

# J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge

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Charles Antzelevitch, PhD, FHRS\*, Gan-Xin Yan, MD, PhD†, Michael J. Ackerman, MD, PhD‡, Martin Borggrefe, MD§, Domenico Corrado, MD, PhD¶, Jihong Guo, MD#, Ihor Gussak, MD, PhD\*\*, Can Hasdemir, MD††, Minoru Horie, MD##, Heikki Huikuri, MD§§, Changsheng Ma, MD¶¶, Hiroshi Morita, MD, PhD###, Gi-Byoung Nam, MD, PhD\*\*\*, Frederic Sacher, MD, PhD†††, Wataru Shimizu, MD, PhD###, Sami Viskin, MD§§§, and Arthur A.M. Wilde, MDPH, FHRS¶¶¶

From the \*Lankenau Institute for Medical Research, Wynnewood, Pennsylvania; †Lankenau Medical Center, Wynnewood, Pennsylvania; ‡Departments of Cardiovascular Diseases, Pediatrics, and Molecular Pharmacology & Experimental Therapeutics, Divisions of Heart Rhythm Services and Pediatric Cardiology, Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, Minnesota; §1st Department of Medicine—Cardiology, University Medical Centre Mannheim, and DZHK (German Centre for Cardiovascular Research), partner site Heidelberg/Mannheim, Mannheim, Germany; ¶Department of Cardiac, Thoracic and Vascular Sciences, University of Padua Medical School, Padua, Italy; #Division of Cardiology, Peking University of People's Hospital, Beijing, China; \*\*Rutgers University, New Brunswick, New Jersey; ††Department of Cardiology, Ege University School of Medicine, Izmir, Turkey; ##Shiga University of Medical Sciences, Ohtsu, Shiga, Japan; §§Research Unit of Internal Medicine, Medical Research Center, Oulu University Hospital, and University of Oulu, Oulu, Finland; ¶¶Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, National Clinical Research Center for Cardiovascular Diseases, Beijing, China; ###Department of Cardiovascular Therapeutics, Okayama University Graduate School of Medicine, Okayama, Japan; \*\*\*Heart Institute, Asan Medical Center, and Department of Internal Medicine, University of Ulsan College of Medicine Seoul, Seoul, Korea; †††Bordeaux University Hospital, LIRYC Institute/INSERM 1045, Bordeaux, France; §§§Department of Cardiovascular Medicine, Nippon Medical School, Tokyo, Japan; §§§Tel-Aviv Sourasky Medical Center and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; and ¶¶¶Heart Center, Department of Clinical and Experimental Cardiology, Academic Medical Center, University of Amsterdam, the Netherlands and Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders, Jeddah, Kingdom of Saudi Arabia

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Sudden cardiac death • J wave • Brugada syndrome • Early repolarization syndrome • Cardiac arrhythmia • Ventricular fibrillation • Inherited cardiac arrhythmia syndrome

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## Preamble

The J-wave syndromes (JWSs), consisting of the Brugada syndrome (BrS) and early repolarization syndrome (ERS), have captured the interest of the cardiology community over the past 2 decades following the identification of BrS as a new clinical entity by Pedro and Josep Brugada in 1992.<sup>1</sup> The clinical impact of ERS was not fully appreciated until 2008.<sup>2–4</sup> Consensus conferences dedicated to BrS were held in 2000 and 2004,<sup>5,6</sup> but a consensus conference specifically focused on ERS has not previously been convened other than that dealing with terminology, and guidelines for both syndromes were last considered in 2013.<sup>7</sup> A great deal of new information has emerged since. The present forum was organized to evaluate new information and highlight emerging concepts with respect to differential diagnosis, prognosis, cellular and ionic mechanisms, and approaches to therapy of the JWSs. Leading experts, including members of the Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA), and the Asian-Pacific Heart Rhythm Society (APHRS), met in Shanghai, China, in April 2015. The Task Force was charged with a review of emerging concepts and assessment of new evidence for or against particular diagnostic procedures and treatments. Every effort was made to avoid any actual, potential, or perceived conflict of interest that might arise as a result of outside relationships or personal interest. This consensus report is intended to assist health care providers in clinical decision-making. The ultimate judgment regarding care of a particular patient, however, must be made by the health care provider based on all of the facts and circumstances presented by the patient.

Members of this Task Force were selected to represent professionals involved with the medical care of patients with the JWSs, as well as those involved in research into the mechanisms underlying these syndromes. These selected experts in the field undertook a comprehensive review of the literature. Critical evaluation of methods of diagnosis, risk stratification, approaches to therapy, and mechanistic insights was performed, including assessment of the risk- to-benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded. Recommendations with class designations are taken from HRS, EHRA, APHRS, and/or European Society of Cardiology (ESC) consensus statements or guidelines.<sup>8,9</sup> Recommendations without class designations are derived from unanimous consensus of the authors. The consensus recommendations in this document use the commonly used Class I, IIa, IIb, and III classifications and the corresponding language: “is recommended” for a Class I consensus recommendation; “can be useful” or “is reasonable” for a Class IIa consensus recommendation; “may be considered” for a Class IIb consensus recommendation; and “is not recommended” for a Class III consensus recommendation.

## Introduction

The appearance of prominent J waves in the electrocardiogram (ECG) have long been reported in cases of hypothermia<sup>10–12</sup> and hypercalcemia.<sup>13,14</sup> More recently, accentuation of the J wave has been associated with life-threatening ventricular arrhythmias.<sup>15</sup> Under these circumstances, the accentuated J wave typically may be so broad and tall as to appear as an ST-segment elevation, as in cases of

BrS. In humans, the normal J wave often appears as a J-point elevation, with part of the J wave buried inside the QRS. An early repolarization pattern (ERP) in the ECG, consisting of a distinct J-wave or J-point elevation, or a notch or slur of the terminal part of the QRS with and without an ST-segment elevation, has traditionally been viewed as benign.<sup>16,17</sup> The benign nature of an ERP was challenged in 2000<sup>18</sup> based on experimental data showing that this ECG manifestation predisposes to the development of polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF) in coronary-perfused wedge preparations.<sup>15,18–20</sup> Validation of this hypothesis was provided 8 years later by Haissaguerre et al.,<sup>2</sup> Nam et al.,<sup>3</sup> and Rosso et al.<sup>4</sup> These seminal studies together with numerous additional case-control and population-based studies have provided clinical evidence for an increased risk for development of life-threatening arrhythmic events and sudden cardiac death (SCD) among patients presenting with an ERP, particularly in the inferior and inferolateral leads. The lack of agreement regarding the terminology relative to early repolarization (ER) has led to a great deal of confusion and inconsistency in reporting.<sup>21–23</sup> A recent expert consensus report that focused on the terminology of ER recommends that the 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 0.1 mV in  $\geq 2$  contiguous inferior and/or lateral leads of a standard 12-lead ECG for ER to be present.<sup>24</sup> It was further recommended that the start of the end QRS notch or J wave be designated as  $J_o$  and the termination as  $J_t$ .

ERS and BrS are thought to represent 2 manifestations of the JWSs. Both syndromes are associated with vulnerability to development of polymorphic VT and VF leading to SCD<sup>1–3,15</sup> in young adults with no apparent structural heart disease and occasionally to sudden infant death syndrome.<sup>25–27</sup> The region generally most affected in BrS is the anterior right ventricular outflow tract (RVOT); in ERS, it is the inferior region of the left ventricle (LV).<sup>2,4,28–32</sup> As a consequence, BrS is characterized by accentuated J waves appearing as a coved-type ST-segment elevation in the right precordial leads  $V_1$ – $V_3$ , whereas ERS is characterized by J waves,  $J_o$  elevation, notch or slur of the terminal part of the QRS, and ST segment or  $J_t$  elevation in the lateral (type 1), inferolateral (type 2), or inferolateral + anterior or right ventricular (RV) leads (type III).<sup>15</sup> An ERP is often encountered in ostensibly healthy individuals, particularly in young males, black individuals, and athletes. ERP is also observed in acquired conditions, including hypothermia and ischemia.<sup>15,33,34</sup> When associated with VT/VF in the absence of organic heart disease, ERP is referred to as ERS.

The prevalence of BrS with a type 1 ECG in adults is higher in Asian countries, such as Japan (0.15%–0.27%)<sup>35,36</sup> and the Philippines (0.18%),<sup>37</sup> and among Japanese-Americans in North America (0.15%)<sup>38</sup> than in western countries, including Europe (0%–0.017%)<sup>39–41</sup> and North America (0.005%–0.1%).<sup>42,43</sup> In contrast, the prevalence of an ERP in the inferior and/or lateral leads with a J-point elevation  $\geq 0.1$  mV ranges between 1% and 24% and for J-point elevation  $\geq 0.2$  mV ranges between 0.6% to 6.4%.<sup>44–46</sup> No significant regional differences in the prevalence of an ERP have been reported.<sup>47</sup> However, ERP is significantly more common in blacks than in Caucasians. Little in the way of regional differences in the manifestation of ERS has been reported. ERP appears to be more common in Aboriginal Australians than in Caucasian Australians.<sup>48</sup>

## Updates on the diagnosis of BrS

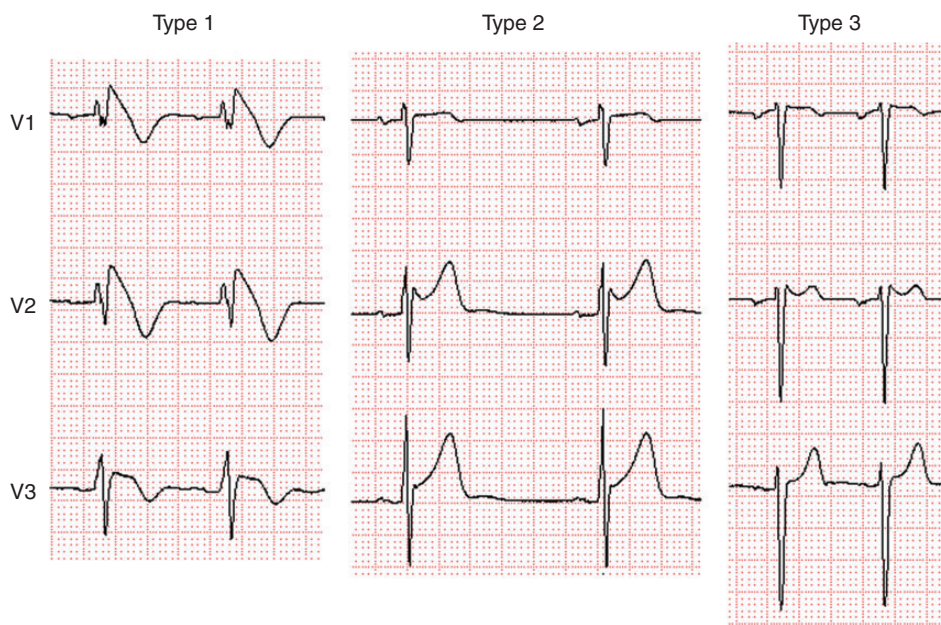
According to the 2013 consensus statement on inherited cardiac arrhythmias<sup>8</sup> and the 2015 guidelines for the management of patients with ventricular arrhythmias and prevention of SCD<sup>9</sup>: “BrS is diagnosed in patients with ST-segment elevation with type 1 morphology  $\geq 2$  mm in  $\geq 1$  lead among the right precordial leads V1, V2, positioned in the 2nd, 3rd or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs. BrS is diagnosed in patients with type 2 or type 3 ST-segment elevation in  $\geq 1$  lead among the right precordial leads V1, V2 positioned in the 2nd, 3rd or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type I ECG morphology.”

The present Task Force is concerned that this could result in overdiagnosis of BrS, particularly in patients displaying a type 1 ECG only after a drug challenge. Data suggest the latter population is at very low risk and that the presumed false-positive rate of pharmacologic challenge is not trivial.<sup>49</sup> Although a rigorous process was undertaken to establish the preceding guidelines, there remains no gold standard for establishing a diagnosis, particularly in patients with weak evidence of disease. Accordingly, we recommend adoption of the following diagnostic criteria and score system for BrS. Consistent with the recommendation of the 2013 and 2015 guidelines, only a type 1 (“coved-type”) ST-segment elevation is considered diagnostic of BrS (Figure 1), and BrS is characterized by ST-segment elevation  $\geq 2$  mm (0.2 mV) in  $\geq 1$  right precordial leads (V<sub>1</sub>–V<sub>3</sub>) positioned in the 4th, 3rd, or 2nd intercostal space. However, as a departure from the guidelines, this consensus report recommends that when a type 1 ST-segment elevation is unmasked using a sodium channel blocker (Table 1), diagnosis of BrS should require that the

patient also present with 1 of the following: documented VF or polymorphic VT, syncope of probable arrhythmic cause, a family history of SCD at  $\leq 45$  years old with negative autopsy, coved-type ECGs in family members, or nocturnal agonal respiration. Inducibility of VT/VF with 1 or 2 premature beats supports the diagnosis of BrS under these circumstances.<sup>50</sup>

A type 2 (“saddle-back type”) or type 3 ST-segment elevation cannot substitute for a type 1, unless converted to type 1 with fever or sodium drug challenge. A drug challenge–induced type 1 can be used to diagnose BrS only if accompanied by 1 of the criteria specified above. Type 2 is characterized by ST-segment elevation  $\geq 0.5$  mm (generally  $\geq 2$  mm in V<sub>2</sub>) in  $\geq 1$  right precordial lead (V<sub>1</sub>–V<sub>3</sub>), followed by a convex ST. The ST segment is followed by a positive T wave in V<sub>2</sub> and variable morphology V<sub>1</sub>. Type 3 is characterized by either a saddleback or coved appearance with an ST-segment elevation  $\leq 1$  mm. Placement of the right precordial leads in more cranial positions (in the 3rd or 2nd intercostal space) in a 12-lead resting ECG or 12-lead Holter ECG increases the sensitivity of ECG.<sup>51–53</sup> It is recommended that ECG recordings be obtained in the standard and superior positions for the V<sub>1</sub> and V<sub>2</sub> leads. Veltman *et al.*<sup>54</sup> showed that RVOT localization using magnetic resonance imaging (MRI) correlates with type 1 ST-segment elevation in BrS and that lead positioning according to RVOT location improves the diagnosis of BrS. Interestingly, in most cases a type I pattern was found in the 3rd intercostal space in the sternal and left parasternal positions.<sup>54</sup> In reviewing ECGs of a large cohort of BrS patients, Richter *et al.*<sup>55</sup> concluded that lead V<sub>3</sub> does not yield diagnostic information in BrS.

