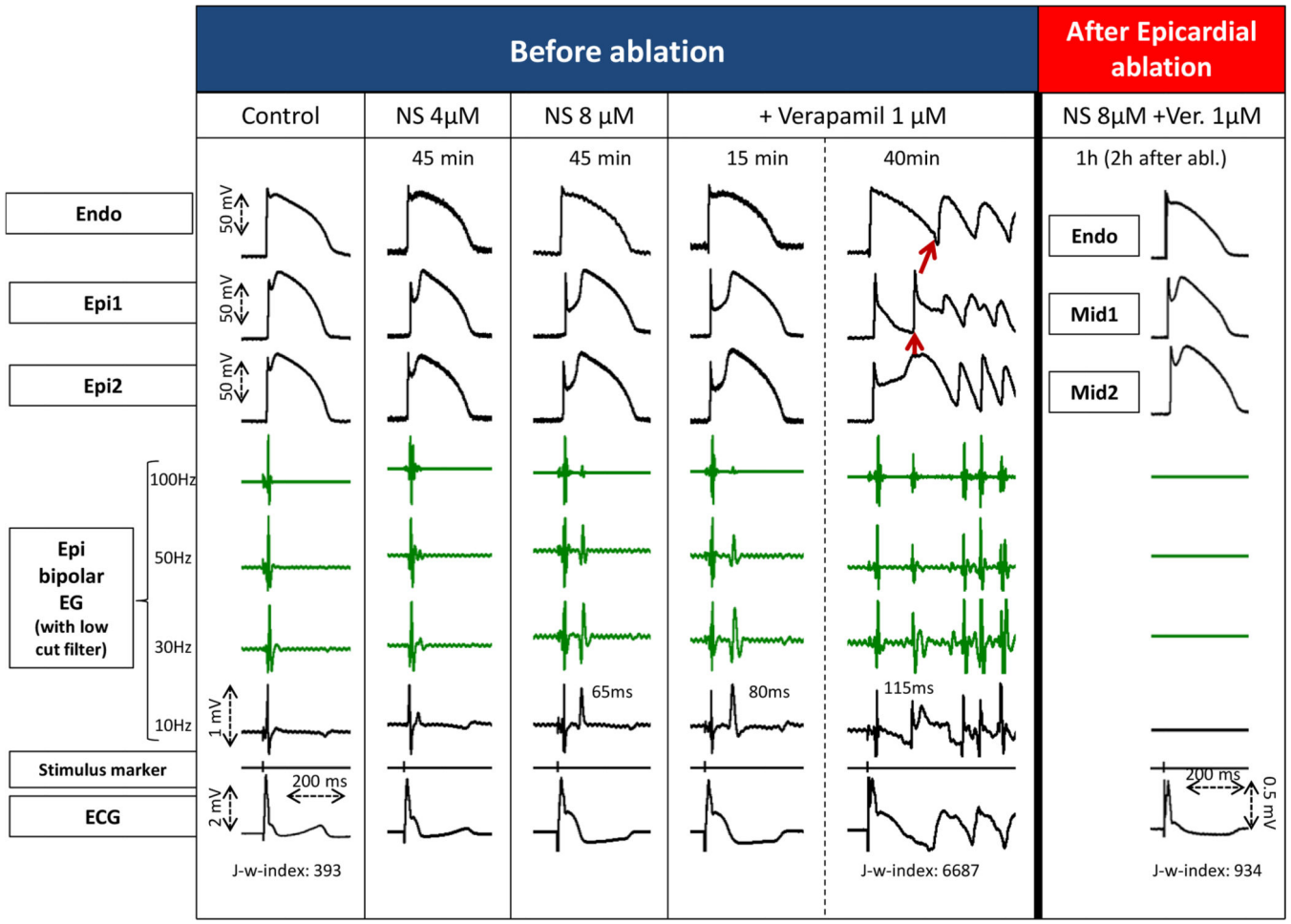

Figure 4.

Radiofrequency ablation of the epicardial surface abolishes the BrS ECG and suppresses arrhythmogenesis in coronary-perfused canine right ventricular wedge model of BrS. Transmembrane action potentials (AP) were simultaneously recorded from one endocardial (Endo) and two epicardial (Epi) sites together with epicardial bipolar electrograms (EG) and a transmural pseudo-ECG. The epicardial bipolar EGs were recorded at 10-1000 Hz bandwidth (black trace), and were simultaneously band-pass filtered at 30-200Hz, 50-200Hz and 100-200Hz (green traces). **Column 1:** Control. **Column 2:** Recorded 45 min after the addition of the I_{to}-agonist NS5806 (4μM) to the coronary perfusate. **Column 3:** Recorded 45 min after the concentration of NS5806 was raised to 8μM. High and low frequency late potentials (LP) are apparent in the EG recordings resulting from progressive delay in the appearance of the second upstroke of the Epi AP secondary to accentuation of the AP notch. **Column 4:** Recorded 15 min after the addition of the I_{Ca}-blocker verapamil (1μM) to the coronary perfusate. **Column 5:** Recorded after 40 min of exposure to verapamil (1μM). Loss of the AP dome at Epi1 but not Epi2 gives rise to a phase 2 reentrant beat, which precipitates polymorphic VT. **Column 6:** Recorded 2h after radiofrequency ablation of the epicardial surface, and 1h after reintroduction of the provocative agents to the perfusate (in the same concentration as before ablation). APs are now recorded from the deep subepicardium-

