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J Wave Syndromes as a cause of Malignant Cardiac Arrhythmias

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Abstract

The J wave syndromes, including the Brugada (BrS) and early repolarization (ERS) syndromes, are characterized by the manifestation of prominent J waves in the electrocardiogram appearing as an ST segment elevation and the development of life-threatening cardiac arrhythmias. 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 (JWS). Despite over 25 years of intensive research, risk stratification and the approach to therapy of these two inherited cardiac arrhythmia syndromes are still rapidly evolving. 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 syndromes that have captured the interest and attention of the cardiology community over the past two decades.

Keywords

Sudden cardiac death; Brugada Syndrome; Early Repolarization syndrome; cardiac arrhythmias; ventricular tachycardia; ventricular fibrillation; inherited cardiac arrhythmias syndrome; sudden cardiac death

Introduction

The appearance of prominent J waves in the surface electrocardiogram (ECG) and their associated risk for development of life-threatening cardiac arrhythmias have been recognized for nearly 100 years in clinical cases of hypothermia^{1–3}, hypercalcemia^{4, 5} and ischemia.⁶ Accentuated J waves have more recently been associated with inherited life-threatening cardiac arrhythmia disorders including Brugada (BrS) and Early Repolarization (ERS) syndromes, the so-called ‘J Wave Syndromes’ (JWS). In BrS, J waves can be so broad and tall as to appear as an ST segment elevation in the right precordial leads. BrS was first introduced as a clinical entity associated with sudden cardiac death (SCD) syndrome by Pedro and Josep Brugada in 1992.⁷

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Early repolarization (ER) pattern in the ECG, consisting of a distinct J wave or J point elevation (when part of the J wave is ‘buried’ inside the QRS), a notch or slur of the terminal part of the QRS (with or without ST segment elevation) has traditionally been viewed as benign.^{8, 9} The risk for SCD in patients afflicted with ERS was not fully appreciated until recently. Its benign nature was challenged by our group in 2000¹⁰ on the basis of experimental data obtained using coronary-perfused canine ventricular wedge preparations^{10–13} showing that an ER pattern was associated with impending polymorphic ventricular tachycardia and fibrillation (VT/VF). Clinical evidence in support of this hypothesis was provided eight years later by Haïssaguerre et al.,¹⁴ Nam et al.¹⁵ and Rosso et al.¹⁶ These foundational, seminal studies, have provided clinical evidence for an increased risk of arrhythmic SCD among patients presenting with an ER pattern.

Diagnosis of JWS

BrS and ERS, two manifestations of the JWS, are both associated with vulnerability to arrhythmic SCD (polymorphic VT and VF)^{7, 11, 14, 15} in young adults with no apparent structural heart disease and, occasionally, to sudden infant death syndrome.^{17–19}

Three distinct manifestations of ST segment elevation have been described in association with the J wave syndromes. Consistent with the recommendation of the 2013 consensus statement on inherited cardiac arrhythmias,²⁰ the 2015 guidelines for the management of patients with ventricular arrhythmias and prevention of SCD²¹ and the most recent 2016 HRS/APHRS/EHRA/SOLAECE Consensus Conference report,²² the only form diagnostic of BrS is a **Type 1 (“coved type”)** ST segment elevation characterized by an ST segment elevation of ≥ 2 mm (0.2 mV) in ≥ 1 right precordial leads positioned in the 4th intercostal space (V1 and/or V2) or in more cranial positions (2nd or 3rd intercostal space). A **Type 2 ST segment elevation**, described as a “saddle-back” configuration with an ST segment elevation of ≥ 0.5 mm (commonly ≥ 2 mm in V2) in ≥ 1 right precordial leads (V1–V3) and a **Type 3 ST segment elevation**, characterized by a “saddle-back or coved type” appearance with an ST segment elevation of < 1 mm, are NOT diagnostic of BrS unless converted to a Type 1 with fever or sodium drug challenge (Figure 1). The cardiac region most affected in BrS patients is the anterior part of the right ventricular outflow tract (RVOT), accounting for why the typical BrS ECG is observed in the (anterior) right precordial leads.

Early repolarization *pattern* (**ERP**) is often encountered in apparently healthy individuals, particularly in young males, black individuals and athletes. When associated with VT/VF in the absence of organic heart disease, ERP is referred to as early repolarization *syndrome* (**ERS**).