A proposed diagnostic score system for BrS, referred to as the Proposed Shanghai BrS Score, is presented in Table 2. These recommendations are based on the available literature and the clinical experience of the Task Force members.<sup>8,56–60</sup> Weighting of variables



**Figure 1** Three types of ST-segment elevation associated with Brugada syndrome. Only type 1 is diagnostic of Brugada syndrome.

**Table 1** Drugs used to unmask the Brugada ECG

Drug	Dose	Administration
Ajmaline	1 mg/kg over 10 minutes	Intravenous
Flecainide	2 mg/kg over 10 minutes 200–300 mg	Intravenous Oral (41 hour)
Procainamide	10 mg/kg over 10 minutes	Intravenous
Pilsicainide	1 mg/kg over 10 minutes	Intravenous

**Table 2** Proposed 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- or 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
<b>Score (requires at least 1 ECG finding)</b>	
≥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.

is based on expert opinion informed by cohort studies that typically do not include all variables presented. Thus, rigorous, objectively weighted coefficients were not derived from large-scale risk factor and outcome-informed datasets. Nonetheless, the authors believed that some inferential weighting would be of benefit when applied to patients. As with all such recommendations, they will need to undergo initial and ongoing validation in future studies.

## Pharmacologic tests and other diagnostic tools

When there is clinical suspicion of BrS in the absence of spontaneous type 1 ST-segment elevation, a pharmacologic challenge using a sodium channel blocker is recommended. A list of agents used for this purpose is presented in *Table 1* (also see [www.brugadadrugs.org](http://www.brugadadrugs.org)). The test is considered positive only if a type 1 ECG pattern is obtained, and it should be discontinued in case of frequent ventricular extrasystoles or other arrhythmias, or widening of the QRS 4130% over the baseline value.<sup>6</sup> As an alternative, the “full stomach test” has been proposed for diagnosing BrS.<sup>61</sup> In this case, ECGs are performed before and after a large meal. The use of “high electrodes” increases the sensitivity for recognizing spontaneous type I ST-segment elevation at night or after heavy meals.<sup>62</sup> A type 1 ST-segment elevation recorded using a Holter is a spontaneous type 1, and it is reasonable to assume that a spontaneous type 1 recorded by Holter at night or after a large meal has more value—both diagnostic and prognostic—than a drug-induced type 1.

Drug challenge is not indicated in asymptomatic patients displaying the type 1 ECG under baseline conditions because of the lack of the additional diagnostic value. These provocative drug tests are also not recommended in cases in which fever has been documented to induce a type I ECG, other than for research purposes. Much debate has centered around the definition of a false-positive sodium channel block challenge.<sup>63</sup> The consensus is that a false-positive is difficult to define because of the lack of a gold standard. The development of a type 1 ST-segment elevation in response to sodium block challenge should be considered as probabilistic, rather than binary, in nature. As will be discussed later, a similar approach is recommended in evaluating the ability of genetic variants to promote the BrS phenotype.

Asymptomatic patients with a family history of BrS or SCD should be informed of the availability of a sodium channel blocker challenge test to provide a more definitive diagnosis of BrS. However, patients should be advised that no therapy may be recommended regardless of the outcome because the long-term risk of patients with BrS diagnosed by this test is significantly lower than the risk of patients with spontaneous type 1. Patients also should be informed about the risk of the test and about the emotional consequences of having a positive test not followed by definitive therapy. The decision as to whether to undergo the drug challenge ultimately should be left up to the well-informed patient.

Performing an ajmaline test in children is problematic for 2 reasons. First, the test is apparently less sensitive in children than in adults. In fact, in 1 study, a repeat ajmaline challenge performed after puberty unmasked BrS in 23% of relatives with a previously negative drug test performed during childhood.<sup>64</sup> Second, the test is associated with greater risk than in adults. In 1 series, 10% of children undergoing the ajmaline test, including 3% of the asymptomatic subgroup, developed sustained VT.<sup>64,65</sup> Caution also should be exercised when performing a sodium blocker challenge in adults with a known pathogenic sodium channel mutation or in patients with prolonged PR intervals, pointing to a carrier of such a mutation.<sup>66</sup>



## Differential diagnosis

Other causes of ST-segment elevation should be excluded before establishing the diagnosis of BrS (Table 3). Artifacts secondary to low-pass filtering should be ruled out.<sup>67</sup>

Circumstances that produce a type 1 Brugada-like ECG include right bundle branch block (RBBB), pectus excavatum, arrhythmogenic right ventricular cardiomyopathy (ARVC), and occlusion of the left anterior descending artery or the conus branch of the right coronary artery, which supplies the RVOT (Table 3A).

Discrimination between BrS and ARVC is particularly challenging. Although debate continues as to the extent to which structural abnormalities are present in BrS, most investigators consider BrS to be a channelopathy. Concealed structural abnormalities, such as histologic myocardial fibrosis of the RVOT, which may not become evident using conventional imaging techniques, have been proposed to account for or contribute to delayed conduction and ventricular arrhythmias in BrS. MRI and electron beam computed tomographic studies of BrS patients consistently show subtle abnormalities, including wall motion abnormalities and reduced contractile function of the RV and, to a lesser extent, of the LV, and dilation of the RVOT.<sup>68–71</sup> In the only study that discriminated between patients

with and those without *SCN5A* mutations, no difference was observed in RVOT dimensions or RV ejection fraction between these patients. Slightly greater depressions of LV dimensions and ejection fraction were observed in patients with *SCN5A* mutations. Significant differences were observed in RV and LV dimensions and ejection fraction compared to healthy controls.<sup>72</sup> Cardiac dilation and reduced contractility in all of these studies were attributed to structural changes (fibrosis, fatty degeneration). However, as noted by van Hoorn *et al*,<sup>72</sup> virtually no signs of fibrosis or fatty degeneration could be detected, perhaps because the spatial resolution of the imaging used was too low to detect such subtle changes.

Antzelevitch and colleagues have long suggested an alternative explanation.<sup>31,73,74</sup> Loss of the action potential (AP), which has been shown in experimental models to create the arrhythmogenic substrate in BrS, leads to contractile changes that could explain the wall motion abnormalities observed. The all-or-none repolarization at the end of phase 1 of the epicardial AP responsible for loss of the dome causes the calcium channel to inactivate very soon after it activates. As a consequence, calcium channel current is dramatically reduced, the cell becomes depleted of calcium, and contractile function ceases in those cells. This is expected to lead to wall motion abnormalities, particularly in the RVOT, dilation of the RVOT region, and reduced ejection fraction observed in patients with BrS. It has also been proposed that the loss of the AP dome, because it creates a hibernation-like state, may, over long periods of time, lead to mild structural changes, including intracellular lipid accumulation, vacuolization, and connexin 43 redistribution. These structural changes may, in turn, contribute to the arrhythmogenic substrate of BrS, although they are very different from those encountered in arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D).<sup>31,75</sup> This hypothesis would predict that some of the changes observed by recent studies may be the result of, rather than the cause of, the BrS phenotype.<sup>76</sup>

In a recent study, Nademanee *et al*.<sup>76</sup> reported additional evidence pointing to pathologic changes in the RVOT of patients with BrS that have proved undetectable by echocardiography or MRI.

In contrast, imaging techniques in ARVC clearly display morphologic and functional changes (e.g., dilation, bulging/aneurysms, wall motion abnormalities). ARVC is an inherited cardiac disease resulting from genetically defective desmosomal (DS) proteins,<sup>77,78</sup> characterized by fibrofatty myocardial replacement predisposing to scar-related ventricular arrhythmias that may lead to SCD, mostly in young people and athletes.<sup>79</sup> Life-threatening ventricular arrhythmias may occur early, during the “concealed phase” of the disease, before overt structural changes.<sup>77,78,80</sup> Recent experimental studies demonstrated that loss of expression of DS proteins may induce electrical ventricular instability by causing sodium channel dysfunction and current reduction as a consequence of the cross-talk between these molecules at the intercalated discs, which predisposes to sodium current-dependent lethal arrhythmias, similar to those leading to SCD in patients with J-wave syndromes.<sup>80–82</sup> Further evidence of the overlap between phenotypic manifestation of ARVC and BrS comes from (1) clinicopathologic studies showing that a subset of ARVC patients may share ECG changes and patterns of ventricular arrhythmias with BrS;<sup>83</sup> and (2) genotype–phenotype correlation studies demonstrating that PKP2 mutation may cause a

**Table 3 Differential diagnosis and modulating factors in Brugada syndrome**

A. Differential diagnosis	B. Modulating factors
<ul style="list-style-type: none"> <li>• Atypical right bundle branch block</li> <li>• Ventricular hypertrophy</li> <li>• Early repolarization (especially in athletes)</li> <li>• Acute pericarditis/myocarditis</li> <li>• Acute myocardial ischemia or infarction (especially of the right ventricle)</li> <li>• Pulmonary thromboembolism</li> <li>• Prinzmetal angina</li> <li>• Dissecting aortic aneurysm</li> <li>• Central and autonomic nervous system abnormalities</li> <li>• Duchenne muscular dystrophy</li> <li>• Friedreich ataxia</li> <li>• Spinobulbar muscular atrophy</li> <li>• Myotonic dystrophy</li> <li>• Arrhythmogenic right ventricular dysplasia</li> <li>• Mechanical compression of the right ventricular outflow tract (e.g., pectus excavatum, mediastinal tumor, hemopericardium,</li> <li>• Hypothermia</li> <li>• Postdefibrillation ECG</li> </ul>	<ul style="list-style-type: none"> <li>• Electrolyte abnormalities:               <ul style="list-style-type: none"> <li>○ Hyperkalemia</li> <li>○ Hypokalemia</li> <li>○ Hypercalcemia</li> <li>○ Hyponatremia</li> </ul> </li> <li>• Temperature: hyperthermia (fever), hypothermia</li> <li>• Hypertestosteronemia</li> <li>• Treatment with:               <ul style="list-style-type: none"> <li>○ Antiarrhythmic drugs: sodium channel blockers (Class IC, Class IA), calcium antagonists, beta-blockers</li> <li>○ Antianginal drugs: calcium antagonists, nitrates, potassium channel openers</li> <li>○ Psychotropic drugs: tricyclic/tetracyclic antidepressants, phenothiazines, selective serotonin reuptake inhibitor, lithium, benzodiazepines</li> <li>○ Anesthetics/analgesics: propofol, bupivacaine, procaine</li> <li>○ Others: histamine H<sub>1</sub> antagonist, alcohol intoxication, cocaine, cannabis, ergonovine</li> </ul> </li> </ul>

Brugada phenotype in the human heart by reducing sodium current.<sup>84</sup> These findings support the concept that specific DS gene mutations involved in the pathogenesis of ARVC can lead to a decreased depolarization reserve that manifests as J-wave/BrSs. Thus, ARVC and J wave syndromes are not completely different conditions but are the ends of a spectrum of structural myocardial abnormalities and sodium current deficiency that share a common origin as diseases of the connexome.<sup>84</sup> The ECG abnormalities in ARVC are not dynamic and display a constant T-wave inversion, epsilon waves, and, in the progressive stage, reduction of the R amplitude. End-stage ARVC is usually associated with monomorphic VT with left bundle branch morphology and is precipitated by catecholamines,<sup>85</sup> whereas BrS is associated with polymorphic VT predominantly during sleep or rest.<sup>86</sup> A positive ajmaline challenge has been reported in 16% of patients with ARVC.<sup>87,88</sup>

## Modulating factors

Sympathovagal balance, hormones, metabolic factors, and pharmacologic agents are thought to modulate not only ECG morphology but also explain the development of ventricular arrhythmias under certain conditions.<sup>89</sup> Any of these modulating factors, if present, should be promptly corrected (Table 3B).

## Acquired Brugada pattern and phenocopies

The Brugada ECG is often concealed and can be unmasked with a wide variety of drugs and conditions, including a febrile state, vagotonic agents and maneuvers,  $\alpha$ -adrenergic agonists,  $\beta$ -adrenergic blockers, Class IC antiarrhythmic drugs, tricyclic or tetracyclic antidepressants, hyperkalemia, hypokalemia, hypercalcemia, and alcohol and cocaine toxicity.<sup>90–100</sup> Preexcitation of RV can unmask the BrS phenotype in cases of RBBB.<sup>101</sup> An up-to-date list of agents known to unmask the Brugada ECG that should be avoided by patients with BrS can be found at [www.brugadadrugs.org](http://www.brugadadrugs.org).<sup>89</sup>

Environmental factors leading to the appearance of an ECG similar or identical to a type 1 BrS pattern in the absence of any apparent genetic dysfunction has been suggested to represent a Brugada ECG phenocopy.<sup>102</sup> Features of the Brugada phenocopies include (1) Brugada-like ECG pattern; (2) presence of an identifiable underlying condition; (3) disappearance of the ECG pattern after resolution of the condition; (4) absence of family history of sudden death in relatively young first-degree relatives ( $\leq 45$  years) or of type 1 BrS pattern; (5) absence of symptoms such as syncope, seizures, or nocturnal agonal respiration; and (6) a negative sodium channel blocker challenge test. Debate continues as to the appropriateness of this terminology given that it is very difficult to rule out a genetic predisposition, which is a prerequisite for designating the ECG manifestation as a phenocopy. Designation of these conditions as acquired forms of Brugada ECG pattern or BrS may be more appropriate and better aligned with the terminology used in the long QT syndrome.

