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Novel Therapeutic Strategies for the Management of Ventricular Arrhythmias Associated with the Brugada Syndrome

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Abstract

Introduction—Brugada syndrome (BrS) is an inherited cardiac arrhythmia syndrome characterized by prominent J waves appearing as distinct coved type ST segment elevation in the right precordial leads of the ECG. It is associated with a high risk for sudden cardiac death.

Areas Covered—We discuss 1) ECG manifestations of BrS which can be unmasked or aggravated by sodium channel blockers, febrile states, vagotonic agents, as well as tricyclic and tetracyclic antidepressants; 2) Genetic basis of BrS; 3) Ionic and cellular mechanisms underlying BrS; 4) Therapy involving devices including an implantable cardioverter defibrillator (ICD); 5) Therapy involving radiofrequency ablation; and 6) Therapy involving pharmacological therapy which is aimed at producing an inward shift in the balance of the currents active during phase 1 of the right ventricular action potential either by boosting calcium channel current (isoproterenol, cilostazol and milrinone) or by inhibition of transient outward current I_{to} (quinidine, bepridil and the Chinese herb extract Wenxin Keli).

Expert Opinion—This review provides an overview of the clinical and molecular aspects of BrS with a focus on approaches to therapy. Available data suggest that agents capable of inhibiting the transient outward current I_{to} can exert an ameliorative effect regardless of the underlying cause.

1. Clinical Characteristics

Brugada syndrome usually first presents at an average age of 41 ± 15 years. The prevalence of the disease is highest in Southeast Asia and is estimated to be > 5 per 10,000 inhabitants.¹ The true prevalence of the disease in the general population is difficult to estimate because the ECG pattern is often concealed.²

The majority of patients with a Brugada ECG pattern are asymptomatic, diagnosed incidentally and may remain asymptomatic for life. Others can present with VF or SCD (particularly at night), nocturnal agonal breathing, syncope and/or palpitations. Although

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syncope and sudden death are a consequence of ventricular tachycardia/fibrillation (VT/VF), approximately 20% of BrS patients also develop supraventricular arrhythmias, including atrial fibrillation (AF), flutter, AV nodal reentrant tachycardia (AVNRT) and pre-excitation syndromes such as Wolf-Parkinson-White (WPW) syndrome. AF is reported in approximately 10–20% of cases.³ Ventricular inducibility is positively correlated with a history of atrial arrhythmias⁴.

Brugada syndrome is characterized by prominent J waves appearing as an ST segment elevation in the right precordial leads. Three types of ST segment elevation are generally recognized^{5–7}. Type 1 is diagnostic of Brugada syndrome and is characterized by a coved ST segment elevation ≥ 2 mm (0.2 mV) followed by a negative T wave (Figure 1). The initial guidelines also required one of the following for the definitive diagnosis of BrS: documented ventricular fibrillation, polymorphic ventricular tachycardia, a family history of SCD (< 45 years old), coved type ECGs in family members, syncope or nocturnal agonal respiration. In the latest guidelines, clinical symptoms remain important in risk stratification, although they are no longer listed among the diagnostic criteria⁸.

Sodium channel blockers, including flecainide, ajmaline, procainamide, disopyramide, propafenone and pilsicainide are used to aid in a differential diagnosis when ST segment elevation is not diagnostic under baseline conditions^{9–13}. However a negative I_{Na} -block test does not exclude a latent forms of BrS.^{13, 14} The electrocardiographic manifestations of Brugada syndrome when concealed can also be unmasked by a febrile state as well as with vagotonic agents.^{9, 15–20}

Differentiating RBBB from BrS can at times be difficult, particularly because RBBB has been reported to mask BrS.^{21, 22} Pre-excitation of the right ventricle has been shown to be helpful in unmasking BrS under these circumstances. Criteria have been proposed to distinguish RBBB from BrS ECG pattern^{23–25}.