Early repolarization is recognized with the appearance of: 1) an **end QRS notch (J wave)** or **slur** on the downslope of a prominent R wave (with or without ST segment elevation). The onset of the J wave is referred to as **J₀**; 2) a distinct J wave with a peak (designated as **J_P**) ≥ 0.1 mV in two or more contiguous ECG leads, excluding leads V1–V3; and 3) a QRS duration (measured in leads in which a notch or slur is absent) must be < 120 ms. The end of the **J wave** or that of the **QRS slur or notch** is designated as **J_T** (Figure 2).^{23, 24} Thus, ERP is characterized by distinct J waves, **J₀** elevation, notch or slur of the terminal part of the

QRS and ST-segment or **J_T** elevation in the lateral (**Type I**), infero-lateral (**Type II**) or in infero-lateral + (anterior) right precordial leads (**Type III**; Figure 3).¹¹

Pharmacological tests

In the absence of a spontaneous Type 1 ST segment elevation, BrS is suspected if there is documented polymorphic VT or VF, or a family history of SCD at <45 years old (with negative autopsy), or the presence family members with spontaneous Type 1 ECGs, or nocturnal agonal respiration. If this is the case, a provocative drug test using a sodium channel blocker is recommended. Table 1 shows a list of agents used for this purpose (also see www.brugadadrugs.org). The test is considered positive if a Type 1 ECG pattern is obtained, although it should be discontinued if frequent ventricular extrasystoles or other arrhythmias occur and/or the QRS widens >130% relative to the baseline values.²⁵

Although sodium channel blockers unmask or accentuate the J wave manifestation in patients with BrS, they have been shown to reduce the amplitude of the J wave in individuals with ERS.²⁶ But this, by no means, implies that the pathophysiological basis for ERS and BrS are fundamentally different. Indeed, a recent study by Nakagawa et al. reported that J waves recorded using unipolar LV epicardial leads in ERS patients are augmented following provocative drug testing with a sodium channel blocker, while the J waves concurrently recorded in the lateral precordial leads are diminished demonstrating that the J waves in the surface leads are reduced because they are engulfed by the widening QRS.^{26, 27} Also, in support of the hypothesis that the pathophysiological basis for ERS and BrS are closely related are reports of cases in which ERS transitions into ERS plus BrS phenotypes.^{28, 29}

Tables 2 and 3 show the Shanghai Score system proposed for the diagnosis of BrS and ERS.²² An initial test of the scoring system was recently performed by Kawada and co-workers using 393 patients evaluated for BrS. The authors concluded that the study provides validation for the use of the Shanghai Score System for the diagnosis as well as risk stratification of BrS.³⁰

Prevalence of JWS and arrhythmic SCD risk assessment

The discovery of a J wave on a routine ECG recording should not be interpreted as a marker of “high risk” for SCD in that the probabilities for these life-threatening arrhythmias are approximately 1:10,000.³¹ Rosso et al. reported that the presence of a J wave on the ECG increases the probability of VF from 3.4:100,000 to 11:100,000.^{16, 32} However, careful attention needs to be paid to subjects with “high risk” ER or J waves.

In general, J waves in the lateral ECG leads have a high prevalence but are associated with a very low arrhythmic risk. Patients displaying a rapidly ascending ST segment elevation also have a high prevalence and low risk. In contrast, J waves appearing in the inferior leads or infero-lateral leads are associated with a much higher risk, particularly when displaying a flat or descending ST segment.³³ J waves appearing globally in the ECG have a very low prevalence, but are associated with a very high level of arrhythmic risk as are subjects resuscitated from cardiac arrest.²² Figure 4 summarizes the prevalence and arrhythmic risk

associated with the appearance of J waves and clinical manifestations of both Brugada and Early Repolarization syndromes.

The prevalence of BrS with a type 1 ECG in adults is higher in Asian countries, such as Japan (0.15 to 0.27%),^{34, 35} and the Philippines (0.18%),³⁶ than in Western countries, including Europe (0 to 0.017%)^{37–39} or North America (0.005 to 0.1%).^{40, 41} In contrast, the prevalence of an ER pattern in the inferior and/or lateral leads with a J point (**J₀**) elevation of 0.1 mV ranges between 1% and 24%, and for **J₀** elevation of 0.2 mV ranges between 0.6% to 6.4%.^{42–44} No significant regional differences have been reported in the prevalence of an ER pattern,⁴⁵

Differential diagnosis and Modulating factors

Other causes of ST segment elevation should be excluded before making the diagnosis of BrS including right bundle branch block (RBBB), pectus excavatum, arrhythmogenic right ventricular cardiomyopathy (ARVC), as well as occlusion of the left anterior descending coronary artery or the conus branch of the right coronary artery, which supplies the RVOT (Table 4A).

Sympatho-vagal balance, hormones, metabolic factors, and pharmacological agents are thought to modulate not only the ECG morphology but also explain the development of ventricular arrhythmias under certain conditions.⁴⁶ If any of these modulating factors is present, it should be promptly corrected (Table 4B).

The Brugada ECG, often concealed, can be unmasked with a wide variety of drugs and conditions, including a febrile state, vagotonic agents and maneuvers, α -adrenergic agonists, β -adrenergic blockers, Class IC antiarrhythmic drugs, tricyclic or tetracyclic antidepressants, hyperkalemia, hypokalemia, hypercalcemia, as well as by alcohol and cocaine toxicity.^{47–57} Pre-excitation of RV can unmask the BrS phenotype in cases of RBBB.⁵⁸ An up-to-date list of agents known to unmask the Brugada ECG and that should be avoided by patients with BrS can be found at www.brugadadrugs.org.⁴⁶ (Table 4B).