## Update on the diagnosis of ERS

ERS is generally diagnosed in patients who display ER in the inferior and/or lateral leads presenting with aborted cardiac arrest, documented VF, or polymorphic VT. Consistent with the

recent consensus report on ERP,<sup>24</sup> ER is recognized if (1) there is an end QRS notch (J wave) or slur on the downslope of a prominent R wave with and without ST-segment elevation; (2) the peak of the notch or J wave ( $J_p$ )  $\geq 0.1$  mV in  $\geq 2$  contiguous leads of the 12-lead ECG, excluding leads  $V_1$ – $V_3$ ; and (3) QRS duration (measured in leads in which a notch or slur is absent)  $\leq 120$  ms. Table 4 lists the exclusion criteria in the differential diagnosis of ERS.

A proposed diagnostic score system for ERS, referred to as the Proposed Shanghai ERS Score, is presented in Table 5. The scoring system is based on evidence available in the literature to date. As in BrS, weighting of variables is based on expert opinion informed by cohort studies that do not include all variables presented. Thus, rigorous, objectively weighted coefficients were not derived from large-scale risk factor- and outcome-informed datasets. Nonetheless, the authors believed that some inferential weighting would be of benefit when applied to patients. As with all such recommendations, they will need to undergo initial and ongoing validation in future studies.

## Similarities and difference between BrS and ERS

BrS and ERS display several clinical similarities, suggesting similar pathophysiology (Table 6).<sup>19,21,103–105</sup> Males predominate in both syndromes, with BrS presenting in 71%–80% among Caucasians and 94%–96% among Japanese.<sup>106,107</sup> In the setting of ERP, VF occurred mainly in males (72%) when studied in an international cohort<sup>2</sup> but in a much higher percentage in a report by Japanese

**Table 4** Differential diagnosis of early repolarization pattern

**Other causes of early repolarization pattern include the following:**

- Juvenile ST pattern
- Pericardial disease (pericarditis, pericardial cyst, pericardial tumor)
- Hypothermia
- Hyperthermia
- Myocardial tumor (lipoma)
- Hypertensive heart disease
- Athlete's heart
- Myocardial ischemia
- STEMI (i.e., anteroapical myocardial infarction)
- Fragmented QRS (terminal notching)
- Hypocalcemia
- Hyperpotassemia
- Thymoma
- Aortic dissection
- Arrhythmogenic right ventricular cardiomyopathy
- Takotsubo cardiomyopathy
- Neurologic causes (intracerebral bleeding, acute brain injury)
- Myocarditis
- Chagas disease
- Cocaine use

STEMI = ST segment elevation myocardial infarction.

**Table 5 Proposed 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 $\geq 0.2$ mV in $\geq 2$ inferior and/or lateral ECG leads with horizontal/descending ST segment	2
B. Dynamic changes in J-point elevation ( $\geq 0.1$ mV) in $\geq 2$ inferior and/or lateral ECG leads	1.5
C. $\geq 0.1$ 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. $\geq 2$ first-degree relatives with a II.A. ECG pattern	2
C. First-degree relative with a II.A. 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
<b>Score (requires at least 1 ECG finding)</b>	
$\geq 5$ 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.

investigators.<sup>108</sup> BrS and ERS patients may be totally asymptomatic until they present with cardiac arrest. In both syndromes, the highest incidence of VF or SCD occurs in the third decade of life, perhaps related to testosterone levels in males.<sup>109</sup> In both syndromes, the appearance of accentuated J waves and ST-segment elevation is generally associated with bradycardia or pauses.<sup>110,111</sup> This can explain why VF in both syndromes often occurs during sleep or during a low level of physical activities.<sup>108,112</sup> The QT interval is relatively short in patients with ERS,<sup>2,113</sup> and BrS who carry mutations in calcium channel genes.<sup>114</sup>

As will be discussed in more detail later, ERS and BrS also share similarities with respect to the response to pharmacologic therapy. In both, electrical storms and associated J-wave manifestations can be suppressed using  $\beta$ -adrenergic agonists.<sup>115–118</sup> Chronic oral pharmacologic therapy using quinidine,<sup>119,120</sup> bepridil,<sup>117</sup> denopamine,<sup>115,121</sup> and cilostazol<sup>115,117,121–125</sup> is reported to suppress the development of VT/VF in both ERS and BrS secondary to inhibition of  $I_{to}$ , augmentation of  $I_{Ca}$ , or both.<sup>3,122,126</sup>

Differences between the 2 syndromes include (1) the region of the heart most affected (RVOT vs inferior LV); (2) the presence of (discrete) structural abnormalities in BrS but not in ERS; (3) the incidence of late potentials in signal-averaged ECGs (BrS 60% 4 ERS 7%)<sup>108</sup>; and (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 higher prevalence of atrial fibrillation in BrS vs ERS.<sup>127</sup> Early studies

suggested a different pathophysiologic basis for ERS and BrS based on the observation that sodium channel blockers unmask or accentuate J-wave manifestation in BrS but reduces the amplitude in ERS.<sup>108</sup> However, the recent study by Nakagawa *et al.*<sup>357</sup> showed that J waves recorded using unipolar LV epicardial leads introduced into the left lateral coronary vein in ERS patients are indeed augmented, even though J waves recorded in the lateral precordial leads are diminished, due principally to engulfment of the surface J wave by the widened QRS.<sup>29,108</sup> The case report of Nakagawa *et al.* has recently been supplemented with additional cases in which this technique was used; 2 of these 3 cases showed pilsicainide-induced accentuation of the J waves in electrograms recorded from the epicardial surface of the LV (H. Morita, unpublished observations). Also in support of the thesis that these ECG patterns and syndromes are closely related are reports of cases in which ERS transitions into ERS plus BrS.<sup>105,128</sup>

The principal difference between BrS and ERS is related to the region of the ventricle most affected. Epicardial mapping studies in BrS patients report accentuated J waves and fragmented and/or late potentials in the epicardial region of the RVOT,<sup>129–131</sup> whereas in ERS only accentuated J waves, particularly in the inferior wall of LV, are observed.<sup>29</sup> Fractionated electrogram activity and late potentials have been observed in experimental models of ERS<sup>30</sup> but have not yet been reported clinically. Noninvasive mapping electroanatomic studies have reported very steep localized repolarization

**Table 6** Similarities and differences between Brugada and early repolarization syndromes and possible underlying mechanisms

	BrS	ERS	Possible Mechanism(s)
<b>Similarities between BrS and ERS</b>			
Male predominance	Yes (>75%)	Yes (>80%)	Testosterone modulation of ion currents underlying the epicardial AP notch
Average age of first event	30–50	30–50	
Associated with mutations or rare variants in <i>KCNJ8</i> , <i>CACNA1C</i> , <i>CACNB2</i> , <i>CACNA2D</i> , <i>SCN5A</i> , <i>ABCC9</i> , <i>SCN10A</i>	Yes	Yes	Gain of function in outward currents ( $I_{K-ATP}$ ) or loss of function in inward currents ( $I_{Ca}$ or $I_{Na}$ )
Relatively short QT intervals in subjects with Ca channel mutations	Yes	Yes	Loss of function of $I_{Ca}$
Dynamicity of ECG	High	High	Autonomic modulation of ion channel currents underlying early phases of the epicardial AP
VF often occurs during sleep or at a low level of physical activity	Yes	Yes	Higher level of vagal tone and higher levels of $I_{to}$ at the slower heart rates
VT/VF trigger	Short-coupled PVC	Short-coupled PVC	Phase 2 reentry
Ameliorative response to quinidine and bepridil	Yes	Yes	Inhibition of $I_{to}$ and possible vagolytic effect
Ameliorative response to isoproterenol, denopamine 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)
Effect of sodium channel blockers on unipolar epicardial electrogram	Augmented J waves	Augmented J wave	Outward shift of balance of current in the early phases of the epicardial AP
Fever	Augmented J waves	Augmented J waves (rare)	Accelerated inactivation of $I_{Na}$ and accelerated recovery of $I_{to}$ from inactivation.
Hypothermia	Augmented J waves mimicking BrS	Augmented J waves	Slowed activation of $I_{Ca}$ , leaving $I_{to}$ unopposed. Increased phase 2 reentry but reduced pVT due to prolongation of APD <sup>358</sup>
<b>Differences between BrS and ERS</b>			
Region most involved	RVOT	Inferior LV wall	Higher levels of $I_{to}$ and/or differences in conduction
Leads affected	V <sub>1</sub> –V <sub>3</sub>	II, II a, VF, V <sub>4</sub> , V <sub>5</sub> , V <sub>6</sub> ; I, aVL, Both: inferolateral	
Regional difference in prevalence			Europe: BrS = ERS Asia: BrS > ERS
Incidence of late potential in signal-averaged ECG	Higher	Lower	
Prevalence of atrial fibrillation	Higher	Lower	
Effect of sodium channel blockers on surface ECG	Increased J-wave manifestation	Reduced J-wave manifestation	Reduction of J wave in the setting of ER is thought to be due largely to prolongation of QRS. Accentuation of repolarization defects predominates in BrS, whereas accentuation of depolarization defects predominates in ERS.
Structural changes, including mild fibrosis and reduced expression of Cx43 in RVOT or fibrofatty infiltration in cases of arrhythmogenic right ventricular cardiomyopathy. Imaging studies have also revealed wall motion abnormalities and mild dilation in the region of the RVOT.	Higher in some forms of the syndrome	Unknown	Some investigators have hypothesized that some of these changes may be the result of, rather than the cause of the BrS substrate, which may create a hibernation-like state due to loss of contractility in the RVOT secondary to loss of the AP dome.

AP = action potential; APD = action potential duration; BrS = Brugada syndrome; ERS = early repolarization syndrome; RVOT = right ventricular outflow tract; PVC = premature ventricular contraction; pVT = polymorphic ventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia.

gradients across the inferior/lateral regions of LV of ERS patients, preceded by normal ventricular activation,<sup>132</sup> whereas in BrS both slow discontinuous conduction and steep dispersion of

repolarization are present in the RVOT.<sup>133</sup> Another presumed difference is the presence of structural abnormalities in BrS, which have not yet been described in ERS.<sup>76</sup>



Although J waves are accentuated or induced by both hypothermia and fever,<sup>33,34,134–139</sup> the development of arrhythmias in ERS is much more sensitive to hypothermia, and arrhythmogenesis in BrS appears to be promoted only by fever.<sup>33,34,138,139</sup> Hypothermia has been reported to increase the risk of VF in ERS,<sup>33,34,134,135,140</sup> and fever is well recognized as a major risk factor in BrS.<sup>138,139</sup> It is noteworthy that hypothermia can diminish the manifestation of a BrS ECG when already present.<sup>141,142</sup>

An ERP is associated with an increased risk for VF in patients with acute myocardial infarction<sup>143</sup> and hypothermia.<sup>33,144</sup> A concomitant ERP in the inferolateral leads has also been reported to be associated with an increased risk of arrhythmic events in patients with BrS. Kawata *et al.*<sup>145</sup> reported that the prevalence of ER in inferolateral leads was high (63%) in BrS patients with documented VF.

## Genetics

BrS has been associated with variants in 18 genes (Table 7). To date, more than 300 BrS-related variants in *SCN5A* have been described.<sup>21,146–148</sup> Figure 2 shows the overlap syndromes attributable to genetic defects in *SCN5A*. Loss-of-function mutations in *SCN5A* contribute to the development of both BrS and ERS, as well as to a variety of conduction diseases, Lenegre disease, and sick sinus syndrome. The available evidence suggests that the presence of a prominent  $I_{to}$  determines whether loss-of-function mutations resulting in a reduction in  $I_{Na}$  will manifest as BrS/ERS or as conduction disease.<sup>59,149–151</sup>

Variants in *CACNA1C* (Cav1.2), *CACNB2b* (Cav $\beta$ 2b), and *CACNA2D1* (Cav $\alpha$ 2 $\delta$ ) have been reported in up to 13% of probands.<sup>152–155</sup> Mutations in glycerol-3-phosphate dehydrogenase 1-like enzyme gene (*GPD1L*), *SCN1B* ( $\beta_1$  subunit of Na channel), *KCNE3* (MiRP2), *SCN3B* ( $\beta_3$  subunit of Na channel), *KCNJ8* (Kir6.1), *KCND3* (Kv4.3), *RANGRF* (MOG1), *SLMAP*, *ABCC9* (SUR2A), (Nav $\beta$ 2), *PKP2* (plakophilin-2), *FGF12* (FHAF1), *HEY2*, and *SEMA3A* (semaphorin) are relatively rare.<sup>156–176</sup> An association of BrS with *SCN10A*, a neuronal sodium channel, was recently reported.<sup>167,177,178</sup> A wide range of yields of variants was reported by the 2 studies that examined the prevalence of pathogenic *SCN10A* mutations and rare variants (5%–16.7%).<sup>177–179</sup> Mutations in 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 ( $I_{K-ATP}$ ).<sup>178</sup>

New susceptibility genes recently proposed and awaiting confirmation include the transient receptor potential melastatin protein-4 gene (*TRPM4*)<sup>180</sup> and the *KCND2* gene. The mutation uncovered in *KCND2* in a single patient was shown to cause a gain of function in  $I_{to}$  when heterologously expressed.<sup>181</sup>

Variants in *KCNH2*, *KCNE5*, and *SEMA3A*, although not causative, have been identified as capable of modulating the substrate for the development of BrS.<sup>182–185</sup> Loss-of-function mutations in *HCN4* causing a reduction in the pacemaker current  $I_f$  can unmask BrS by reducing heart rate.<sup>186</sup>

An ERP in the ECG has been shown to be familial.<sup>187–189</sup> ERP and ERS have been associated with variants in 7 genes. Consistent with the findings that  $I_{K-ATP}$  activation can generate an ERP in canine ventricular wedge preparations, variants in *KCNJ8* and *ABCC9*, responsible for the pore-forming and