Most cases of BrS display prominent J waves, appearing as ST segment elevation limited to the right precordial leads, although rare cases of inferior lead²⁶ or left precordial lead²⁷ ST segment elevation have been reported in Brugada-like syndromes, in some cases associated with *SCN5A* mutations²⁸. Coexistence of early repolarization in Brugada-patients is not uncommon.²⁹ Early repolarization pattern in the inferolateral leads, is one of the most recently identified risk factors for ventricular fibrillation in Brugada syndrome.^{30, 31} From a different perspective, the appearance of early repolarization in inferior, lateral and anterior (right precordial) leads is referred to as global ER and has been designated as Type 3 early repolarization pattern (ERS3).³²

2. Risk stratification in BrS

Because patients with BrS have a relatively low annual rate of cardiac events,³³ risk stratification is crucial in determining appropriate therapy. Commonly accepted risk factors include Spontaneous Type 1 BrS ECG, history of cardiac events or syncope likely due to VT/VF,^{8, 33–35} aborted sudden cardiac death, documented VT/VF, nocturnal agonal respiration, late potentials on epicardial bipolar electrogram or SAECG,^{36–42} T wave

amplitude variability,³⁷ short ventricular refractory period (< 200 ms),³⁴ fragmented QRS,^{34, 43} and ST segment elevation in the peripheral leads, particularly aVR.⁴⁴

Several other factors have been suggested to be associated with higher mortality, but are controversial or not confirmed by multicenter comprehensive clinical studies, e.g.:⁴⁴ prolonged QRS duration^{31, 45–47} and early repolarization pattern in the inferolateral leads.^{30, 31, 47, 48}

3. Genetic Basis

Brugada syndrome is traditionally considered to be inherited via an autosomal dominant mode of transmission. Mutations in 19 genes have been associated with Brugada phenotype (Table 1). These mutations affect sodium, potassium or calcium currents by impairing channel function via an effect on the α or auxiliary subunits comprising the channel. These genetic defects cause a decrease in inward sodium or calcium current or an increase in outward potassium current resulting in an outward shift in the balance of current active during the early phases of the action potential.^{49–5657–5953, 60–7071–7874, 75, 79–85}

Several recent studies have suggested a more complex genetic background for BrS. Bezzina et al.⁶⁰ reported that BrS can be associated with common genetic variants suggesting a multigenic origin of the syndrome. Other authors, including Le Scouarnec et al.⁸⁶ and Behr et al.⁸⁷, have questioned the impact of rare gene-variants, excepting SCN5A, in the pathogenesis of the syndrome. These studies suggest that great caution needs to be exercised in the interpretation of genetic results and that genotype-phenotype correlation as well as functional expression studies are needed to support conclusions that rare variants are causative of the disease.

4. Ionic and Cellular Basis for BrS

The cellular mechanisms underlying Brugada syndrome have long been a matter of debate^{88, 89}. Two principal hypotheses have been advanced: 1) The repolarization hypothesis maintains that an outward shift in the balance of currents in right ventricular epicardium leads to repolarization abnormalities resulting in the development of phase 2 reentry, which generates closely coupled premature beats capable of precipitating VT/VF; 2) The depolarization hypothesis maintains that slow conduction in the right ventricular outflow tract plays a primary role in the development of the electrocardiographic and arrhythmic manifestations of the syndrome. Although these theories are not mutually exclusive and may indeed be synergistic, from the standpoint of appropriate therapy, correct assessment of the cellular pathophysiology is important.

In the repolarization hypothesis, an outward shift in the balance of currents active during the early phases of the epicardial action potential via either a reduction of inward current (I_{Na} or I_{Ca}) or increase in outward current (I_{Kr} or I_{K-ATP}), permits the already prominent I_{to} to accentuate phase 1 of the action potential. When phase 1 is repolarized beyond the voltage range at which L-type Ca^{+2} channels activate, the Ca^{+2} channels fail to activate, resulting in loss of the action potential dome. This happens most readily in the right ventricular subepicardial cells where I_{to} is most prominent. When the AP dome conducts from

epicardial sites at which it is maintained to sites at which it is lost, it results in development of phase 2 reentry, giving rise to a very closely coupled extrasystole (Figure 2).⁹⁰ These repolarization abnormalities give rise to low voltage fractionated electrogram activity and high frequency late potentials when a bipolar electrogram is recorded in the region of the RVOT (Figure 3).⁹¹ The low voltage fractionated electrogram activity is due to dysynchrony in the appearance of the epicardial action potential dome secondary to accentuation of the action potential notch and the high frequency late potentials are due to concealed phase 2 reentry (Figure 4).