Similarities and difference between BrS and ERS

BrS and ERS present several clinical similarities, which suggest a closely related pathophysiology.^{12, 28, 59–61} Males predominate in both syndromes.^{62, 63} They may be totally asymptomatic until presenting with cardiac arrest. The highest incidence of VF or SCD occurs in the third decade of life in both syndromes.⁶⁴ In general, the occurrence of accentuated J waves and ST segment elevation are concurrent with bradycardia or pauses,^{65, 66} and thus VF often occurs during sleep or at a low level of physical activities.^{26, 67}

ERS and BrS also share similarities with respect to the response to pharmacological therapy. Electrical storms (and the associated accentuated J waves) can be suppressed with β -adrenergic agonists.^{68–71} Chronic oral administration of quinidine,^{72, 73} bepridil,⁷⁰ denopamine,^{68, 74} and cilostazol,^{68, 70, 74–78} are reported to prevent VT/VF in both syndromes, probably secondary to inhibition of I_{to} and/or augmentation of I_{Ca} .^{15, 75, 79}

Differences between the two syndromes include: 1) the region of the heart most affected (RVOT in BrS vs. inferior LV in ERS); 2) the presence of subtle structural abnormalities in BrS, which as yet have not been reported in ERS⁸⁰; 3) the incidence of late potentials in signal-averaged ECGs (SAECG): 60% in BrS/7% in ERS²⁶; 4) greater elevation of J_O , J_P or J_T (ST segment elevation) in response to sodium channel blockers in BrS vs. ERS; and 5) higher prevalence of atrial fibrillation in BrS vs. ERS.⁸¹

Steep and localized repolarization gradients in the inferior and lateral regions of the LV have been reported in ERS patients in conjunction with normal ventricular activation.⁸² In contrast, fractionated electrogram activity was recorded in the RVOT of BrS patients in addition to a steep dispersion of repolarization gradients.⁸³

ERS patients are at greater risk of VF during hypothermia^{84–88} as well as in the event of an acute myocardial infarction.⁸⁹ BrS patients are known to be at greater risk of VF in febrile states^{90, 91} as well as when accompanied by an ER pattern in the infero-lateral leads.⁹² Available data suggest that mild therapeutic hypothermia to a temperature of 34°C can be used safely in cases of Brugada syndrome.^{93, 94}

Genetics

ERS and BrS have been associated with variants in 7 and 19 genes, respectively (Table 5). The gene most often associated with BrS is *SCN5A*, accounting for 11–28% of cases depending largely on geographic location. Over 300 BrS-related variants in *SCN5A*, the gene encoding the cardiac Na channel, have been described.^{60, 95–97} Loss-of-function mutations in *SCN5A* contribute to the development of both BrS and ERS, as well as to various conduction diseases, Lenegre disease and Sick Sinus Syndrome.

Variants in genes encoding the calcium channels including *CACNA1C* (Cav1.2), *CACNB2b* (Cavβ2b) and *CACNA2D1* (Cavα2δ) have been reported in up to 13% of probands.^{98–101} Mutations in glycerol-3-phosphate dehydrogenase 1-like enzyme gene (*GPD1L*), *SCN1B* (β₁-subunit of Na channel), *KCNE3* (MiRP2), *SCN3B* (β₃-subunit of Na channel), *KCNJ8* (Kir 6.1), *KCND3* (Kv4.3), *RANGRF* (MOG1), *SLMAP*, *ABCC9* (SUR2A), (Navβ2), *PKP2* (Plakophilin-2), *FGF12* (FHAF1), *HEY2*, *SEMA3A* (Semaphorin) and *KCNAB2* (Kvβ2) are relatively rare.^{102–114} An association of BrS with *SCN10A*, a gene encoding a neuronal Na channel, was reported in 2014.^{113, 115, 116} There is controversy as to the pathogenicity of many *SCN10A* mutation with yields ranging between 5% and 16.7%.^{115–117} Mutations in all of these genes lead to loss of function in sodium (I_{Na}) and calcium (I_{Ca}) channel currents, as well as to a gain of function in transient outward potassium current (I_{to}) or ATP-sensitive potassium current (I_{K-ATP}).^{116, 118}

New susceptibility genes proposed and awaiting confirmation include the Transient Receptor Potential Melastatin Protein 4 gene (*TRPM4*)¹¹⁹ and the *KCND2* gene. Variants in *KCNH2*, *KCNE5* and *SEMA3A* although not causative, have been identified as capable of modulating the substrate for the development of BrS.^{120–123} *KCNE4* has recently been identified as a BrS susceptibility gene (unpublished observation, J. Clatot and C.