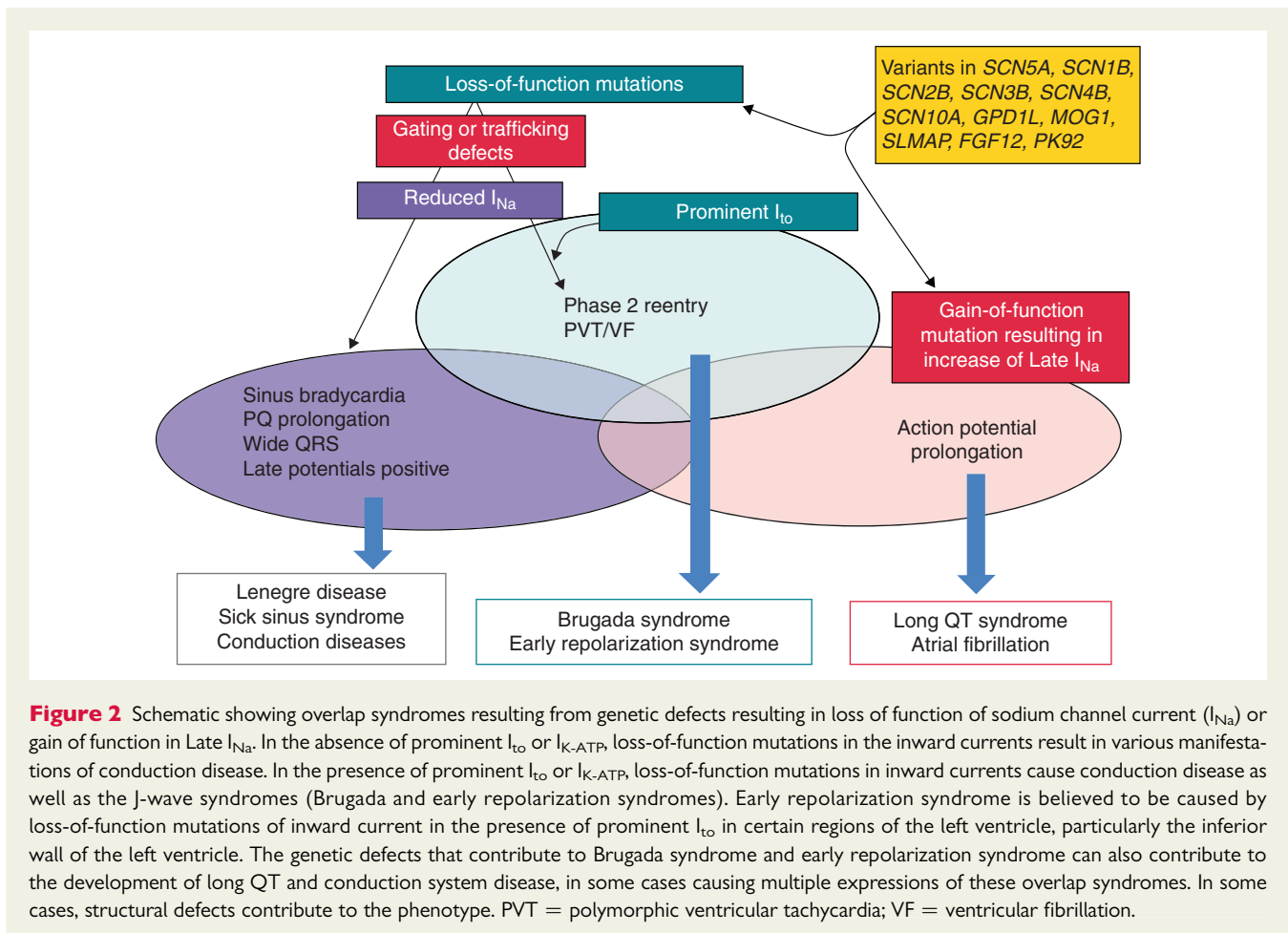
**Table 7** Gene defects associated with the early repolarization syndrome (ERS) and Brugada (BrS) syndrome

Genetic Defects Associated with ERS				
	Locus	Gene/protein	Ion channel	Percent of Probands
ERS1	12p11.23	<i>KCNJ8</i> , Kir6.1	$\uparrow I_{K-ATP}$	Rare
ERS2	12p13.3	<i>CACNA1C</i> , Ca <sub>v</sub> 1.2	$\downarrow I_{Ca}$	4.1%
ERS3	10p12.33	<i>CACNB2b</i> , Ca <sub>v</sub> $\beta$ 2b	$\downarrow I_{Ca}$	8.3%
ERS4	7q21.11	<i>CACNA2D1</i> , Ca <sub>v</sub> $\alpha$ 2 $\delta$ 1	$\downarrow I_{Ca}$	4.1%
ERS5	12p12.1	<i>ABCC9</i> , SUR2A	$\uparrow I_{K-ATP}$	Rare
ERS6	3p21	<i>SCN5A</i> , Na <sub>v</sub> 1.5	$\downarrow I_{Na}$	Rare
ERS7	3p22.2	<i>SCN10A</i> , Na <sub>v</sub> 1.8	$\downarrow I_{Na}$	Rare
Genetic Defects Associated with BrS				
BrS1	3p21	<i>SCN5A</i> , Na <sub>v</sub> 1.5	$\downarrow I_{Na}$	11%–28%
BrS2	3p24	<i>GPD1L</i>	$\downarrow I_{Na}$	Rare
BrS3	12p13.3	<i>CACNA1C</i> , Ca <sub>v</sub> 1.2	$\downarrow I_{Ca}$	6.6%
BrS4	10p12.33	<i>CACNB2b</i> , Ca <sub>v</sub> $\beta$ 2b	$\downarrow I_{Ca}$	4.8%
BrS5	19q13.1	<i>SCN1B</i> , Na <sub>v</sub> $\beta$ 1	$\downarrow I_{Na}$	1.1%
BrS6	11q13-14	<i>KCNE3</i> , MiRP2	$\uparrow I_{to}$	Rare
BrS7	11q23.3	<i>SCN3B</i> , Na <sub>v</sub> $\beta$ 3	$\downarrow I_{Na}$	Rare
BrS8	12p11.23	<i>KCNJ8</i> , Kir6.1	$\uparrow I_{K-ATP}$	2%
BrS9	7q21.11	<i>CACNA2D1</i> , Ca <sub>v</sub> $\alpha$ 2 $\delta$ 1	$\downarrow I_{Ca}$	1.8%
BrS10	1p13.2	<i>KCND3</i> , K <sub>v</sub> 4.3	$\uparrow I_{to}$	Rare
BrS11	17p13.1	<i>RANGRF</i> , MOG1	$\downarrow I_{Na}$	Rare
BrS12	3p21.2-p14.3	<i>SLMAP</i>	$\downarrow I_{Na}$	Rare
BrS13	12p12.1	<i>ABCC9</i> , SUR2A	$\uparrow I_{K-ATP}$	Rare
BrS14	11q23	<i>SCN2B</i> , Na <sub>v</sub> $\beta$ 2	$\downarrow I_{Na}$	Rare
BrS15	12p11	<i>PKP2</i> , Plakophilin-2	$\downarrow I_{Na}$	Rare
BrS16	3q28	<i>FGF12</i> , FHAF1	$\downarrow I_{Na}$	Rare
BrS17	3p22.2	<i>SCN10A</i> , Na <sub>v</sub> 1.8	$\downarrow I_{Na}$	5%–16.7%
BrS18	6q	<i>HEY2</i> (transcriptional factor)	$\uparrow I_{Na}$	Rare

Listed in chronologic order of their discovery.

ATP-sensing subunits of the  $I_{K-ATP}$  channel, have been reported in patients with ERS.<sup>156,158,190</sup> Loss-of-function variations in the  $\alpha_1$ ,  $\beta_2$ , and  $\alpha_2\delta$  subunits of the cardiac L-type calcium channel (*CACNA1C*, *CACNB2*, *CACNA2D1*) and the  $\alpha_1$  subunit of Na<sub>v</sub>1.5 and Na<sub>v</sub>1.8 (*SCN5A*, *SCN10A*) have been reported in patients with ERS.<sup>113,152,177</sup>

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. Only a handful have been studied in genetically engineered animal models, 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 biologic validation of mutation effects remains the most severe



limitation of genetic test interpretation, as recently highlighted by Schwartz et al.<sup>191</sup>

Recent technological advances have resulted in expansion of disease-specific panels.<sup>192</sup> Large public databases of genetic variation from next-generation sequencing programs such as the 1000 Genomes Project, the National Heart Lung and Blood Institute Grand Opportunity Exome Sequencing Project (GO-ESP), and the Exome Aggregation Consortium (ExAC), have challenged drastically our understanding of the “normal” burden and extent of background genetic variation within cardiac channelopathy susceptibility genes.<sup>193–195</sup>

Although *SCN5A* variants account for 18%–28% of BrS,<sup>196</sup> *SCN5A* genetic testing is complicated by an approximately 3%–5% “benign” variant frequency in the general population.<sup>194</sup> Therefore, even in the most common genetic cause of BrS, 1 in 10 “positive” tests could be a “false-positive” even if found in an individual with a robust BrS phenotype. To date, there are more than 20 JWS susceptibility genes.<sup>146,195,197</sup> However, these additional genes have only magnified the issues of interpretation by adding to the overall “genetic noise” without significantly increasing the true mutation yield.<sup>178,198–200</sup> In fact, 1 study revealed that 1:23 individuals in the GO-ESP population possess a previously published BrS-associated variant that would prompt a “positive” genetic test had it been identified in a patient.<sup>201</sup>

These issues reinforce the necessity to interpret JWS genetic test results as strictly probabilistic, rather than binary/deterministic, in nature. Additional lines of evidence<sup>202</sup> can be amassed to aid in the probabilistic interpretation of variants in JWS susceptibility genes, such as case phenotype,<sup>203</sup> segregation, functional studies,<sup>204</sup> *in silico* predictions,<sup>205–208</sup> variant type and location,<sup>194</sup> and variant frequency in cases and control databases.<sup>193</sup> Despite these aids, a large number of variants remain in “genetic purgatory,” and this number will only increase as exome/genome sequencing becomes more utilized. This then demands the development and utilization of a uniform variant repository that would include clinical assertions and evidence for variant classification. Even with these issues, the emergence of exome/genome sequencing holds promise for the opportunity to study genetic variation like never before, holding the promise of improvements in diagnostic, prognostic, and therapeutics for the JWSs and the other heritable cardiac channelopathies. Kapplinger et al.<sup>209</sup> recently reported the synergistic use of up to 7 *in silico* tools to help promote or demote a variant’s pathogenic status and alter its relegation to genetic purgatory.

It is noteworthy that in a recent study, Le Scouarnec et al.<sup>199</sup> estimated the burden of rare coding variation in arrhythmia susceptibility genes among 167 BrS index patients and compared that with 167 individuals  $\geq 65$  years old with no history of cardiac arrhythmia. The authors concluded that, except for *SCN5A*, rare coding

variations in all previously reported BrS susceptibility genes do not contribute significantly to the occurrence of BrS in a population of European ancestry, emphasizing that caution should be taken when interpreting genetic variations in these other genes because rare coding variants are observed to a similar extent in both cases and controls.<sup>199</sup> Similar data were obtained and a similar conclusion was reached by Kapplinger *et al.*<sup>209</sup> by analyzing the prevalence of rare variants in the BrS susceptibility genes in the publicly available ExAC exomes.

Collectively, 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 (classic mendelian view) but rather to inheritance of multiple BrS susceptibility variants (oligogenic) acting in concert through one or more mechanistic pathways.<sup>167</sup> This also fits with the findings of Probst *et al.*<sup>210</sup> that in 5 of 13 large families with a putative *SCN5A* mutation, the genotype did not co-segregate with the phenotype. In addition to the multifactorial nature of the genetics, expressivity of the syndrome may be multifactorial in that the genetic predisposition can be modulated by hormonal (testosterone,<sup>211,212</sup> thyroxine<sup>213</sup>) and other environmental factors, as well as morphologic changes (fibrosis).<sup>76</sup>

## Update on the ionic and cellular mechanisms underlying BrS and ERS

The JWSs are so named because they involve accentuation of the ECG J wave. Experimental evidence indicates that the J wave is inscribed as a consequence of a transmural voltage gradient caused by the manifestation of an AP notch in epicardium but not endocardium due to a heterogeneous transmural distribution of  $I_{to}$ .<sup>104</sup> An end of QRS notch, resembling a J wave, has been proposed to be due to intraventricular conduction delays. The 2 ECG manifestations can be distinguished based on their response to rate, with the latter showing accentuation at faster rates.<sup>24,59</sup>

The cellular mechanisms underlying JWS have long been a matter of debate.<sup>214,215</sup> In the case of BrS, 2 principal hypotheses have been advanced. (1) The repolarization hypothesis asserts that an outward shift in the balance of currents in RV epicardium can lead 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 suggests that slow conduction in the RVOT, secondary to fibrosis and reduced Cx43 leading to discontinuities in indeterminate conduction, plays a primary role in the development of the ECG and arrhythmic manifestations of the syndrome. Conduction slowing is not necessarily limited to the RVOT area. Some investigators have postulated that changes in ion channel current responsible for BrS (i.e., loss of function  $I_{Na}$  and  $I_{Ca}$  and gain of function of  $I_{to}$ ) can alter AP morphology so as to reduce the safety of conduction at high-resistance junctions, such as regions of extensive fibrosis.<sup>216,217</sup> Others have argued that this is highly unlikely because conduction at critical junctions of current-to-load mismatch is exquisitely sensitive to changes in rate. The typical behavior of patients with BrS to acceleration of rate is diminution of ST-segment elevation, opposite to that expected at a site of

discontinuous conduction. The diminution of ST-segment elevation is consistent with the reduced availability of  $I_{to}$  at the faster rate due to slow recovery of the current from inactivation.<sup>59,214</sup> The repolarization and depolarization theories are not necessarily mutually exclusive and may indeed be synergistic.