The discovery of phase 2 reentry and other characteristics of Brugada syndrome were identified in the early 1990's and evolved in parallel with the clinical syndrome.^{92–95}

The appearance of prominent J waves, appearing as ST segment elevation, in the right precordial leads of patients with Brugada syndrome is due the accentuation of the right ventricular epicardial action potential notch secondary to the rebalancing of the currents active at the end of phase 1 (see ⁹⁶ for references)(Figure 2). A transient outward current (I_{to})-mediated spike and dome morphology, or notch, in ventricular epicardium, but not endocardium, generates a voltage gradient responsible for the inscription of the electrocardiographic J wave in larger mammals and in man.⁹⁷ ST segment is normally isoelectric because of the absence of transmural voltage gradients at the level of the action potential plateau. Under pathophysiologic conditions, accentuation of the right ventricular notch leads to exaggeration of transmural voltage gradients and thus to accentuation of the J wave, causing an apparent ST segment elevation.⁹⁶ Epicardial activation and repolarization delay leads to progressive inversion of the T wave. The down-sloping ST segment elevation, or accentuated J wave, observed in the experimental wedge models often appears as an R', suggesting that the appearance of a right bundle branch block (RBBB) morphology in Brugada patients may be due at least in part to early repolarization of right ventricular (RV) epicardium, rather than to marked impulse delay or conduction block in the right bundle. Indeed RBBB criteria are not fully met in many case of Brugada syndrome ⁹⁸.

Accentuation of the right ventricular action potential notch can give rise to the typical Brugada ECG without creating an arrhythmogenic substrate (Figure 2B). The arrhythmogenic substrate arises when a further shift in the balance of currents causes to loss of the action potential dome at some epicardial sites but not others. Loss of the action potential dome in epicardium but not endocardium results in the development of a marked transmural dispersion of repolarization and refractoriness, responsible for the development of a vulnerable window. A closely coupled extrasystole can then capture this vulnerable window and induce a reentrant arrhythmia. Loss of the epicardial action potential dome is usually heterogeneous, leading to the development of epicardial dispersion of repolarization. Conduction of the action potential dome from sites at which it is maintained to sites at which it is lost causes local re-excitation via a phase 2 reentry mechanism (P2R). The phase 2 reentrant extrasystole is often concealed because it is surrounded by refractory tissue. (Figure 4). These concealed P2Rs are responsible for the appearance of high frequency late potentials in epicardial electrograms recorded over these epicardial sites in patients with BrS.⁹¹ When the P2R succeeds in propagating out of its protected focus and capturing the vulnerable window, it can trigger a circus movement reentry, usually manifest as

polymorphic VT/VF (Figure 2).^{99–101} The phase 2 reentrant beat fuses with the negative T wave of the basic response. Because the extrasystole originates in epicardium, the QRS complex is largely comprised of a negative Q wave, which serves to accentuate the inverted T wave, giving the ECG a more symmetrical appearance, a morphology commonly observed in the clinic preceding the onset of polymorphic VT. Support for these hypotheses derives from experiments involving the arterially-perfused right ventricular wedge preparation.¹⁰⁰ Further evidence in support of these mechanisms derives from the studies of Kurita et al. in which monophasic action potential (MAP) electrodes were positioned on the epicardial and endocardial surfaces of the right ventricular outflow tract (RVOT) in patients with Brugada syndrome.^{95, 102}

The available information supports the hypothesis that Brugada syndrome is the result of amplification of heterogeneities intrinsic to the early phases of the action potential among the different transmural cell types. The amplification is secondary to a rebalancing of currents active during phase 1, including a decrease in I_{Na} or I_{Ca} or augmentation of any one of a number of outward currents including I_{Kr} , I_{Ks} , $I_{Cl(Ca)}$ or I_{to} . ST segment elevation occurs as a consequence of the accentuation of the action potential notch, eventually leading to loss of the action potential dome in right ventricular epicardium, where I_{to} is most prominent. Loss of the dome gives rise to both a transmural as well as epicardial dispersion of repolarization. The transmural dispersion is responsible for the development of ST segment elevation and the creation of a vulnerable window across the ventricular wall, whereas the epicardial dispersion leads to phase 2 reentry, which provides the extrasystole that captures the vulnerable window, thus precipitating VT/VF. The VT generated is usually polymorphic, resembling a very rapid form of Torsade de Pointes (Figure 2).