Antzelevitch). Loss-of-function mutations in *HCN4* have been associated with BrS but may be modulatory by acting to unmask BrS by reducing heart rate.¹²⁴

An ER pattern in the ECG is reported to be familial.^{125–127} Consistent with the findings that I_{K-ATP} activation can generate an ER pattern in canine ventricular wedge preparations, variants in *KCNJ8* and *ABCC9*, responsible for the pore forming and ATP-sensing subunits of the I_{K-ATP} channel, have been reported in patients with ERS.^{102, 104, 128} Loss-of-function variations in the $\alpha 1$, $\beta 2$ and $\alpha 2\delta$ subunits of the cardiac L-type calcium channel (*CACNA1C*, *CACNB2*, and *CACNA2D1*) and the α subunit of Nav1.5 and Nav1.8 (*SCN5A* and *SCN10A*) have also been reported in patients with ERS.^{98, 115, 129}

It is important to point out that only a small fraction of identified genetic variants in the genes associated with BrS and ERS have been examined using functional expression studies to ascertain causality and establish a plausible contribution to pathogenesis. 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.¹³⁰

Together, these data suggest the possibility that in the individual patient, BrS and the susceptibility to VF and SCD may not be due to a single mutation but rather to inheritance of multiple BrS-susceptibility variants (oligogenic) acting in concert through one or more mechanistic pathways.¹¹³ In addition to the multifactorial nature of the genetics, expressivity of the syndrome is multifactorial in that phenotypic expression can be importantly modulated by hormonal factors including testosterone,^{131, 132} and thyroxine¹³³ as well as by other environmental factors and structural remodeling involving development of fibrosis.⁸⁰

Ionic and cellular mechanisms underlying the JWS

Experimental evidence indicates that the electrocardiographic J wave is the expression of a transmural voltage gradient in I_{to} -mediated action potential (AP) notch in ventricular epicardium but not endocardium.^{61, 134, 135} The transmural gradient and associated J wave is much greater in the right vs. left ventricle, particularly in the region of the RVOT, because of the more prominent I_{to} -mediated AP notch in right ventricular epicardium.¹³⁶ This distinction is the basis for why BrS is a right ventricular disease. An end of QRS notch, resembling a J wave, has been proposed to be caused by intramural conduction delays. The distinction can be made on the basis of their response to heart rate, with the latter showing accentuation at faster rates.^{23, 137}

The cellular mechanisms underlying JWS have long been a matter of debate.^{138, 139} In the case of BrS, two principal hypotheses have been advanced: 1) The **repolarization hypothesis** states that an outward shift in the balance of currents at the end of phase 1 of the right ventricular epicardial AP explains the BrS ECG phenotype and the underlying early repolarization abnormalities (heterogeneous loss of epicardial AP dome) leading to phase 2 reentry, which generates closely coupled premature beats that can trigger polymorphic VT/VF (Figure 5); and 2) The **depolarization hypothesis** proposes that slow conduction in the RVOT (secondary to fibrosis) and reduced Cx43 leads to discontinuities in conduction and explains the development of the BrS ECG and the arrhythmic manifestations.

It is important to acknowledge that the typical behavior of patients with BrS to acceleration of heart rate is a reduction of the ST segment elevation, which is consistent with the repolarization hypothesis in that there is a reduced availability of I_{to} and smaller AP RV epicardial notches at the faster rate. In contrast, in the depolarization hypothesis, acceleration of rate is expected to have the opposite effect (i.e., exacerbation of the ST segment elevation at fast rates).^{137, 138}

Using the noninvasive ECG imaging technique (ECGI) on 25 BrS and 6 RBBB patients, Zhang et al.⁸³ concluded that both slow, discontinuous conduction and steep dispersion of repolarization are present in the RVOT of BrS patients. Unlike BrS, RBBB showed delayed activation in the entire RV (not just in the RVOT like in BrS patients), without ST-segment elevation, fractionation, or repolarization abnormalities shown on the electrograms. Increasing the heart rate in 6 of the BrS patients led to augmented fractionation of the electrograms *but* to a reduction of the ST-segment elevation, indicating that the conduction impairment was not the principal cause of the BrS ECG phenotype.

In 2011, Nademanee et al.¹⁴⁰ showed that radiofrequency (RF) ablation of epicardial sites displaying fractionated bipolar electrograms (EGs) and late potentials (LP) in the RVOT of patients with BrS suppresses the electrocardiographic and arrhythmic manifestations of BrS. These authors hypothesized that LP and fractionated electrogram activity are due to conduction delays within the RVOT.¹⁴⁰ Similar results and conclusions were reported by two other groups.^{134, 141, 142} Szél and co-workers¹⁴³ provided a direct test of this hypothesis and showed, using experimental models of BrS, that the electrophysiologic and arrhythmic manifestations BrS are due to repolarization defects rather than depolarization or conduction defects.