The most compelling apparent evidence in support of the depolarization hypothesis derives from the seminal studies of Nadeem *et al.*<sup>129</sup> showing that radiofrequency ablation (RFA) of epicardial sites displaying late potentials and fractionated bipolar electrograms in the RVOT of patients with BrS significantly reduced the arrhythmia vulnerability as well as the ECG manifestation of the syndrome. Similar results were reported by Brugada *et al.*<sup>131</sup> and by Sacher *et al.*<sup>130</sup> who also observed in an isolated case that accentuation of the Brugada ECG by ajmaline was associated with an increased area of low-voltage and fragmented electrogram activity. A wider area of low-voltage activity was associated with a more prominent ST-segment elevation.<sup>131</sup> These authors concluded that the late potentials and fractionated electrogram activity are due to conduction delays within the RVOT/RV anterior wall and that ablation of the sites of slow conduction is the basis for the ameliorative effect of ablation therapy.<sup>129–131</sup> In a direct test of this hypothesis, Szel and Antzelevitch<sup>150</sup> provided evidence for an alternative mechanism using an experimental model of BrS. The low-voltage fractionated electrogram activity was shown to develop as a result of regional desynchronization in the appearance of the second AP upstroke, secondary to accentuation of the epicardial AP notch, and high-frequency late potentials to develop in the RV epicardium secondary to concealed phase 2 reentry. Delayed conduction of the primary beat was never observed in a wide variety of BrS models created by exposing canine RV wedge preparations to drugs mimicking the different genetic defects known to give rise to BrS.<sup>150</sup> In more recent studies, ablation of the RV epicardium was shown to diminish the manifestation of J waves and ST-segment elevation and to abolish all arrhythmic activity by destroying the cells with the most prominent AP notch, thus eliminating the cells responsible for the repolarization abnormalities that give rise to phase 2 reentry and VT/VF.<sup>15,218</sup> Confirmation of all of these results in *in vivo* animal models is desirable. In an attempt to create such a model, Park *et al.*<sup>149</sup> recently genetically engineered Yucatan minipigs to heterozygously express a nonsense mutation in *SCN5A* (E558X) originally identified in a child with BrS. Patch clamp analysis of atrial myocytes isolated from the *SCN5A*<sup>E558X/+</sup> pigs showed a loss of function of  $I_{Na}$ . Conduction abnormalities consisting of prolongation of P wave, QRS complex, and PR interval were observed, but a BrS phenotype was not observed, not even after administration of flecainide. These observations are expected because of the lack of  $I_{to}$  in the pig, which is a prerequisite for the development of the repolarization abnormalities associated with BrS. Some have argued that the absence of a BrS phenotype is due to the young age of the minipigs (22 months).<sup>219</sup> However, it is difficult to reconcile why the minipigs manifest major conduction delays at this age but not a BrS phenotype, if indeed the latter depends on the former. Finally, it is noteworthy that monophasic APs recorded from the epicardial and endocardial surfaces of the RVOT of a patient with BrS are nearly identical to transmembrane APs recorded from the epicardial and endocardial surfaces of the wedge model of BrS.<sup>220,221</sup> These differences were not observed in an isolated heart explanted from a BrS

patient after transplantation of a new heart. However, the epicardium of this heart was very depressed, perhaps as a result of the 129 shocks delivered by the implantable cardioverter-defibrillator (ICD) in an attempt to control the multiple electrical storms.<sup>32</sup>

Zhang et al.<sup>133</sup> recently performed noninvasive electrocardiographic imaging (ECGI) on 25 BrS and 6 RBBB patients. The authors concluded that both slow discontinuous conduction and steep dispersion of repolarization are present in the RVOT of patients with BrS. ECGI was able to differentiate between BrS and RBBB. Unlike BrS, RBBB showed delayed activation in the entire RV, without ST-segment elevation, fractionation, or repolarization abnormalities showing on the electrograms. Importantly, the response to an increase in rate was studied in 6 BrS patients. Increasing rate increased fractionation of the electrogram but reduced ST-segment elevation, indicating that the conduction impairment was not the principal cause of the BrS ECG.

The congruence between BrS and ERS with respect to clinical manifestations and response to therapy lends further support to the repolarization hypothesis. Using an experimental model of ERS, Koncz et al.<sup>30</sup> recently provided evidence in support of the hypothesis that, similar to the mechanism operative in BrS, an accentuation of transmural gradients in the LV wall are responsible for the repolarization abnormalities underlying ERS, giving rise to J-point elevation, distinct J waves, or slurring of the terminal part of the QRS. 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.<sup>30,222</sup> Higher intrinsic levels of  $I_{to}$  in the inferior LV were also shown to underlie the greater vulnerability of the inferior LV wall to VT/VF.<sup>30</sup> The advent and implementation of ECGI by Rudy and colleagues provided additional evidence for repolarization abnormalities by identifying abnormally short activation–recovery intervals in the inferior and lateral regions of LV and a marked dispersion of repolarization.<sup>132</sup> More recent studies involving ECGI mapping in an ERS patient during VF have demonstrated VF rotors anchored in the inferior lateral LV wall.<sup>22</sup>

Conduction delay is known to give rise to notching of the QRS complex. When it occurs on the rising phase of the R wave, it is due to a conduction defect within the ventricle. When it occurs at the terminal portion of the QRS, thus masquerading as a J wave, it may be due to either a conduction defect or a repolarization defect.<sup>21,223</sup> The response to prematurity or to an increase in rate can differentiate between the two.<sup>59</sup> Delayed conduction invariably becomes more exaggerated at faster rates or during premature beats, thus leading to accentuation of the QRS notch, whereas repolarization defects usually are mitigated, resulting in diminution of the J wave at faster rates. Although typical J waves usually are accentuated with bradycardia or long pauses, the opposite has also been described.<sup>224,225</sup> J waves are often seen in young males with no apparent structural heart diseases, whereas intraventricular conduction delay is often observed in older individuals or those with a history of myocardial infarction or cardiomyopathy.<sup>223,224</sup> The prognostic value of a fragmented QRS has been demonstrated in BrS,<sup>49,226</sup> although fragmentation of the QRS is not associated with increased risk in the absence of cardiac disease.<sup>227</sup> Factors

**Table 8** Differential diagnosis of J wave vs intraventricular 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

that may aid in the differential diagnosis of J wave vs intraventricular conduction delay (IVCD)-mediated syndromes are summarized in Table 8.

## Risk stratification

### J-wave syndromes

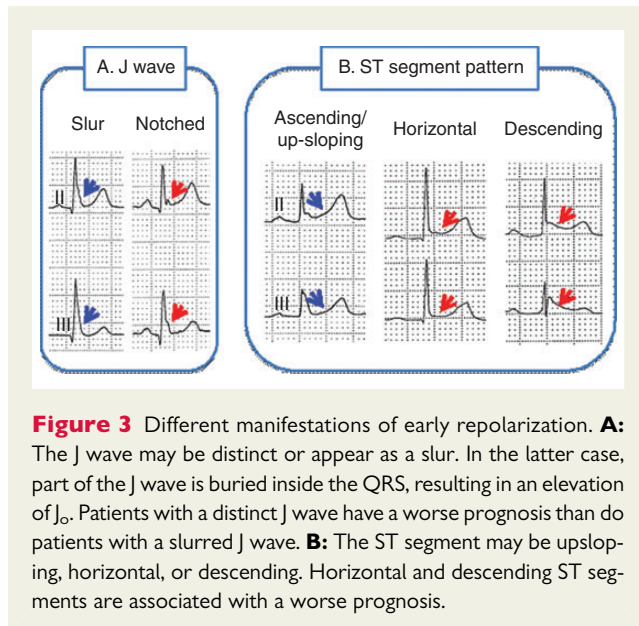
A great deal of attention has been devoted to risk assessment for the development of life-threatening arrhythmias in BrS and ERS.<sup>1,228</sup> The incidental discovery of a J wave on routine screening should not be interpreted as a marker of “high risk” for SCD because the odds for this fatal disease are approximately 1:10,000.<sup>229</sup> 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.<sup>4,230</sup> However, careful attention needs to be paid to subjects with “high-risk” ER or J waves. Figure 3 illustrates the various ECG manifestations of ER. Figure 4 shows a graphic representation of the prevalence and arrhythmic risk associated with the appearance of ECG J waves and clinical manifestations of BrS and ERS. Tables 9, 10, and 11 list the available data from studies designed to identify patients at high risk for BrS and ERS. Among these risk stratifiers, some are highly predictive, including (1) history of cardiac events or syncope likely due to VT/VF and (2) prominent J waves in global leads including type 1 ST-segment elevation in the right precordial leads (Figure 5).

### Early repolarization syndrome

The majority of the studies using the criteria of Haissaguerre et al.<sup>2</sup> for diagnosing the ERP have shown that ER, especially in the inferior ECG leads, predicts cardiac and arrhythmic death. Negative studies are few and may be attributable to the exclusion criteria



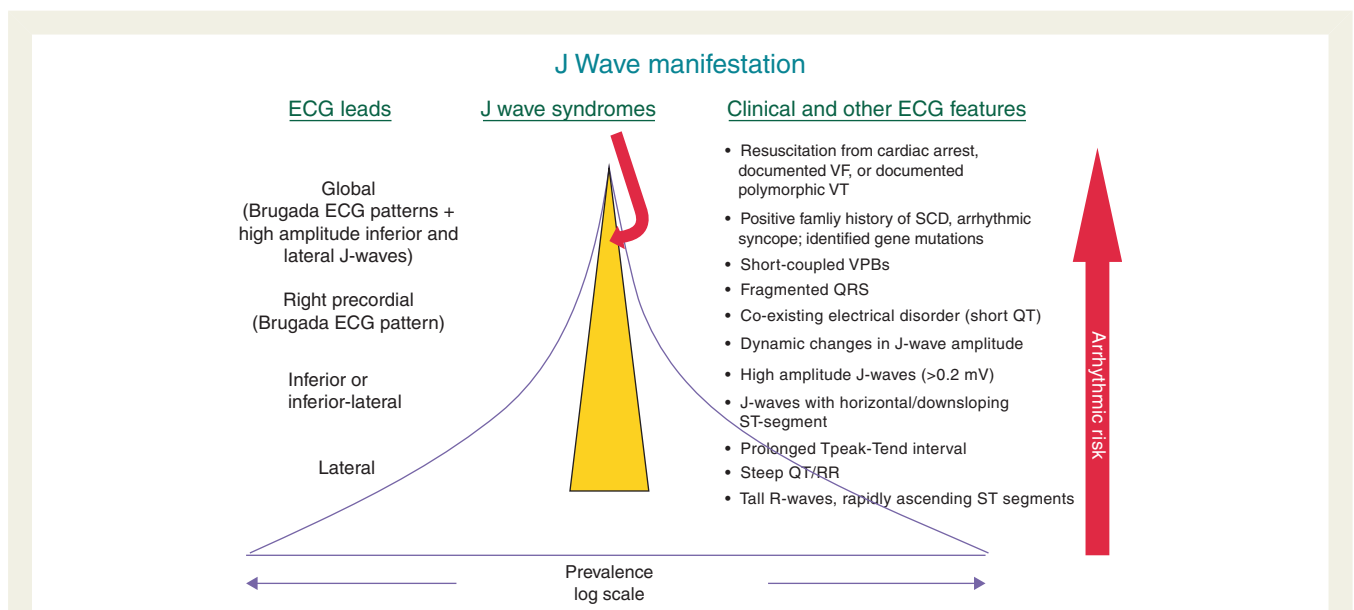
used (e.g., atrial fibrillation, flutter, acute coronary syndrome), a relatively short follow-up period,<sup>231,232</sup> or different definitions of ERP.<sup>233</sup> The recent consensus paper by Macfarlane *et al.*<sup>24</sup> dealing with the terminology of J-wave-related phenomena in the setting of ER should enable us to avoid such confusion in the future. The inclusion of Africans or African-Americans, in whom ER is prevalent but apparently not associated with high risk, may alter outcomes as well.<sup>234</sup>



Huikuri and colleagues reported in a series of seminal papers the results of a population-based study in Finland involving long-term prognosis of subjects with an ERP in the ECG.<sup>44</sup> Tikkanen *et al.*<sup>44</sup> showed that J-point elevation  $\geq 0.1$  mV was present in 5.8% of the population and that only 0.3% of the population had significant J-point elevation  $\geq 0.2$  mV. J-point elevation  $\geq 0.1$  mV in the inferior leads was associated with cardiovascular death (relative risk [RR] 1.28) and arrhythmic death (RR 1.43), and J-point elevation  $\geq 0.2$  mV had a markedly elevated risk of death from cardiac causes (RR 2.92) and from arrhythmia (RR 2.92). Subsequent studies confirmed the association of J wave or ER with death from all causes, death from cardiovascular disease, sudden/unexpected death, and death from arrhythmias.<sup>44–46,127,235–238</sup> A horizontal or descending ST segment is associated with a worse prognosis than is an ascending ST segment (Figure 3).<sup>237,239</sup> Individuals with a high-amplitude J wave  $\geq 0.2$  mV followed by a horizontal or descending ST segment in the inferior/inferolateral leads have a higher risk of lethal arrhythmias than do those with a lower-amplitude J wave, especially those with a rapidly ascending ST segment following the J wave.