The most compelling evidence in support of the depolarization hypothesis comes from a study by Nademanee et al.³⁸ showing that radiofrequency (RF) ablation of epicardial sites displaying late potentials and fractionated bipolar electrograms (EGs) in the right ventricular outflow tract (RVOT) of BrS patients significantly reduced the arrhythmia-vulnerability and ECG-manifestation of the disease. These authors concluded that the late potential (LP) and fractionated electrogram activity are due to conduction delays within the RVOT and elimination of the sites of slow conduction is the basis for the ameliorative effect of ablation therapy.³⁸ In a direct test of this hypothesis, Szel et al. provided an alternative cellular electrophysiological mechanism as the basis for late potentials and fractionated electrogram activity in the setting of BrS.⁹¹ In experimental models of BrS, they showed that the electrogram abnormalities are due to repolarization defects and not to depolarization defects. These results are discussed in more detail in the section on ablation below.

5. Approach to Therapy

Table 2 lists the device and pharmacologic therapies evaluated clinically or suggested on the basis of experimental evidence.

5.1 Invasive approach to therapy

Device Therapy

Intracardiac (intra-vessel) implantable cardioverter defibrillator (ICD): Implantation of an ICD is the mainstay of therapy for patients presenting with aborted SCD or documented VT/VF with or without syncope.^{103, 104}

The HRS/EHRA/APHRS expert consensus statement⁸ recommendations for ICD implantation are illustrated in Table 2 and summarized as follows:

1. Recommended (Class I):

Symptomatic patients displaying the Type 1 Brugada ECG (either spontaneously or after sodium channel blockade) who present with aborted sudden death should receive an ICD. Similar patients presenting with related symptoms such as syncope, seizure or nocturnal agonal respiration and have **documented** ventricular fibrillation or tachycardia should also undergo ICD implantation (Class I). Electrophysiologic study (EPS) is recommended in symptomatic patients only for the assessment of supraventricular arrhythmia.

2. Can be useful (Class IIa) in symptomatic patients with Type 1 pattern, in whom syncope was likely caused by VT/VF.

3. May be considered (Class IIb) in asymptomatic patients inducible by PES.

The relatively low annual rate of arrhythmic events in asymptomatic patients (0.5% vs. 7.7–10.2% in patients with VF and 0.6–1.2% in patients with syncope), warrants careful consideration for ICDs in asymptomatic patients^{33, 105}. In the recent HRS/EHRA/APHRS guidelines,

4. ICDs are not indicated (Class III) in asymptomatic patients⁸.

The validity of HRS/EHRA/APHRS (Class II) recommendation for patients with a history of syncope and spontaneous Type 1 ECG was recently confirmed by Takagi et al in a multicenter large-cohort study in the Japanese population.¹⁰⁶ These authors reported that in patients with Class II indication, the combination of a history of syncope and spontaneous Type 1 ECG may be an important factor in distinguishing intermediate- from low-risk patients with BrS in Japan.

The effectiveness of ICD in reverting VF and preventing sudden cardiac death was 100% in a multicenter trial in which 258 patients diagnosed with Brugada syndrome received an ICD.¹⁰⁷ Appropriate shocks were delivered in 14%, 20%, 29%, 38% and 52% of cases at 1, 2, 3, 4, and 5 years of follow-up, respectively. In the case of initially asymptomatic patients, appropriate ICD discharge was delivered 4%, 6%, 9%, 17% and 37% at 1, 2, 3, 4, and 5 years of follow-up, respectively. Later other long-term follow-up studies confirmed the effectiveness of this approach.^{108, 109}

Although the intracardiac ICD is very effective in preventing sudden arrhythmic death, it should be emphasized that this invasive approach can be associated with severe complications. A recently published comprehensive multicenter large-cohort trial from France, including 14 centers and 378 patients with a mean follow-up of 77±42 months (range: 6 – 220 months), reported that at 10 years after the implantation, the rate of appropriate therapy was 48% in patients with previous aborted SCD, 19 % in patients with syncope, and 12% in asymptomatic cases.^{110, 111} Whereas the aggregate rate of inappropriate shocks and lead failure was 37% and 29%, at 10 years after the implantation. The study also highlights the need for optimal ICD-programming and follow-up, which can reduce the occurrence of inappropriate shocks. The indication for ICD in symptomatic patients is clear, but it is complicated in asymptomatic cases. They are at relatively low but not insignificant risk for SCD and there are no reliable diagnostic tools to distinguish asymptomatic individuals who are vulnerable to arrhythmic events.