It remained to be explained why ablation of regions of the RVOT exhibiting fractionated electrogram activity and LP are effective in suppressing the ECG and arrhythmic manifestations of BrS. Patocskaï et al.¹⁴⁴ demonstrated that ablation was effective because it eliminated the cells in the surface of the RVOT responsible for the repolarizations defects giving rise to the BrS phenotype.

It is noteworthy that the repolarization and depolarization hypotheses are not necessarily mutually exclusive and may be synergistic.

Using a canine ventricular wedge model of ERS, Koncz et al.¹⁴⁵ recently provided evidence in support of the hypothesis that in ERS, as in the BrS, accentuation of transmural gradients in the LV wall are responsible for the repolarization abnormalities underlying the ECG phenotype. Additional evidence for repolarization abnormalities in ERS patients was provided by Rudy and colleagues who identified, by employing the non-invasive ECGI technique, short activation-recovery intervals and marked dispersion of repolarization in the inferior and lateral regions of the LV in ERS patients.⁸²

Approaches to therapy of JWS

Implantable Cardioverter Defibrillator

The approach to therapy of BrS and ERS as recommended in the 2016 HRS, APHRS, EHRA, SOLAECE Consensus Report is presented in Figures 6 and 7. The most effective therapy for the prevention of SCD in high risk BrS and ERS patients is an implantable cardioverter defibrillator (ICD).^{146, 147} However, ICDs are associated with complications, especially in young active individuals^{148, 149} and, over time, inappropriate shocks and lead failure are not uncommon. Remote monitoring can identify lead failure and prevent inappropriate shocks.¹⁵⁰ The advent of sub-cutaneous ICDs is a welcome innovation associated with fewer complications over a lifetime.¹⁵¹

Pacemaker therapy

Although life-threatening arrhythmias and SCD in JWS are generally associated with slow heart rates, the potential therapeutic benefit for cardiac pacing at relatively fast rates remains largely unexplored.^{152–154}

Radiofrequency Ablation (RFA) Therapy

As discussed above, Nademanee et al.¹⁴⁰ in a seminal study demonstrated that RFA of epicardial sites displaying late potentials (LP) and fractionated bipolar electrograms (EGs) in the RVOT of BrS patients can significantly reduce arrhythmia risk and the ECG phenotype and that, over time (weeks or months), the ablation renders VT/VF non-inducible and normalizes the Brugada ECG pattern in most patients. Case reports have been published in support of the beneficial effects of RFA.¹⁵⁵ Additional evidence in support of the effectiveness of epicardial RVOT ablation was provided by Sacher et al., Shah et al. and Brugada and coworkers.^{141, 156, 142} RF ablation may be considered in BrS patients with frequent appropriate ICD-shocks due to repeated electrical storms.¹⁵⁷ With regards to the ERS, no clinical data are available regarding the effectiveness of epicardial RFA, despite the fact that low-voltage fractionated electrogram activity and high-frequency LP are observed in the LV in patients with ERS.¹⁵⁸ RFA has been shown to suppress arrhythmogenesis by eliminating the extrasystoles precipitating VT/VF.^{159–161} Of note, in patients in whom BrS combines with ERS, ablation of the anterior RVOT is not ameliorative.

Pharmacologic therapy

In that ICD implantation may lead to complications (particularly in children) and is unaffordable in many regions of the world, a pharmacologic approach to therapy has long been the focus of basic and clinical research. Because the presence of a prominent Ito is believed to be a prerequisite for the development of both **BrS** and **ERS**, partial inhibition of this current is thought to be effective regardless of the underlying ionic or genetic basis. Regrettably, ion-channel specific and cardio-selective I_{to} blockers are not currently available. The best drug currently available in the clinic capable of blocking I_{to} is **quinidine**. Quinidine was first recommended as therapy for BrS by our group in 1999 based on experimental evidence acquired using the coronary-perfused RV wedge model of BrS.^{12, 162, 124, 143, 163–165} Clinical evidence for the effectiveness of quinidine has been reported in

numerous studies and case reports.^{70, 73, 77, 166–178} Hermida et al. reported 76% efficacy in prevention of VF induced by PES.⁷² Belhassen, Viskin and colleagues, who pioneered the use of quinidine in VF,¹⁷⁹ recently reported a 90% efficacy in prevention of VF induction following treatment with quinidine, despite the use of very aggressive protocols of extrastimulation.¹⁷⁹

Agents that augment the L-type calcium channel current, such as **β-adrenergic agents** like isoproterenol or orciprenaline, are useful as well.^{12, 70, 74, 175, 180, 181} Increasing I_{Ca} is believed to prevent the arrhythmogenesis associated with **JWS** by opposing the relative augmented repolarization forces and thus restoring the epicardial AP dome in both BrS¹⁸² and ERS.¹⁸³ Isoproterenol, sometimes in combination with quinidine, has been used to successfully control VF storms and normalizing ST elevation.^{69, 167, 168, 184–186} 50, 68, 70, 71, 157, 173, 187–193