The appearance of J wave or ER is now recognized to predispose to the development of arrhythmogenesis when associated with other cardiac disorders, such as ischemia, heart failure, and hypothermia. The J wave might predict prognosis of cardiac events in various heart diseases, and the appearance of a new J wave during acute ischemia seems to be a messenger of VF.<sup>240,241</sup>

Family history of sudden death in subjects with ERP has been identified as a risk factor.<sup>189,242</sup> The presence of coexisting Brugada ECG pattern (J waves in  $V_1$ – $V_3$ ) or short QT intervals in subjects with ER also suggests a more malignant nature.<sup>243,244</sup>



**Table 9 Clinical variables associated with an increased risk of major arrhythmic events in Brugada syndrome\***

Variable	No. patients	Prevention	Study endpoint	Multivariable analysis [hazard ratio (95% confidence interval), P value]	Reference
History					
Previous VF	93	P/S	SD, cardiac arrest, or sustained VT/VF (N = 25)	N/A (N/A), .005	Makimoto <sup>292</sup>
Cardiac arrest	1029	P/S	SD (N = 7), appropriate ICD shocks (N = 44), or sustained VT/VF (N = 0)	11 (4.8–24.3), .001	Probst <sup>359</sup>
Syncope or cardiac arrest	460	P/S	VF or SD (N = 38)	12.7 (4.5–53.4), <.0001	Takagi <sup>360</sup>
Syncope of unknown origin	547	P	SD (N = 16), VF (N = 29)	2.5 (1.2–5.3), .017	Brugada <sup>361</sup>
Syncope	44	P/S	SCD (N = 5), polymorphic VT or VF (recorded by ECG, Holter, or ICD) (N = 7), or syncope of unknown etiology (11)	3.6 (1.09–11.7), .035	Huang <sup>362</sup>
Syncope + spontaneous type 1 ECG	200	P/S	VF or SD from birth (N = 22)	6.4 (1.9–21), <.002	Priori <sup>363</sup>
Syncope of probable arrhythmic origin	1029	P/S	SD (N = 7), appropriate ICD shocks (N = 44), or sustained VT/VF (N = 0)	3.4 (1.6–7.4), .002	Kamakura <sup>364</sup>
Syncope	320	P	SD (N = 3), appropriate ICD shocks (N = 14), or sustained VT/VF (N = 0)	2.8 (1.1–8.1), .03	Delise <sup>262</sup>
Syncope + spontaneous type 1 ECG	308	P	VF (N = 1) or appropriate ICD intervention (N = 13)	4.2 (1.4–12.8), .012	Priori <sup>49</sup>
Ventricular refractoriness					
Ventricular refractory period <200 ms	308	P	VF (N = 1) or appropriate ICD intervention (N = 13)	3.9 (1.03–12.8), .045	Priori <sup>49</sup>
ECG characteristics					
Spontaneous type 1 ECG	1029	P/S	SD (N = 7), appropriate ICD shocks (N = 44), or sustained VT/VF (N = 0)	1.8 (1.03–3.3), .04	Probst <sup>247</sup>
Spontaneous type 1 ECG	320	P	SD (N = 3), appropriate ICD shocks (N = 14) or sustained VT/VF (N = 0)	6.2 (1.8–40), .002	Delise <sup>262</sup>
QRS fragmentation ( $\geq 2$ spikes within the QRS complex in leads $V_1$ – $V_3$ )	308	P	VF (N = 1) or appropriate ICD intervention (N = 13)	4.9 (1.5–1.8), .007	Priori <sup>49</sup>
Family history of sudden cardiac death at age 45 years	330	P	VF (N = 56), syncope (N = 67), or asymptomatic (N = 207)	3.28 (1.4–7.6), .005	Kamakura <sup>364</sup>
J wave in inferior and lateral leads	330	P	VF (N = 56), syncope (N = 67), or asymptomatic (N = 207)	2.66 (1.1–6.7), .005	Kamakura <sup>364</sup>
QRS duration >90 ms in lead $V_2$	460	P/S	VF or SD (N = 38)	3.6 (1.4–12.2), .007	Takagi <sup>360</sup>
Horizontal ST segment after J wave (ST-segment elevation $\leq 0.1$ mV within 100 ms after J point and continued as a flat ST segment until onset of T wave in $\geq 1$ lead with J wave)	460	P/S	VF or SD (N = 38)	>10 (1.9–20.2), .02	Takagi <sup>360</sup>
Late potentials (root mean square voltage of terminal 40 ms of filtered QRS complex <20 $\mu$ V + duration of low-amplitude signals <40 $\mu$ V of QRS in terminal filtered QRS complex >38 ms)	44	P/S	SCD (N = 5), polymorphic VT or VF (recorded by ECG, Holter, or ICD) (N = 7), or syncope of unknown etiology (11)	10.9 (1.1–104), .038	Huang <sup>362</sup>
ST-segment augmentation at early recovery of exercise test (ST-segment amplitude increase $\geq 0.05$ mV in at least 1 of $V_1$ – $V_3$ leads at 1–4 minutes of recovery compared with ST-segment amplitude at pre-exercise)	93	P/S	SD, cardiac arrest, or sustained VT/VF (N = 25).	N/A (N/A), .007	Makimoto <sup>292</sup>

ICD = implantable cardioverter-defibrillator; N/A = not available; P = primary prevention patients only; P/S = primary and secondary prevention patients; SD = sudden death, VF = ventricular fibrillation, VT = ventricular tachycardia

\*The list includes predictor variables that have been associated with an increased risk of major arrhythmic events (i.e., SCD, appropriate ICD interventions, or ICD therapy on fast VT/VF) in at least 1 published multivariable analysis in prospective studies.

**Table 10** Prognostic value of programmed ventricular stimulation resulting from multivariate analysis in large multicenter studies on Brugada syndrome

No.	Prevention	Inducibility	Multivariable hazard ratio (95% confidence interval), P value	Reference
408	P	40%	5.88 (2.0–16.7), <.001	Brugada <sup>364</sup>
308	P	41%	0.89 (0.3–2.6), .84	Priori <sup>49</sup>
638	P/S	62%	N/A, 0.48	Probst <sup>247</sup>
245	P	39%	Not tested on multivariable analysis, but an analysis based on C-statistics demonstrated that results of electrophysiologic studies in combination with other risk factors provided additional value for risk stratification	Delise <sup>262</sup>
334	P/S	67%	0.63 (0.3–1.3), .20*	Takagi <sup>360</sup>
1312 <sup>†</sup>	P/S	42%	2.66 (1.44–4.92), .002	Sroubek <sup>50</sup>

N/A = not available, P = primary prevention patients only, P/S = primary and secondary prevention patients.

\*Univariate analysis; not included in multivariable analysis.

<sup>†</sup>Pooled analysis from 8 international databases.

ER is commonly observed in the young, especially in fit and highly trained athletes, with a prevalence ranging up to 40%. In the majority of cases, the ensuing ST segment is rapidly ascending, suggesting that this is a benign ECG manifestation.<sup>237,245</sup>

Mahida *et al.*<sup>246</sup> recently reported that electrophysiologic (EP) study using programmed stimulation protocols does not enhance risk stratification in ERS.

## Brugada syndrome

Numerous studies consistently show that clinical presentation is the strongest predictor of risk in BrS, overshadowing all other risk factors. The risk of recurrent VF among patients presenting with cardiac arrest is considerable:  $\approx 35\%$  at 4 years,<sup>247,248</sup>  $44\%$  at 7 years,<sup>249</sup> and  $48\%$  at 10 years.<sup>250</sup> Fortunately, only a minority of patients with BrS ( $6\%$  in Europe<sup>247</sup> but  $18\%$  in Japan<sup>248</sup>) diagnosed today have a history of cardiac arrest.

Approximately one-third of contemporary BrS cohorts present with syncope.<sup>247</sup> Their risk of arrhythmic events during follow-up is intermediate: approximately 4 times higher than the risk of asymptomatic patients<sup>49,247,251</sup> but 4 times lower than that of patients diagnosed after cardiac arrest.<sup>247</sup> One explanation for this observation is that the syncope population consists of 2 different groups, one with arrhythmic syncope and bad prognosis, and a second with vagal syncope and good prognosis. Although a detailed clinical history may be of great value in differentiating between these 2 groups, it is not infallible.<sup>252</sup> In reviewing the records of 342 BrS patients, Olde Nordkamp *et al.*<sup>60</sup> concluded that arrhythmic and nonarrhythmic syncope can be distinguished by clinical characteristics, including the absence of prodromes and specific triggers. Compared to patients with suspected nonarrhythmic syncope, patients presenting with presumed arrhythmic syncope were more likely to be male (RR 2.1) and to have urinary incontinence (RR 4.6) and were less likely to report prodromes. They also were older at first event (45 vs 20 years), and their syncope was never triggered by hot/crowded surroundings, pain or other emotional stress, sight of blood, or prolonged standing as in the case of nonarrhythmic syncope. During follow-up, all of the spontaneous arrhythmic events occurred in patients who originally presented with presumed

arrhythmic syncope; patients with benign syncope had an excellent long-term prognosis.

Today asymptomatic patients represent a majority ( $\sim 63\%$ ) of newly diagnosed Brugada patients.<sup>247,248</sup> Their risk of developing symptoms is relatively low (0.5% per year).<sup>247,248</sup> Unfortunately, for most the first symptom is cardiac arrest or SCD. Therefore, risk stratification of asymptomatic patients is of utmost importance, and strategies for doing so are discussed later. In cardiac arrest patients or patients with presumed arrhythmic syncope, these strategies are of little benefit because these patients are recognized to be at high risk.

## Age and gender

Mean age at the time of cardiac arrest in Brugada patients is 39–48 years, and the vast majority develop symptoms between 20 and 65 years of age.<sup>247–249</sup> Asymptomatic elderly patients with BrS are thought to be at relatively low risk for future cardiac events.<sup>253</sup> BrS in children is very rare, but sudden death in this population has been described.<sup>65,254,255</sup> As in adults, cardiac arrest survivors are at high risk for recurrence, but data regarding risk stratification of asymptomatic children are limited. In a large series,  $64\%$ – $94\%$  of patients with BrS who presented with cardiac arrest were male.<sup>247,248,250</sup> Males are also at increased risk for displaying a spontaneous type I Brugada ECG and for having inducible VF during EP studies.<sup>106</sup> Nevertheless, because the majority of asymptomatic patients are also male, gender is not an independent predictor of arrhythmic events.<sup>106,248</sup>

## Familial and genetic background

Neither family history of SCD nor the presence of a mutation (of any type) in the SCN5A gene has consistently been demonstrated to be of value in risk stratification.<sup>247–249</sup> However, 1 study has shown that SCN5A mutations resulting in protein truncation do confer greater risk.<sup>256</sup> Certain rare variants and polymorphisms in SCN5A and in other genes have also been associated with prognosis.<sup>167,257–261</sup> Nevertheless, the data are limited, and genetic testing is not generally used for risk stratification at this time.

**Table 1 | Early repolarization patterns associated with idiopathic ventricular fibrillation, cardiac death, or all-cause mortality**

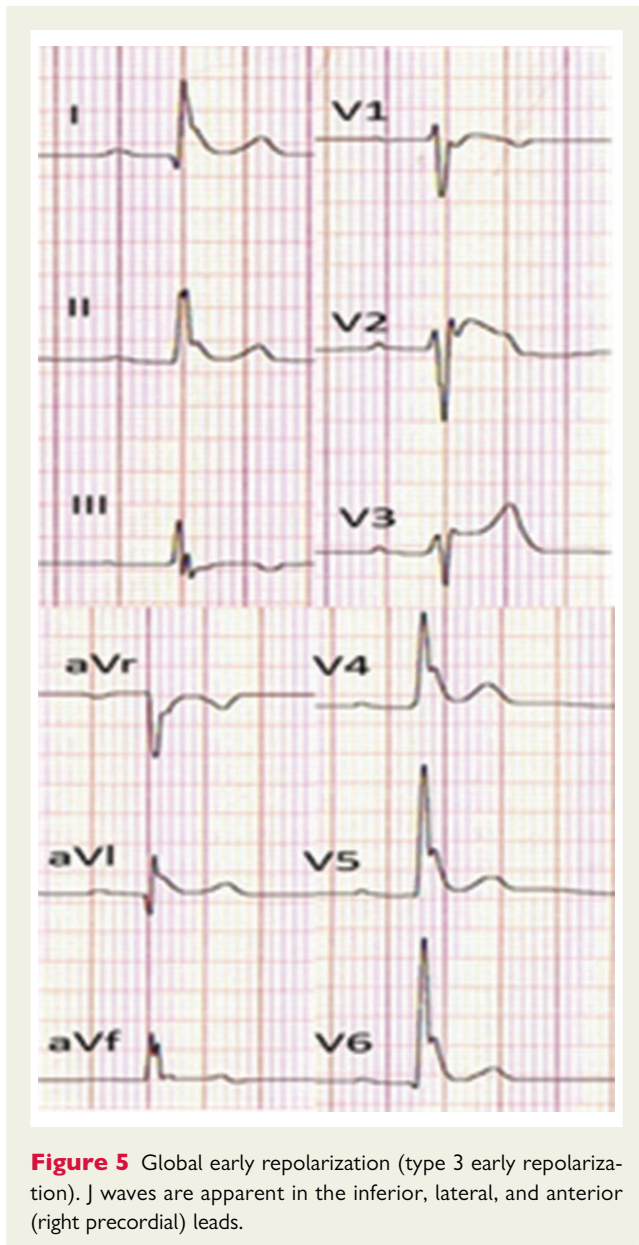
Study design	Patient population	Early repolarization patterns	Endpoint	Odds/Hazard ratio (95% confidence intervals) P value*	Reference
Case-control	206 idiopathic VF 412 matched controls	J-point elevation $\geq 0.1$ mV	Idiopathic VF	10.9 (6.3–18.9)	Haissaguerre <sup>2</sup>
Case-control	45 idiopathic VF 124 matched controls	J-point elevation in inferior leads	Idiopathic VF	3.2 (1.4–7.5), $P = .006$	Rosso <sup>4</sup>
Case-control	121 noncompetitive athletes	J-point elevation in I/aVL	Idiopathic VF	16.9 (2.0–140), $P = .009$	Rosso <sup>2,45</sup>
		J-point elevation in $V_4$ – $V_6$	Idiopathic VF	NS	
		J-point elevation	Idiopathic VF	4.0 (2.0–7.9)	
Case-control	124 matched controls	J-point elevation + horizontal ST segment	Idiopathic VF	13.8 (5.1–37.2)	
Case-control	121 noncompetitive athletes	J-point elevation $\geq 0.1$ mV in inferolateral leads	Idiopathic VF	4.63 (1.67–12.9), $P = .007$	Cappato <sup>3,65</sup>
Case-control	21 athletes with idiopathic VF 365 controls athletes	QRS slurring in any lead	Idiopathic VF	4.81 (1.73–13.4), $P = .007$	
Prospective	10,864 middle-aged people enrolled in the Finnish Social Insurance Institution's Coronary Heart Disease Study (CHD study) between 1966 and 1972	J-point elevation $\geq 0.1$ mV in inferior leads	Death from cardiac causes	1.28 (1.04–1.59), $P = .03$	Tikkanen <sup>44</sup>
Prospective	10,864 middle-aged people enrolled in the Finnish Social Insurance Institution's Coronary Heart Disease Study (CHD study) between 1966 and 1972	J-point elevation $\geq 0.2$ mV in inferior leads	Death from arrhythmias	1.43 (1.06–1.94), $P = .03$	Tikkanen <sup>237</sup>
		J-point elevation $\geq 0.1$ mV and horizontal/descending ST segment	Death from any cause	1.54 (1.06–2.24), $P = .03$	
		J-point elevation $\geq 0.1$ mV and upsloping ST segment	Death from cardiac causes	2.98 (1.85–4.92), $P < .001$	
		J-point elevation $\geq 0.1$ mV	Death from arrhythmias	2.92 (1.45–5.89), $P = .01$	
		J-point elevation $\geq 0.2$ mV	Sudden death	1.43 (1.05–1.94)	
Prospective	1161 middle-aged people enrolled in the third French Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Project between 1994 and 1997	J-point elevation $\geq 0.1$ mV in inferior leads	Total mortality Cardiovascular mortality	2.45 (1.44–4.15), $P = .001$ 5.6 (2.27–11.8), $P = .001$	Rollin <sup>236</sup>
Prospective	1161 middle-aged people enrolled in the third French Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Project between 1994 and 1997	J-point elevation $\geq 0.2$ mV	Total mortality Cardiovascular mortality	NS 5.14 (1.72–15.4), $P = .004$	Rollin <sup>236</sup>
		J-point elevation $\geq 0.1$ mV in inferior leads	Total mortality Cardiovascular mortality	2.85 (1.62–5.02), $P = .001$ 5.28 (1.96–14.2), $P = .001$	
		J-point elevation $\geq 0.1$ mV in lateral leads	Total mortality Cardiovascular mortality	NS 6.27 (1.85–21.3), $P = .003$	
Prospective	1161 middle-aged people enrolled in the third French Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Project between 1994 and 1997	J-point elevation $\geq 0.1$ mV and horizontal ST-segment elevation	Total mortality Cardiovascular mortality	3.04 (1.71–5.41), $P = .001$ 6.93 (2.75–17.4), $P = .001$	