Subcutaneous ICD: The relatively high complication rate of transluminal implantation and chronic presence of intravessel electrodes suggest the need for alternative therapeutic options, especially in young patients or patients with active lifestyle and severe complications. A completely subcutaneous ICD can be a useful approach for these individuals^{112–114,115}, however long-term clinical experience is lacking at present.

Pacemaker therapy: Although arrhythmias and sudden cardiac death generally occur during sleep or at rest and have been associated with slow heart rates, a potential therapeutic role for cardiac pacing remains largely unexplored.¹¹⁶ Only a few case reports are available in the literature.^{117, 118}

BrS patients who suffer from electrical storms leading to numerous appropriate ICD discharges highlight the need for adjunctive therapy and the need for alternatives to an ICD. Before the development of a widely applicable and efficient ablation technique (see below)³⁸, a heart transplantation was the only option for these patients.¹¹⁹

Ablation therapy: The idea of using ablation to suppress focal arrhythmogenic substrates in BrS was first suggested around the turn of the century. Several studies reported the potential utility of focal **endocardial** radiofrequency ablation of sites generating monomorphic extrasystoles.^{120–123}

One of the most promising innovations in the treatment of BrS was recently presented by Nademanee et al.³⁸, who showed that radiofrequency (RF) ablation of **epicardial** sites displaying late potentials and fractionated bipolar electrograms (EGs) in the right ventricular outflow tract (RVOT) of BrS patients significantly reduced the arrhythmia-vulnerability and ECG-manifestation of the disease. Ablation at these sites can render VT/VF non-inducible and can normalize the Brugada ECG pattern in the majority of patients over a period of weeks or months. Long-term outcomes (20±6months) were excellent, with no recurrent VT/VF with only 1 patient on medical therapy with amiodarone. Since then, case reports have been published in support of these effects.¹²⁴ Ablation therapy can be life-saving in otherwise uncontrollable cases, or cases in which ICD therapy is impractical (e.g. contraindications or financial hardship in developing countries). In the recent HRS/EHRA/

APHRS expert consensus guideline, radiofrequency ablation has a **Class IIb** recommendation in BrS-patient with frequent appropriate ICD-shocks due to recurrent electrical storms.⁸

The cellular mechanism underlying the ameliorative effect of epicardial ablation in BrS is a matter of debate. Szel et al.⁹¹ demonstrated that late potentials and fractionated electrogram activity are due to concealed phase 2 reentry and dysnchrony in the appearance of the second upstroke of the action potential secondary to heterogeneous accentuation of the epicardial action potential notch (Figure 4 and 5). We hypothesize that ablation of the RVOT eliminates these sites of abnormal repolarization, thus suppressing the arrhythmogenic substrate. In a recent test of this hypothesis employing the canine right ventricular wedge model of BrS, we provide evidence showing that epicardial ablation destroys the cells with the most prominent action potential notch, thus eliminating the cells responsible for the repolarization abnormalities that give rise to phase 2 reentry and VT/VF (Figure 5)¹²⁵.