midmyocardium (Mid1, Mid2) instead of the epicardial surface. Ablation markedly suppressed the BrS phenotype and abolished all arrhythmic activity. Modified from [168], with permission.

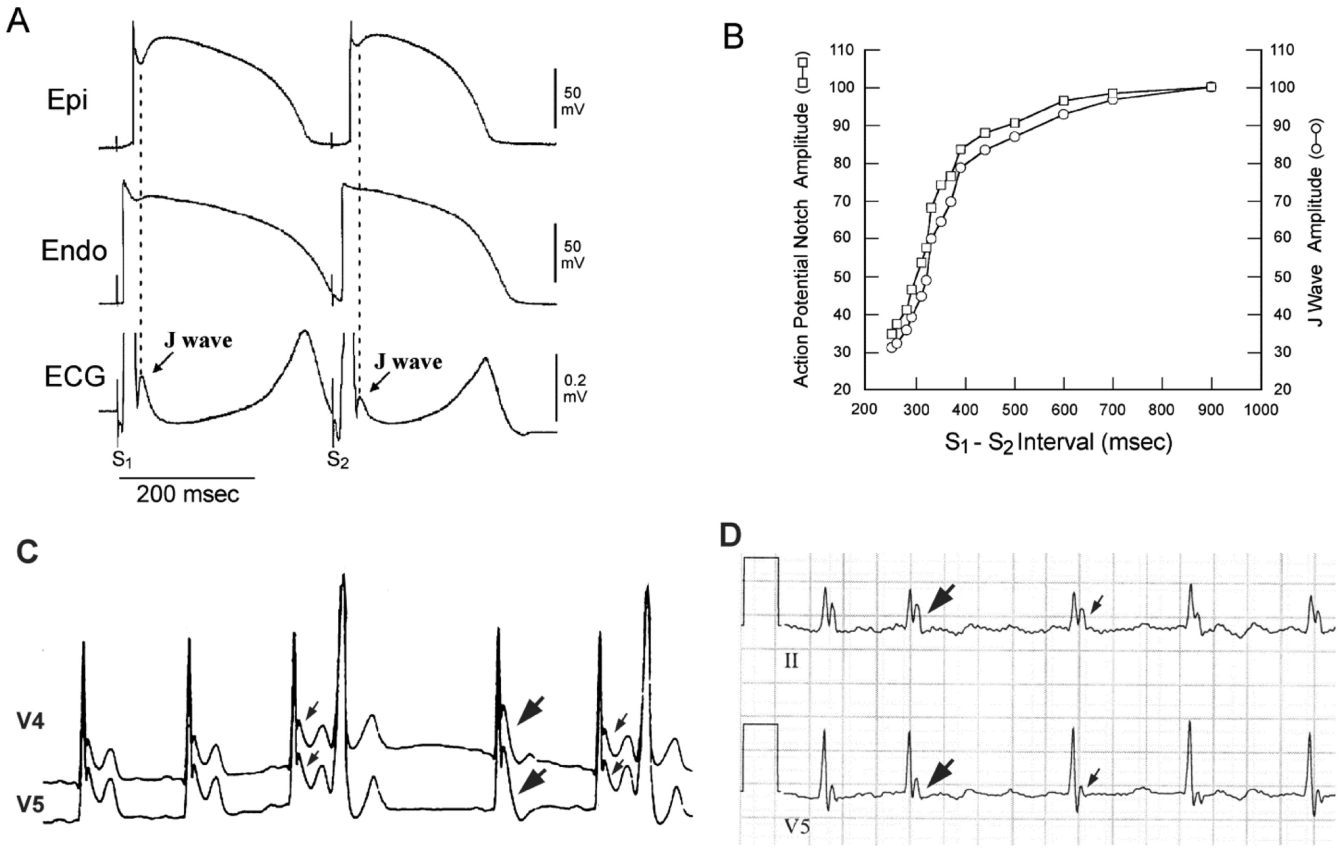

Figure 5.