Prospective	15,792 middle-aged biracial people enrolled in the US Atherosclerosis Risk in Communities (ARIC) between 1987 and 1989	J-point elevation $\geq 0.1$ mV and ascending ST-segment elevation	Total mortality Cardiovascular mortality	NS NS	Olson <sup>238</sup>
		J-point elevation $\geq 0.1$ mV with notching pattern	Total mortality Cardiovascular mortality	3.11 (1.72–5.6), $P = .001$ 8.32 (3.32–20.8), $P = .001$	
		J-point elevation $\geq 0.1$ mV with slurring pattern	Total mortality Cardiovascular mortality	NS NS	
		J-point elevation $\geq 0.1$ mV in white men	Sudden death Coronary events	NS NS	
		J-point elevation $\geq 0.1$ mV in white women	All cause mortality Sudden death	NS 8.77 (3.19–24.13)	
		J-point elevation $\geq 0.1$ mV in black men	Coronary events All cause mortality	NS NS	
		J-point elevation $\geq 0.1$ mV in black women	Sudden death Coronary events	NS NS	
		J-point elevation $\geq 0.1$ mV in black individuals	All cause mortality Sudden death	NS NS	
		J-point elevation $> 0.1$ mV in black individuals	Coronary events All cause mortality	1.47 (1.03–2.09) NS	
		J-point elevation $> 0.1$ mV in non-black individuals	Cardiovascular death Cardiovascular death	NS 1.6, $P = .02$	
Prospective	29,281 subjects evaluated at the Palo Alto Veterans Affairs Hospital				Perez-Riera <sup>367</sup>

NS = not significant; VF = ventricular fibrillation.

\*Adjusted odds ratio/hazard ratio reported when available.



### Spontaneous vs drug-induced type I Brugada pattern

A consistent finding in nearly all BrS series is that patients with spontaneous type I ECG at the time of diagnosis have a greater risk of arrhythmic events than do patients who develop such an ECG pattern *only* when challenged with a sodium channel blocker.<sup>247,262</sup> This observation is true for asymptomatic patients<sup>247</sup> as well as for patients who present with syncope<sup>49,247,251,263</sup> and remains an independent predictor of arrhythmic events in multivariate analysis. The problem is that only a minority of patients have a consistent spontaneous type 1 pattern when repeated ECGs are analyzed.<sup>264,265</sup> Therefore, caution is needed when using a single ECG for risk stratification.

Ventricular arrhythmias are rarely induced during a sodium channel block challenge<sup>65,262,266,267</sup> and are likely to be dose dependent

(i.e., will not occur when the infusion is stopped for safety reasons before the full dose is reached).

Their long-term prognostic significance remains unclear. Extra caution should be exercised when administering sodium channel blockers to patients with significant conduction disease.

Placing the right precordial leads over the 2nd and 3rd intercostal spaces in addition to the standard 4th intercostal space increases the sensitivity for detecting the coved ST-segment elevation of the type 1 Brugada pattern. Available data suggest that this increased detection of spontaneous type 1 pattern does not affect the value of this parameter for predicting VF.<sup>52,268,269</sup>

### EP studies with programmed ventricular stimulation

The role of programmed ventricular stimulation during EP studies continues to be passionately debated.<sup>270–272</sup> The question is not whether VF inducibility correlates with arrhythmic risk. In all series, the VF inducibility rate is highest for survivors of cardiac arrest, intermediate for those with syncope, and lowest for those who were asymptomatic at presentation.<sup>273</sup> The central question is whether the prognostic information provided by VF inducibility is robust enough for clinical decision-making. Some studies suggest that this is the case,<sup>262,274,275</sup> but others do not.<sup>248,249</sup> One central issue suggested as an explanation for the discrepancy between studies is the extrastimulation protocol used. Specifically, the prognostic impact of site (RV apex vs RV apex + RVOT)<sup>49,270,276</sup> and the number of extrastimuli (2 vs 3)<sup>49,276</sup> has been analyzed but with inconsistent results. The only prospective study specifically designed to examine the prognostic yield of EP studies in BrS was the PRELUDE registry.<sup>49</sup> It did not show that sustained VF induction identifies high-risk patients but did demonstrate that a short effective ventricular refractory period (o200 ms) is a risk marker.

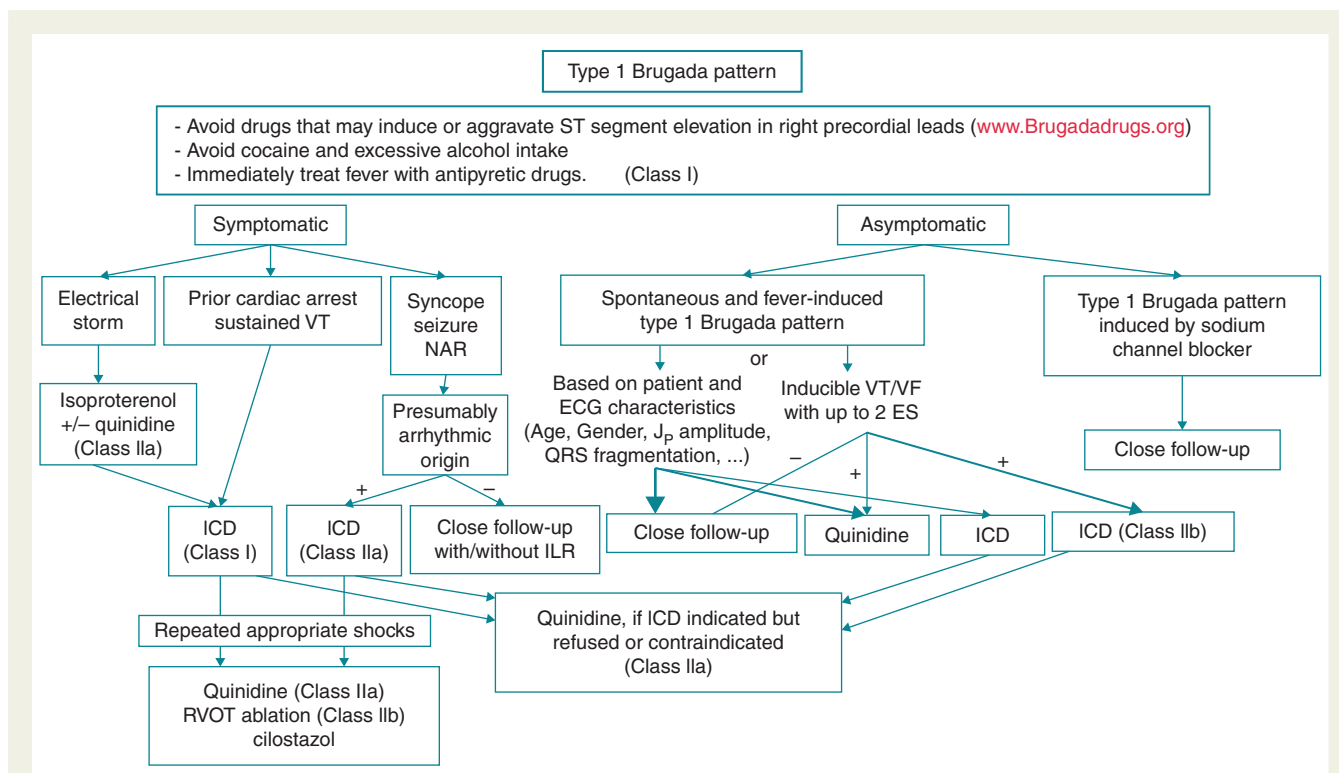
### Other risk markers

Several ECG markers have been associated with risk in BrS. These include (1) fragmentation of the QRS,<sup>226,277,278</sup> (2) the concomitant finding of a type 1 Brugada pattern and an ERP in inferolateral leads,<sup>145,248,279–281</sup> and (3) dynamic changes in the manifestation of prominent J waves or ST-segment elevation.<sup>282</sup>

Other markers associated with increased risk but with limited or inconsistent data include (1) late potentials recorded using signal-averaged ECG,<sup>283–285</sup> (2) microscopic T-wave alternans,<sup>286</sup> (3) macroscopic T-wave alternans during a sodium blocker challenge test,<sup>285,287,288</sup> (4) increased QRS width,<sup>49,248,277,289,290</sup> (5) prominent R wave in aVR,<sup>289–291</sup> and (6) augmented ST-segment elevation of a type 1 Brugada pattern during the recovery phase of an exercise test.<sup>292</sup> Prolonged Tpeak-Tend<sup>293–296</sup> and relatively steep QT/RR slope have been associated with higher risk in cases of BrS.<sup>297,298</sup> Combining several risk factors (e.g. fragmented QRS + ERP<sup>277</sup>) appears to confer an additive risk; however, data supporting this are limited.

## Update on approaches to therapy for BrS and ERS

Figures 6 and 7 graphically present recommendations for the management of BrS and ERS as modified from the 2013 HRS/ EHRA/



**Figure 6** Indications for therapy of patients with Brugada syndrome. Recommendations with class designations are taken from Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm* 2013;10:1932–1963, and Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;36:2757–9. Recommendations without class designations are derived from unanimous consensus of the authors. ES = extrastimuli at right ventricular apex; ICD = implantable cardioverter-defibrillator; ILR = implantable loop recorder; NAR = nocturnal agonal respiration; RVOT = right ventricular outflow tract; VF = ventricular fibrillation; VT = ventricular tachycardia.

APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes and the 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD.<sup>8,9</sup> Those recommendations are based on the available literature and on the clinical experience of the Task Force members. As with all such recommendations, they will need to undergo continuous validation in future studies.