Another promising pharmacologic approach for **BrS** is **cilostazol**, a phosphodiesterase (PDE) III inhibitor^{70, 74, 76} which normalizes the ST segment by augmenting I_{Ca} as well as by reducing I_{to} secondary to an increase in cAMP and heart rate.¹⁹⁴ Of note, failure of cilostazol in the treatment of BrS has been described in a single case report.¹⁹⁵

Milrinone, another PDE III inhibitor, was recently identified as a more potent alternative to cilostazol in suppressing ST segment elevation and arrhythmogenesis in an experimental model of **BrS**^{143, 182} although there are no clinical data available as yet. **Wenxin Keli**, a traditional Chinese medicine has recently been shown to inhibit I_{to} and suppress arrhythmogenesis in experimental models of **BrS** when combined with low concentrations of quinidine (5 μ M).¹⁶⁴

Agents that augment peak and late I_{Na} , including **bepiridil** and **dimethyl lithospermate B** (dmLSB), are suggested to be of value in **BrS**. Bepiridil has been reported to suppress VT/VF in several studies of patients with **BrS**.^{70, 196–198} The drug's action are thought to be mediated by: 1) inhibition of I_{to} ; 2) augmentation of I_{Na} via up-regulation of the sodium channels¹⁹⁹ and 3) prolongation of QT interval at slow rates thus increasing the QT/RR slope.^{196, 198} 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 AP, thereby reducing the AP notch and restoring the epicardial AP dome and, in the process, suppressing arrhythmogenesis in experimental models of **BrS**.²⁰⁰

Acacetin, a natural flavone, has been shown to inhibit I_{to} in human atrial myocytes in a frequency-dependent manner.²⁰¹ The potential ameliorative effect of this agent in experimental models of **BrS and ERS** is currently under study by our group.

Because the mechanisms underlying **BrS** and **ERS** are closely related, the approach to therapy is similar. Quinidine, PDE III inhibitors (cilostazol and milrinone) and isoproterenol have all suppress arrhythmogenesis associated with **ERS** and **BrS**. Isoproterenol has been shown to be effective in quieting electrical storms developing in patients with both **BrS**^{70, 187} and **ERS**.^{75, 128} All of these agents have been shown to correct the repolarization

defects responsible for development of phase 2 reentry and VT/VF in experimental models of **BrS** and **ERS**.^{12, 145, 163.}

The effectiveness of **bepiridil** in ERS has been reported in a single patient thus far.²⁰²

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Figure 1.

Three types of ST segment elevation associated with Brugada syndrome. Only Type 1 is diagnostic of BrS. Reproduced from ²², with permission.

Figure 2.

Different manifestations of Early Repolarization. **A.** The J wave may be distinct or appear as a slur. In the latter case, part of the J wave is buried inside the QRS, resulting in an elevation of J_0 . Patients with a **very prominent J waves** have a **worse prognosis**. **B.** The ST segment may be upsloping, horizontal or descending. **Horizontal and descending ST segments** are associated with a **worse prognosis**. Reproduced from ²², with permission.

Figure 3. Global Early Repolarization (**Type 3 ER**). J waves are apparent in the inferior, lateral and anterior (right precordial) leads. Reproduced from ²², with permission.

Figure 4.

Prevalence and arrhythmic risk associated with the appearance of ECG J waves and clinical manifestations of Brugada and Early Repolarization syndromes. The yellow highlighted region estimates the prevalence of the J wave syndromes. J waves in the lateral ECG leads have a high prevalence but are associated with a very low arrhythmic risk in a relatively small fraction of the cohort of individuals displaying J waves. On the other extreme, J waves appearing globally in the ECG have a very low prevalence, but are associated with a very high level of arrhythmic risk in a large fraction of the cohort presenting with J waves. Likewise, individuals displaying rapidly ascending ST segment elevation have a high prevalence but low risk, whereas subjects resuscitated from cardiac arrest have a very low prevalence by the highest level of arrhythmic risk. Reproduced from ²², with permission.

Figure 5.

Cellular basis for electrocardiographic and arrhythmic manifestation of BrS. Each panel shows transmembrane APs from one endocardial (**top**) and two epicardial sites together with a transmural ECG recorded from a canine coronary-perfused right ventricular wedge preparation. **A:** Control (Basic cycle length (BCL) 400 msec). **B:** Combined sodium and calcium channel block with terfenadine (5 μ M) accentuates the epicardial AP notch creating a transmural voltage gradient that manifests as an ST segment elevation or exaggerated J wave in the ECG. **C:** Continued exposure to terfenadine results in all-or-none repolarization at the end of phase 1 at some epicardial sites but not others, creating a local epicardial

dispersion of repolarization (EDR) as well as a transmural dispersion of repolarization (TDR). **D:** Phase 2 reentry occurs when the epicardial AP dome propagates from a site where it is maintained to regions where it has been lost giving rise to a closely coupled extrasystole. **E:** Extrastimulus ($S1-S2 = 250$ msec) applied to epicardium triggers a polymorphic VT. **F:** Phase 2 reentrant extrasystole triggers a brief episode of polymorphic VT. (Modified from reference²⁰³, with permission)

Figure 6.