Rate and pause-dependence of the J wave in an experimental model and two clinical cases of BrS. **A:** Transmural ECG and transmembrane action potentials (APs) simultaneously recorded from a canine right ventricular wedge preparation: Prominent J waves and associated AP notches were observed during basic stimulation (S1-S1=4000ms). Premature stimulation (S1-S2=300ms) reduced the epicardial AP notch and J wave amplitude. **B:** Plot of epicardial AP notch (□) and J wave (○) amplitude over a range of S1-S2 intervals. Restitution of action potential notch amplitude parallels that of the J wave. Reproduced from [169] with permission. **C:** ECG lead V4-V5 recorded from a 34 year-old Chinese man with idiopathic ventricular fibrillation, showing prominent J waves that are more accentuated after a pause (thick arrows) compared to those (thin arrows) recorded at shorter R-R intervals. Note that the amplified J wave after the pause was accompanied by T wave inversion (V5), an ECG marker associated with a high risk of ventricular fibrillation. **D:** A J-wave-like deflection at the terminal portion of the QRS in a patient with intra-ventricular conduction delay. In contrast to the J wave behavior observed in **Figure 5C**, the end of QRS notch observed in this case is tachycardia-dependent. The terminal deflection is attenuated at longer the R-R interval (thin arrows) and amplified at the shorter R-R interval (thick arrows). Reproduced from [86], with permission.

Table 1

Features Common to Brugada and Early Repolarization Syndromes and Possible Underlying Mechanisms

	BrS	ERS	Possible Mechanism(s)
Region Associated with highest arrhythmic risk	RVOT	Inferior myocardium	Higher levels of I_{to}
Male Predominance	Yes (>75%)	Yes (>80%)	Testosterone modulation of ion currents underlying the epicardial AP notch
Average age of first event	~35-40	~36-42	
Dynamicity of ECG	High	High	Autonomic modulation of ion channel currents underlying early phases of the epicardial AP
VT/VF trigger	Short-coupled PVC	Short-coupled PVC	Phase 2 reentry
Ameliorative response to quinidine	Yes	Yes	Inhibition of I_{to} and possible vagolytic effect
Ameliorative response to Isoproterenol and and milrinone	Yes	Yes	Increased I_{Ca} and faster heart rate
Ameliorative response to cilostazol	Yes	Yes	Increased I_{Ca}, reduced I_{to} and faster heart rate
Ameliorative response to pacing	Yes	Yes	Reduced availability of I_{to} due to slow recovery from inactivation
Vagally-mediated accentuation of ECG pattern	Yes	Yes	Direct effect to inhibit I_{Ca} and indirect effect to increase I_{to} (due to slowing of heart rate)

RVOT=right ventricular outflow tract, AP=action potential; PVC=premature ventricular contraction

Table 2

Gene defects associated with the Early Repolarization (ERS) and Brugada (BrS) syndromes.

Genetic Defects Associated wih ERS				
	Locus	**Gene/Protein**	**Ion Channel**	**% of Probands**
ERS1	12p11.23	*KCNJ8, Kir6.1*	↑$I_{K\text{-}ATP}$	
ERS2	12p13.3	*CACNA1C, $Ca_v1.2$*	↓ I_{Ca}	4.1%
ERS3	10p12.33	*CACNB2b, $Ca_vß32b$*	↓ I_{Ca}	8.3%
ERS4	7q21.11	*CACNA2D1, $Ca_vá2ä$*	↓ I_{Ca}	4.1%
ERS5	12p12.1	*ABCC9, SUR2A*	↑ $I_{K\text{-}ATP}$	Rare
ERS6	3p21	*SCN5A, $Na_v1.5$*	↓ I_{Na}	Rare
ERS7	3p22.2	*SCN10A, $Na_v1.8$*	↓ I_{Na}	

Genetic Defects Associated with BrS				
	Locus	**Gene/Protein**	**Ion Channel**	**% of Probands**
BrS1	3p21	*SCN5A, $Na_v1.5$*	↓ I_{Na}	11-28%
BrS2	3p24	*GPD1L*	↓ I_{Na}	Rare
BrS3	12p13.3	*CACNA1C, $Ca_v1.2$*	↓ I_{Ca}	6.6%
BrS4	10p12.33	*CACNB2b, $Ca_vß2b$*	↓ I_{Ca}	4.8%
BrS5	19q13.1	*SCN1B, $Na_vß1$*	↓ I_{Na}	1.1%
BrS6	11q13-14	*KCNE3, MiRP2*	↑ I_{to}	Rare
BrS7	11q23.3	*SCN3B, $Na_vß3$*	↓ I_{Na}	Rare
BrS8	12p11.23	*KCNJ8, Kir6.1*	↑ $I_{K\text{-}ATP}$	2%
BrS9	7q21.11	*CACNA2D1, $Ca_vá2ä$*	↓ I_{Ca}	1.8%
BrS10	1p13.2	*KCND3, $K_v4.3$*	↑ I_{to}	Rare
BrS11	17p13.1	*RANGRF, MOG1*	↓ I_{Na}	Rare
BrS12	3p21.2-p14.3	*SLMAP*	↓ I_{Na}	Rare
BrS13	12p12.1	*ABCC9, SUR2A*	↑ $I_{K\text{-}ATP}$	Rare
BrS14	11q23	*SCN2B, $Na_vß2$*	↓ I_{Na}	Rare
BrS15	12p11	*PKP2, Plakophillin-2*	↓ I_{Na}	Rare
BrS16	3q28	*FGF12, FHAF1*	↓ I_{Na}	Rare
BrS17	3p22.2	*SCN10A, $Na_v1.8$*	↓ I_{Na}	~16.7%
BrS18	6q	*HEY2 (transcriptional factor)*	↑ I_{Na}	Rare
BrS19	7p12.1	*SEMA3A, Semaphorin*	↑ I_{to}	Rare