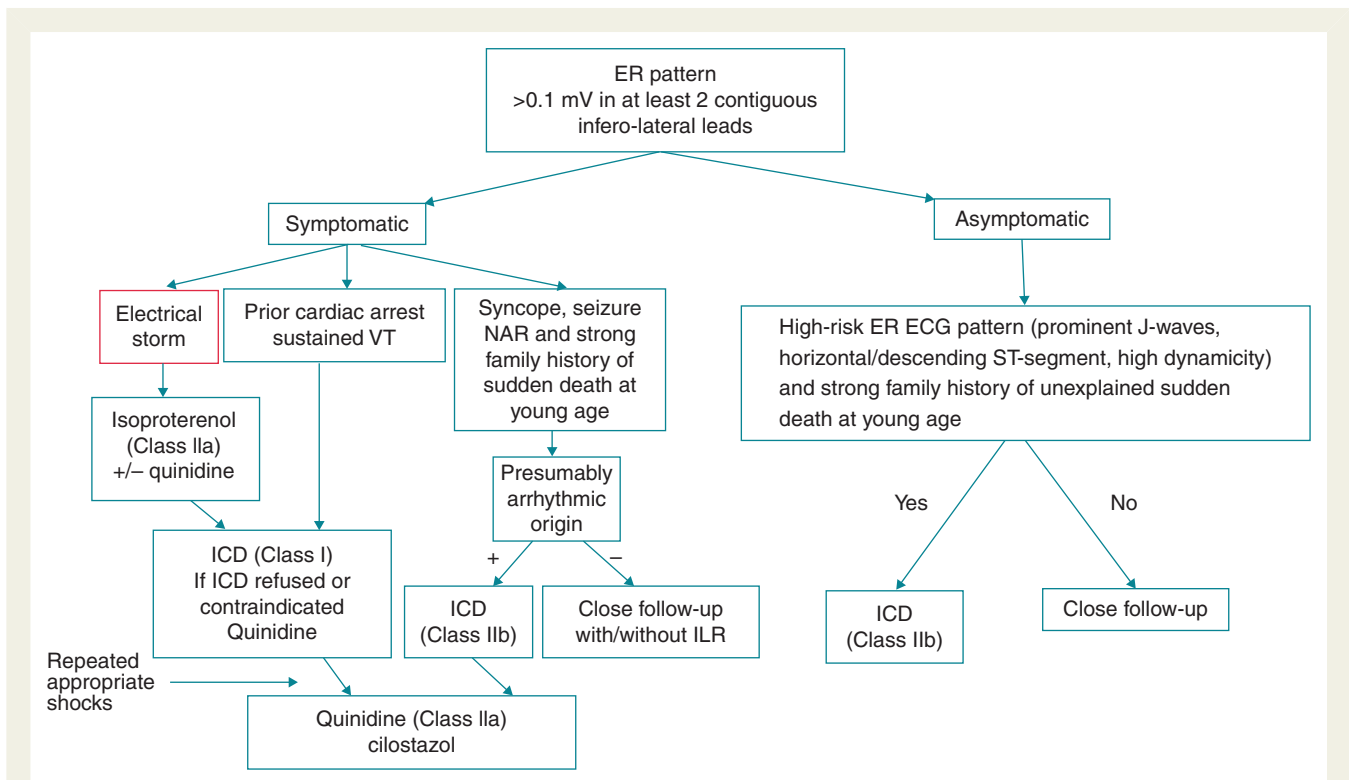
Education and lifestyle changes for the prevention of arrhythmias are critical in BrS. Patients should be informed of the various modulators and precipitating factors that could cause malignant arrhythmias. A prominent S-wave in Lead I has recently been identified as an ECG marker of BrS.<sup>298A</sup> Fever should be treated aggressively with antipyretics, and contraindicated substances should be avoided (see [www.brugadadrugs.org](http://www.brugadadrugs.org)).<sup>89</sup> Referral for ECG is recommended during high fever. Family members may be referred for cardiopulmonary resuscitation training and advised to consider purchasing an automatic external defibrillator for home use. Because malignant ventricular arrhythmias are infrequent in asymptomatic patients with BrS<sup>247</sup> or ERP<sup>44</sup> and usually unrelated to physical activity, the presence of these patterns does not contraindicate participation in sports.

It is noteworthy, however, that the Brugada pattern is accentuated immediately after exercise, presumably because of an increase in vagal tone.<sup>292,299,300</sup> In reviewing 98 case of BrS studies dealing with exercise, Masrur et al.<sup>299</sup> concluded that there are insufficient data on the risks of exercise in BrS to make recommendations for exercise.

### Implantable cardioverter-defibrillator

The only proven effective therapeutic strategy for the prevention of SCD in high-risk BrS and ERS patients is an ICD.<sup>301,302</sup> It is important to recognize that ICDs are associated with complications, especially in young active individuals.<sup>249,303</sup> At 10 years postimplantation, the rates of inappropriate shock and lead failure are 37% and 29%, respectively. Remote monitoring can identify lead failure and prevent inappropriate shocks.<sup>304</sup> Subcutaneous ICDs are thought to represent the future for this indication because they are expected to be associated with fewer complications over a lifetime.<sup>305</sup>

Implantation of an ICD is first-line therapy for JWS patients presenting with aborted SCD or documented VT/VF with or without syncope (Class I recommendation).<sup>301,306</sup> ICDs can be useful (Class IIa) in symptomatic BrS patients with type 1 pattern, in



**Figure 7** Indications for therapy of patients with early repolarization syndrome. Recommendations with Class designations are taken from Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHS in May 2013 and by ACCF, AHA, PACES, and AEP in June 2013. *Heart Rhythm* 2013;10:1932–1963, and Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;36: 2757–9. Recommendations without Class designations are derived from unanimous consensus of the authors. ER = early repolarization; ICD = implantable cardioverter-defibrillator; ILR = implantable loop recorder; NAR = nocturnal agonal respiration; VT = ventricular tachycardia.

whom syncope was likely caused by VT/VF. The HRS/EHRA/APHS expert consensus states that the ICD may be considered (Class IIb) in asymptomatic patients with inducible VF during programmed electrical stimulation (PES).<sup>8</sup> Some studies suggest that the predictive value of EP studies may be improved by limiting the PES protocol to 2 extrastimuli,<sup>50,276</sup> but that observation is not supported by other studies.<sup>49,307</sup> Similarly, some studies advocate that PES should be limited to the RVA and credit this limited PES strategy for a very high positive predictive value found in some series.<sup>275</sup> Again, that observation is not confirmed by other studies.<sup>276</sup>

The current Task Force proposes that ICDs are reasonable (Class IIa) in symptomatic BrS patients with type 1 pattern but that implantation be considered on a case-by-case basis by an electrophysiologist experienced in BrS, taking into consideration age, gender, clinical presentation, ECG characteristics (QRS fragmentation,  $J_p$  amplitude), and patient preference. The current Task Force also proposes that EP study may be considered in asymptomatic individuals with spontaneous type 1 Brugada pattern. If VT/VF is inducible, an ICD should be considered.<sup>7</sup> More recent studies argue in favor of using  $\leq 2$  extrastimuli to induce VT/VF.<sup>50,276</sup> ICDs are not indicated in asymptomatic patients without any of these

characteristics. At present, there is no clear role for PES in patients with ERS.

### Pacemaker therapy

Arrhythmic events and SCD in both BrS and ERS generally occur during sleep or at rest and are associated with slow heart rates. These observations notwithstanding, a potential therapeutic role for cardiac pacing remains largely unexplored.<sup>308</sup> A few case reports are available.<sup>309,310</sup>

### RFA therapy

Nademanee et al.<sup>129</sup> showed that RFA of epicardial sites displaying late potentials and fractionated bipolar electrograms in the 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 noninducible and to normalize the Brugada ECG pattern in the vast majority of patients over a period of weeks or months. Long-term follow-up (20–6 months) showed no recurrent VT/VF, with only 1 patient on medical therapy with amiodarone. Case reports in support of these effects have been published.<sup>311</sup> Additional evidence in support of the effectiveness



of epicardial substrate ablation was provided by Sacher *et al.*<sup>130</sup> and Shah *et al.*<sup>312</sup>

More recently, Brugada *et al.*<sup>131</sup> used flecainide to identify the full extent of low-voltage electrogram activity in the anterior RV and RVOT and targeted this region for RFA. In all 14 BrS patients, RFA eliminated abnormal bipolar electrograms, normalized ST-segment elevation on right precordial leads of ECG, and VT/VF was no longer inducible. Ablation therapy can be lifesaving in otherwise uncontrollable cases. RF ablation may be considered (Class IIb recommendation) in BrS patients with frequent appropriate ICD shocks due to recurrent electrical storms.<sup>7</sup> There are no clinical reports of ablation of the LV substrate in patients with ERS. In patients in whom BrS combines with ERS, ablation of the anterior RV epicardium (including the RVOT) is not ameliorative.

## Pharmacologic approach to therapy

### Brugada syndrome

ICD implantation may be problematic in infants or young children because of the high complication rate. ICDs are also economically out of reach for patients in some regions of the world. A pharmacologic approach to therapy, based on a rebalancing of currents active during the early phases of the epicardial AP in the RV so as to reduce the magnitude of the AP notch and/or restore the AP dome, has been a focus of basic and clinical research in recent years. Antiarrhythmic agents such as amiodarone and beta-blockers have been shown to be ineffective.<sup>313</sup> Class IC antiarrhythmic drugs (e.g., flecainide, propafenone) and Class IA agents (e.g., procainamide) are contraindicated because of their effects of unmasking BrS and inducing 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.<sup>314</sup>

Because the presence of a prominent  $I_{to}$  is a prerequisite for the development of both BrS and ERS, partial inhibition of this current is thought to be effective regardless of the ionic or genetic basis for the disease. Unfortunately, cardioselective and  $I_{to}$ -specific blockers are not available.

The only agent with significant  $I_{to}$ -blocking properties available in the United States and around the world is quinidine.<sup>19,73</sup> Experimental studies have shown that quinidine is effective in restoring the epicardial AP dome, thus normalizing the ST segment and preventing phase 2 reentry and polymorphic VT in a variety of different experimental models of BrS.<sup>19,150,315–317</sup> A recent experimental study suggests that quinidine, because of its effect of blocking  $I_{to}$ , can also exert a protective effect against hypothermia-induced VT/VF in a JWS model.<sup>144</sup> It is noteworthy that, historically, quinidine was used to prevent VF in patients who required hypothermia for surgical procedures.<sup>317</sup>

Clinical evidence for the effectiveness of quinidine in normalizing ST-segment elevation and/or preventing arrhythmic events in patients with BrS has been reported in numerous studies and case reports.<sup>117,119,120,124,318–331</sup> Hermida *et al.*<sup>119</sup> reported 76% efficacy in prevention of VF-induced by PES. Belhassen *et al.*<sup>332</sup> recently reported a 90% efficacy in prevention of VF induction after treatment with quinidine despite the use of very aggressive protocols of extrastimulation. Furthermore, no arrhythmic events occurred among BrS patients treated with quinidine during a mean follow-up period of 10 years.

In a recent trial conducted at 2 French centers, 44 asymptomatic BrS patients with inducible VT/VF were enrolled (47–10 years, 95% male).<sup>333</sup> Of these patients, 34 (77%) were no longer inducible while treated with 600 mg/day hydroquinidine for 6.2–3 years. Among the 10 other patients (22%) who remained inducible and received ICD (group PVS+), none received appropriate therapy during mean follow-up of 7.7–2 years.

A prospective registry of empiric quinidine for asymptomatic BrS 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](http://clinicaltrials.gov/ct2/show/NCT00789165?term_brugada&rank_2). Doses between 600 and 900 mg were recommended, if tolerated.<sup>322</sup>

Quinidine may be considered (Class IIb indication) in BrS patients presenting with electrical storms and in patients implanted with an ICD who are experiencing repeated appropriate shocks. Quinidine can also be useful in asymptomatic BrS patients displaying a spontaneous type I ECG, if they qualify for an ICD and the device is refused or is contraindicated (Class IIa recommendation).

Agents that augment the L-type calcium channel current, such as beta-adrenergic agents (e.g., isoproterenol, denopamine, orciprenaline) are useful as well.<sup>19,117,121,327,334,335</sup> Isoproterenol, at times in combination with quinidine, has been used successfully to control VF storms and normalize ST elevation, particularly in children.<sup>93,115–118,279,319,320,325,331,336–343</sup> Spontaneous VF in patients with BrS is often related to increases in vagal tone and is amenable to treatment by an increase of sympathetic tone via isoproterenol administration. Administration of isoproterenol is a Class IIa recommendation for BrS patients presenting with electrical storms.<sup>7</sup>

Another promising pharmacologic approach for BrS is the administration of the phosphodiesterase III inhibitor cilostazol,<sup>117,121,123</sup> 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.<sup>344</sup> Other effects of cilostazol may contribute to its actions (e.g., adenosine, NO, mitochondrial  $I_{KATP}$ ).<sup>345</sup> Its efficacy in combination with bepridil in preventing VF episodes was recently reported by Shinohara *et al.*<sup>125</sup> The failure of cilostazol in the treatment of BrS has been described in a single case report.<sup>346</sup>

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.<sup>150,347</sup> No clinical reports have yet been published.

Wenxin Keli, a traditional Chinese medicine, 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  $\mu$ M).<sup>316</sup>

Agents that augment peak and late  $I_{Na}$ , including bepridil and dimethyl lithospermate B, are suggested to be of value in BrS. Bepridil has been reported to suppress VT/VF in several studies of patients with BrS.<sup>117,297,298,348</sup> 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 channels<sup>349</sup>; and (3) prolongation of QT interval at slow rates thus increasing the QT/RR slope.<sup>297,298</sup> 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 and suppressing arrhythmogenesis in experimental models of BrS.<sup>350</sup>

Because malignant ventricular arrhythmias are infrequent in asymptomatic patients with BrS<sup>247</sup> or ERP<sup>44</sup> and usually unrelated to physical activity, the presence of these patterns does not contraindicate participation in sports, although, as previously discussed, insufficient data are currently available to make definitive recommendations for participation in sports.

### Early repolarization syndrome

It is not surprising that the approach to therapy of ERS is similar to that of BrS, because the mechanisms underlying the 2 syndromes are potentially 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<sup>117,338</sup> or ERS.<sup>190</sup> Isoproterenol has been shown to act by reversing the repolarization abnormalities responsible for the disease phenotype secondary to restoration of the epicardial AP dome in experimental models of both BrS<sup>19,315</sup> and ERS.<sup>30</sup> This action of the beta-adrenergic agonist is expected because of its actions to potently increase  $I_{Ca}$ .

The phosphodiesterase III inhibitor cilostazol has been reported to reduce the ECG and arrhythmic manifestations of ERS.<sup>122</sup> Phosphodiesterase inhibitors are known to activate  $I_{Ca}$  secondary to an increase in cAMP.<sup>121,344,351–355</sup> The augmentation of  $I_{Ca}$  is thought to prevent arrhythmias associated with JWS by reversing the repolarization defects and restoring electrical homogeneity across the ventricular wall secondary to restoration of the epicardial AP dome in both BrS<sup>347</sup> and ERS.<sup>144</sup> 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 AP 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.<sup>356</sup>

No clinical data are available regarding the effectiveness of RFA in the setting of ERS, despite the fact that low-voltage fractionated electrogram activity and high-frequency late potentials are observed in the LV of patients with ERS<sup>357</sup> and in experimental models of ERS (Yoon and Antzelevitch, unpublished data). Nakagawa et al.<sup>357</sup> reported the results of a study in which they recorded epicardial electrograms directly from the LV of patients diagnosed with ERS by introducing a multipolar catheter into the left lateral (marginal) coronary vein, anterior interventricular vein, and middle cardiac vein via the coronary sinus. The authors reported late potentials in the bipolar electrograms recorded from the LV epicardium of the ERS patients.<sup>357</sup>

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