5.2 Pharmacologic approach to therapy

ICD implantation is not an appropriate solution for infants and young children or for patients residing in regions of the world where an ICD is out of reach because of economic factors. A pharmacologic approach to therapy, based on a rebalancing of currents active during the early phases of the epicardial action potential in the right ventricle so as to reduce the magnitude of the action potential notch and/or restore the action potential dome, has been a focus of basic and clinical research in recent years. Table 2 lists the various pharmacologic agents thus far investigated. Antiarrhythmic agents such as amiodarone and β blockers have been shown to be ineffective.¹²⁶ Class IC antiarrhythmic drugs (such as flecainide and propafenone) and class IA agents, such as procainamide, are contraindicated because of their effects to unmask Brugada syndrome and induce arrhythmogenesis. Disopyramide is a class IA antiarrhythmic that has been demonstrated to normalize ST segment elevation in some Brugada patients but to unmask the syndrome in others.¹²⁷

Because the presence of a prominent transient outward current is central to the mechanism underlying Brugada syndrome, the most rationale approach to therapy, regardless of the ionic or genetic basis for the disease, is to partially inhibit I_{to} . Cardio-selective and I_{to} -specific blockers are not currently available. 4-aminopyridine (4-AP) is an agent that is ion-channel specific at low concentrations, but is not cardio-selective in that it inhibits I_{to} in the nervous system. Although it is effective in suppressing arrhythmogenesis in wedge models of Brugada syndrome¹⁰⁰ (Figure 6), it is unlikely to be of clinical benefit because of neural-mediated and other side effects.

Quinidine—The only agent on the market in the United States and around the world with significant I_{to} blocking properties is quinidine. It is for this reason that we suggested in 1999 that this agent may be of therapeutic value in BrS.¹²⁸ Experimental studies have since shown quinidine to be effective in restoring the epicardial action potential dome, thus normalizing the ST segment and preventing phase 2 reentry and polymorphic VT in different experimental models of Brugada syndrome, regardless of which pharmacologic agents were used to mimic BrS-phenotype (Figure 6).^{91, 100, 129, 130} Additionally, a recent experimental

study suggests, that quinidine exerts protective effect against hypothermia-induced VT/VF in a J wave syndrome model.¹³¹

Clinical evidence of the effectiveness of quinidine in normalizing ST segment elevation and or preventing arrhythmic events in patients with the BrS has been reported in numerous studies and case reports (Figure 1).^{132,109, 132–144} The first prospective study describing the effects of quinidine to prevent inducible and spontaneous ventricular fibrillation (VF) was reported by Belhassen and coworkers.¹³⁴ All 25 patients studied had inducible VF at baseline electrophysiological study. Quinidine (1483±240 mg) prevented VF induction in 22 of the 25 patients (88%). After a follow-up period of 6 months to 22.2 years, all patients were alive. Of nineteen patients treated with oral quinidine for 6 to 219 months (56±67 months), none developed arrhythmic events. Administration of quinidine was associated with a 36% incidence of side effects, principally diarrhea, that resolved after drug discontinuation. The authors concluded that quinidine effectively suppresses VF induction as well as spontaneous arrhythmias in patients with Brugada syndrome and may be useful as an adjunct to ICD therapy or as an alternative to ICD in cases in which an ICD is refused, is unaffordable or under other circumstances in which ICD implantation is not feasible. These results are consistent with those reported the same group in prior years^{133, 145} and later by other investigators^{146, 147}. The data highlight the need for randomized clinical trials to assess the effectiveness of quinidine, preferably in patients with frequent events who have already received an ICD. Hermida et al. reported 76 % efficacy in prevention of VF induced by PES.¹⁴⁶

Quinidine in asymptomatic patients—Quinidine may has been proposed as a preventative measure in asymptomatic patients, however this has not been evaluated in large double-blinded clinical trials¹³⁵. A prospective registry of empiric quinidine for asymptomatic Brugada syndrome has been established. The study appears at the National Institutes of Health website (ClinicalTrials.gov) and can be accessed at:¹⁴⁸. Doses between 600 and 900 mg are recommended, if tolerated¹³⁵.