Indications for therapy of patients with Brugada syndrome. Recommendations with Class designations are taken from the 2013 HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes²⁰ and the 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.²¹ Recommendations without Class designations are derived from unanimous consensus of the authors of the 2016 HRS, APHRS, EHRA, SOLAECE J wave syndrome expert consensus report.²² Reproduced from²², with permission.

ES= extrastimuli at RV apex, ICD=implantable cardioverter defibrillator. ILR=implantable loop recorder, NAR= nocturnal agonal respiration, VT=ventricular tachycardia.

Figure 7.

Indications for therapy of patients with Early Repolarization syndrome. Recommendations with Class designations are taken from the 2013 HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Heart Rhythm²⁰ and the 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.²¹

Recommendations without Class designations are derived from unanimous consensus of the authors of the 2016 HRS. APHRS, EHRA, SOLAECE J wave syndrome expert consensus report.²² Reproduced from ²², with permission.

ER=early repolarization, ICD=implantable cardioverter defibrillator, ILR=implantable loop recorder, NAR=nocturnal agonal respiration, VT=ventricular tachycardia.

Table 1

Drugs used to unmask the Brugada electrocardiogram.

Drug	Dose	Administration
Ajmaline	1 mg/kg over 10 minutes	Intravenous
Flecainide	2 mg/kg over 10 minutes 200–300 mg	Intravenous Oral (>1 hour)
Procainamide	10 mg/kg over 10 minutes	Intravenous
Pilsicainide	1 mg/kg over 10 minutes	Intravenous

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Table 2**Shanghai Score System for Diagnosis of Brugada Syndrome**

	Points
I. ECG (12-Lead/Ambulatory)	
A. Spontaneous type 1 Brugada ECG pattern at nominal or high leads	3.5
B. Fever-induced type 1 Brugada ECG pattern at nominal or high leads	3
C. Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge	2
<i>*Only award points once for highest score within this category. One item from this category must apply.</i>	
II. Clinical History*	
A. Unexplained cardiac arrest or documented VF/polymorphic VT	3
B. Nocturnal agonal respirations	2
C. Suspected arrhythmic syncope	2
D. Syncope of unclear mechanism/unclear etiology	1
E. Atrial flutter/fibrillation in patients < 30 years without alternative etiology	0.5
<i>*Only award points once for highest score within this category.</i>	
III. Family History	
A. First- or second-degree relative with definite BrS	2
B. Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first or second degree relative	1
C. Unexplained SCD < 45 years in first- second- degree relative with negative autopsy	0.5
<i>*Only award points once for highest score within this category.</i>	
IV. Genetic Test Result	
A. Probable pathogenic mutation in BrS-susceptibility gene	0.5
Score (requires at least 1 ECG finding)	
3.5 points: Probable/definite BrS	
2–3 points: Possible BrS	
<2 points: Nondiagnostic	

BrS = Brugada syndrome; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.

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Table 3**Shanghai Score System for Diagnosis of Early Repolarization Syndrome**

	Points
I. Clinical History	
A. Unexplained cardiac arrest, documented VF or polymorphic VT	3
B. Suspected arrhythmic syncope	2
C. Syncope of unclear mechanism/unclear etiology	1
<i>*Only award points once for highest score within this category</i>	
II. Twelve-Lead ECG	
A. ER 0.2 mV in 2 inferior and/or lateral ECG leads with horizontal/descending ST segment	2
B. Dynamic changes in J-point elevation (0.1 mV) in 2 inferior and/or lateral ECG leads	1.5
C. 0.1 mV J-point elevation in at least 2 inferior and/or lateral ECG leads	1
<i>*Only award points once for highest score within this category</i>	
III. Ambulatory ECG Monitoring	
A. Short-coupled PVCs with R on ascending limb or peak of T wave	2
IV. Family History	
A. Relative with definite ERS	2
B. 2 first-degree relatives with a ILA. ECG pattern	2
C. First-degree relative with a ILA. ECG pattern	1
D. Unexplained sudden cardiac death <45 years in a first- or second-degree relative	0.5
<i>*Only award points once for highest score within this category</i>	
V. Genetic Test Result	
A. Probable pathogenic ERS susceptibility mutation	0.5
Score (requires at least 1 ECG finding)	
5 points: Probable/definite ERS	
3–4.5 points: Possible ERS	
<3 points: Nondiagnostic	

ER = early repolarization; ERS = early repolarization syndrome; PVC = premature ventricular contraction; VF = ventricular fibrillation; VT = ventricular tachycardia.

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Table 4

Differential diagnosis and modulating factors in Brugada Syndrome.