Table 3

Risk stratifiers of patients with the J wave Syndromes

Commonly accepted risk factors

1. Association of ER or BrS pattern with SCD, unexplained syncope, or unexplained family history of SCD[170]
2. History of cardiac events or syncope likely due to VT/VF[88, 101, 171, 172]
3. Nocturnal agonal respiration[173]
4. Spontaneous Type I BrS ECG[88, 173]
5. J point or ST segment elevation of 0.2 mV or greater in right precordial leads in the case of BrS, or inferior and infero-lateral leads or global leads in the case of ERS.[174, 175]
6. Horizontal or downsloping ST segment following the J wave in cases of ERS[96, 97, 174, 176]
7. Appearance of distinct and prominent J waves.[86]
8. Association of BrS or ER pattern with abbreviated QT intervals.[45, 177]
9. Short-coupled extrasystoles[36, 178, 179]
10. Transient J wave augmentation or fluctuation of J wave portends a high risk for VF in patients with ER[37]
11. Pause-dependent augmentation of J waves that is accompanied by T wave inversion, see Figure 5C)[37, 180].
12. Association of ER with Horizontal or Descending ST segment[96]
13. Late potentials on epicardial bipolar electrogram or SAECG[82, 181-186]
14. T wave amplitude variability[182]
15. Short ventricular refractory period (VRP < 200 ms) in BrS[88]
16. Fragmented QRS[87, 88, 98, 187]
17. Prolonged QRS duration in BrS[188]

Proposed new risk stratifiers

1. Increased Tpeak-Tend interval as a marker of dispersion of repolarization[189-194]
2. Reduced QT/RR slope[195]
3. Augmented ST-elevation during recovery from exercise (vagally-mediated)
4. High daily fluctuation of SAECG parameters[197].

Table 4

Differential diagnosis of J wave vs. Intra-ventricular conduction defect-mediated notch syndromes. (IVCD)

	J wave	IVCD-induced end QRS notch
Male Predominance	Yes	No
Average Age at Initial Presentation	Young adults	Older adults
Most common Morphology	dome-like smooth appearance	Relatively sharp appearance
Response to Change in Heart Rate	Bradycardia- and pause-dependent augmentation of J wave which may be accompanied by T wave inversion.	Tachycardia and prematurity-dependent augmentation of the notch
Structural Heart Diseases	Rare	Common History of myocardial infarction and/or cardiomyopathy

Table 5

Device and Pharmacologic Approach to Therapy of the Brugada Syndrome

Devices and Ablation
ICD[99]
Radiofrequency Ablation[82, 105, 198-201]
? Pacemaker[102-104]
Pharmacologic Approach to Therapy
Ineffective or Proarrhythmic
Amiodarone[106]
β Blockers[106]
Class IC antiarrhythmics
Flecainide[202]
Propafenone[203]
? Disopyramide[107]
Class IA antiarrhythmics
Procainamide[204]
Effective for Treatment of Electrical Storms
β Adrenergic agonists – isoproterenol[139, 142], denopamine[125], orciprenaline[121, 133]
Phosphodiesterase III Inhibitors-cilostazol[132]
Effective General Therapy
Quinidine[10, 113-115, 127-129]
Bepridil[157]
Cilostazol combined with bepridil[150]
Experimental Therapy
I_{to} Blockers - cardioselective and ion channel specific
Quinidine[10]
4-aminopyridine[10]
Tedisamil[205]
AVE0118[206]
PDE-3-inhibitors
Cilostazol – Increase in I_{Ca} and inhibition of I_{to}[91, 152]
Milrinone - I_{Ca} augmentation[91, 152]
Traditional Chinese Medicine
Dimethyl lithospermate B – Increase in I_{Na} due to slowed inactivation
Wenxin Keli - combined I_{to}-block and tyramine-like effect[110]