Low dose quinidine therapy—Because of the GI side effects of high dose quinidine, low-dose quinidine (<600mg) has been suggested to be as a therapeutic option. Marquez et al. evaluated the clinical history of symptomatic patients with recurrent arrhythmias and frequent ICD discharges and reported that relatively low dose quinidine, as adjunctive therapy, completely prevented arrhythmias in 85 % of the patients (median follow-up of 4 years).¹³⁷

A prospective multicenter trial, evaluating the effect of low-dose (300mg) hydroquinidine in BrS patients with an ICD implanted, was initiated in France in 2009. However, the study, called QUIDAM, was recently terminated due to insufficient recruitment:¹⁴⁹

In the latest HRS/EHRA/APHRS expert consensus statement, quinidine was given a Class IIa recommendation in BrS patients who are qualified for an ICD but in whom hindering factors are present, IIa in ICD-patients with electrical storms, and IIb recommendation in asymptomatic BrS-patients displaying a spontaneous Type 1 ECG.⁸

The development of a more cardio-selective and I_{to} -specific blocker would be a most welcome addition to the limited therapeutic armamentarium currently available to combat this disease. Another agent considered for this purpose is tedisamil. Tedisamil may be more potent than quinidine because it lacks the inward current blocking actions of quinidine, while potently blocking I_{to} .¹⁵⁰

Quinidine and tedisamil can suppress the substrate and trigger for Brugada syndrome secondary to inhibition of I_{to} . Both, however, have the potential to induce an acquired form of the long QT syndrome, secondary to inhibition of the rapidly activating delayed rectifier current, I_{Kr} . Thus the drugs may substitute one form of polymorphic VT for another, particularly under conditions that promote TdP, such as bradycardia and hypokalemia. This effect of quinidine is minimized at high plasma levels because at these concentrations quinidine block of I_{Na} counters the effect of I_{Kr} block to increase transmural dispersion of repolarization, the substrate for the development of Torsade de Pointes (TdP) arrhythmias.^{151–153}

Selective I_{to} and I_{Kur} blockers such as AVE0118 are also potential candidates¹⁵⁴. This drug has the advantage that it does not block I_{Kr} , and therefore does not prolong the QT interval or have the potential to induce TdP. The disadvantage of this particular drug is that it undergoes first-pass hepatic metabolism and is therefore not effective with oral administration.

Appropriate clinical trials are needed to establish the effectiveness of all of the above pharmacologic agents.

β adrenergic agonists—Agents that boost the calcium current, such as β adrenergic agents like isoproterenol, denopamine or orciprenaline, are useful as well^{96, 100, 140, 144, 155, 156}. Isoproterenol, sometimes in combination with quinidine, has been utilized successfully to control VF storms and normalizing ST elevation particularly in children^{16, 132, 133, 138, 144, 147, 157–168}. The occurrence of spontaneous VF in patients with Brugada syndrome is often related to increases in vagal tone and correspondingly electrical storm is sometimes treatable by the increase of sympathetic tone via isoproterenol administration.

In the latest HRS/EHRA/APHRS guideline, Isoprotereonol has a Class IIa recommendation for BrS patients presenting with electrical storms.⁸

PDE-inhibitors—Another promising pharmacologic approach is the administration of phosphodiesterase III inhibitor cilostazol^{144, 155, 169}, 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.¹⁷⁰ Other diverse effects of cilostazol in playing a role in its beneficial impact cannot be excluded. (e.g.: adenosine, NO, mitochondrial I_{K-ATP} ¹⁷¹) Its efficacy in combination with bepridil in preventing VF-episodes was recently reported by Shinohara et al.¹⁷². A case report describing the failure of cilostazol in the treatment of a BrS-patient is also available in the literature¹⁷³.

Another phosphodiesterase III inhibitor, milrinone, has recently been identified as a more potent alternative to cilostazol in suppressing ST elevation and arrhythmogenesis in an experimental model of BrS (Figure 7)^{91, 174}. No clinical reports have appeared as yet.

Bepridil—Several studies report the effect of bepridil to suppress VT/VF in patients with BrS.^{144, 175–177} The drug seems to be a safe and promising tool in the chronic treatment of symptomatic patients. Its mechanism of action is not fully elucidated. Bepridil possesses multiple effects on cardiac ion channel currents. Three of these appear to be relevant: 1) block of I_{to} ; 2) augmentation of I_{Na} via upregulation of the channels¹⁷⁸; and 3) prolongation of QT at slow rates thus increasing the slope of QT-RR.^{175, 177}

In a recent study, Shinohara et al. tested the combination of cilostazol and bepridil in patients with J-wave-syndrome-associated recurrent VF episodes (5 BrS and 2 ERS patients).¹⁷² They found that the drug combination effectively suppressed arrhythmogenesis in the study group. The administration of bepridil eliminated the palpitation side effect of cilostazol by suppressing or abolishing sinus tachycardia. This action of bepridil may be due to its effect to block I_f (HCN4 isoform)¹⁷⁹ as well as its I_{Ca} -blocking effect. To date, bepridil is available only in Japan.