A. Differential diagnosis	B. Modulating factors
<ul style="list-style-type: none"> • Atypical right bundle branch block • Ventricular hypertrophy • Early repolarization (especially in athletes) • Acute pericarditis/myocarditis • Acute myocardial ischemia or infarction (especially of the right ventricle) • Pulmonary thromboembolism • Prinzmetal angina • Dissecting aortic aneurism • Central and autonomic nervous systems abnormalities • Duchenne's muscular dystrophy • Friedreich's ataxia • Spinobulbar Muscular Atrophy • Myotonic Dystrophy • Arrhythmogenic right ventricular dysplasia • Mechanical compression of the right ventricular outflow tract (e.g., <i>pectus excavatum</i>, mediastinal tumor, hemopericardium, • Hypothermia • Post-defibrillation ECG 	<ul style="list-style-type: none"> • Electrolyte abnormalities: <ul style="list-style-type: none"> – Hyperkalemia – Hypokalemia – Hypercalcemia – Hyponatremia • Temperature: hyperthermia (fever), hypothermia • Hypertestosteronemia • Treatment with: <ul style="list-style-type: none"> – Antiarrhythmic drugs: sodium channel blockers (class IC, class IA), calcium antagonists, beta-blockers – Antianginal drugs: calcium antagonists, nitrates, potassium channel openers – Psychotropic drugs: tricyclic/tetracyclic antidepressants, phenothiazines, <u>selective serotonin reuptake inhibitor</u>, lithium, benzodiazepines – Anesthetics/analgesics: propofol, bupivacaine, procaine – Others: histamine H1 antagonist, alcohol intoxication, cocaine, cannabis, ergonovine

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Table 5

Gene Defects Associated with the Early Repolarization and Brugada Syndromes

Genetic Defects Associated with ERS				
	Locus	Gene/Protein	Ion Channel	% of Probands
ERS1	12p11.23	<i>KCNJ8, Kir6.1</i>	↑ I _{K-ATP}	Rare
ERS2	12p13.3	<i>CACNA1C, Ca_v1.2</i>	↓ I _{Ca}	4.1%
ERS3	10p12.33	<i>CACNB2b, Ca_vβ2b</i>	↓ I _{Ca}	8.3%
ERS4	7q21.11	<i>CACNA2D1, Ca_vα2δ1</i>	↓ I _{Ca}	4.1%
ERS5	12p12.1	<i>ABCC9, SUR2A</i>	↑ I _{K-ATP}	Rare
ERS6	3p21	<i>SCN5A, Na_v1.5</i>	↓ I _{Na}	Rare
ERS7	3p22.2	<i>SCN10A, Na_v1.8</i>	↓ I _{Na}	Rare
Genetic Defects Associated with BrS				
	Locus	Gene/Protein	Ion Channel	% of Probands
BrS1	3p21	<i>SCN5A, Na_v1.5</i>	↓ I _{Na}	11–28%
BrS2	3p24	<i>GPD1L</i>	↓ I _{Na}	Rare
BrS3	12p13.3	<i>CACNA1C, Ca_v1.2</i>	↓ I _{Ca}	6.6%
BrS4	10p12.33	<i>CACNB2b, Ca_vβ2b</i>	↓ I _{Ca}	4.8%
BrS5	19q13.1	<i>SCN1B, Na_vβ1</i>	↓ I _{Na}	1.1%
BrS6	11q13-14	<i>KCNE3, MiRP2</i>	↑ I _{to}	Rare
BrS7	11q23.3	<i>SCN3B, Na_vβ3</i>	↓ I _{Na}	Rare
BrS8	12p11.23	<i>KCNJ8, Kir6.1</i>	↑ I _{K-ATP}	2%
BrS9	7q21.11	<i>CACNA2D1, Ca_vα2δ1</i>	↓ I _{Ca}	1.8%
BrS10	1p13.2	<i>KCND3, K_v4.3</i>	↑ I _{to}	Rare
BrS11	17p13.1	<i>RANGRF, MOG1</i>	↓ I _{Na}	Rare
BrS12	3p21.2-p14.3	<i>SLMAP</i>	↓ I _{Na}	Rare
BrS13	12p12.1	<i>ABCC9, SUR2A</i>	↑ I _{K-ATP}	Rare
BrS14	11q23	<i>SCN2B, Na_vβ2</i>	↓ I _{Na}	Rare
BrS15	12p11	<i>PKP2, Plakophilin-2</i>	↓ I _{Na}	Rare
BrS16	3q28	<i>FGF12, FHAF1</i>	↓ I _{Na}	Rare
BrS17	3p22.2	<i>SCN10A, Na_v1.8</i>	↓ I _{Na}	5–16.7%
BrS18	6q	<i>HEY2 (transcriptional factor)</i>	↑ I _{Na}	Rare
BrS19	1p36.3	<i>KCNAB2, Kvβ2</i>	↑ I _{to}	Rare

Listed in Chronological order of discovery

Modified from ²², with permission.