Wenxin Keli, a Chinese herb extract—Wenxin Keli, a traditional Chinese medicine (TCM), is reported to possess important antiarrhythmic effects. In addition to its actions to suppress atrial fibrillation by atrial-selective inhibition of I_{Na} -dependent parameters¹⁸⁰, the drug 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 μ M).¹³⁰ A recent study has also reported the effect of Wenxin Keli to suppress ischemia-induced ventricular arrhythmias.¹⁸¹

Dimethyl Lithospermate B—Dimethyl lithospermate B (dmLSB) is an extract of Danshen, another traditional Chinese herbal remedy, which slows inactivation of I_{Na} , leading to increased inward current during the early phases of the action potential (AP). dmLS B has been shown to be effective in eliminating the arrhythmogenic substrate responsible for the BrS in experimental models of BrS.¹⁸² No clinical data are available as yet.

6. Conclusion

The past decade has witnessed impressive advances in the genetic, ionic and cellular basis for the BrS, providing us important insights into novel approaches to therapy. While the implantation of an ICD is first line therapy for BrS, pharmacologic approaches to therapy are important, especially in management of asymptomatic patients judged to be at risk. Available data suggest that agents capable of inhibiting I_{to} and augmenting I_{Ca} can exert an ameliorative effect regardless of the underlying cause. It is important to recognize that further study either via registry or randomized clinical trials is needed for all of the drugs discussed in this review and that all of these agents should be used with caution. Recent studies suggest an important role for radiofrequency ablation of the epicardial surface of the RVOT, although long-term follow-up is as yet not available.

7. Expert Opinion

Diagnosis and Prognosis: Past Present and Future

Although significant advances have been realized in the identification and risk stratification of patients with Brugada syndrome (BrS), risk assessment of **asymptomatic** subjects (majority of patients) remains a challenge. There are several promising, but unconfirmed or debated approaches in risk stratification. Among the most controversial is the role of programmed electrical stimulation (PES). The conflicting results presumably originate in part from the different protocols used. Efforts to define the optimal PES protocol are being sought by investigators worldwide. Further research designed to develop diagnostic tools with high sensitivity, specificity and prognostic value for risk assessment of asymptomatic BrS patients would be most welcome. Additional research is also needed to identify genetic defects associated with BrS.

Experimental models

In vivo: Genetically-engineered whole animal models of BrS are highly desirable, but none are available at present. Transgenic mice are not helpful because of the fundamental differences in repolarization characteristics. Transgenic rabbits are not available and most are unlikely to be useful because the transient outward current (I_{to}), which is at the heart of mechanism underlying BrS, is very slow to recover from inactivation and contributes little to phase 1 repolarization at normal heart rates. Transgenic dogs are not available.

In vitro: Induced-pluripotent stem cell-derived cardiomyocytes, produced from somatic cells such as fibroblasts isolated from BrS patients, holds promise for generation of single cell human models of BrS, which could be helpful in unraveling the pathophysiologic basis and in providing insights into novel approaches to therapy. An obstacle that we and others have encountered is the fact that these cells are immature and are unable to recapitulate the BrS phenotype because I_{to} is very slow to recover from inactivation.¹⁸³ The development of wedge preparations or whole hearts by reseeded collagen scaffolds using progenitor cells or iPSC generated from fibroblasts isolated from patients with BrS is another futuristic approach to creation of human models of BrS that we and others are pursuing.

Approaches to Therapy

A search for cardioselective and I_{to} -specific blockers is needed to make available agents that are both safe and effective for preventive therapy in asymptomatic BrS patients as well as for adjunctive therapy in the management of VT/VF and electrical storms.

Compounds that augment I_{Ca} (e.g., isoproterenol) and I_{Na} (e.g., bepridil and dimethyl lithospermate B) during the early phases of the cardiac action potential are effective in suppressing electrical storms associated with BrS but may be useful in long term care as well.

A future goal for treatment of BrS as well as other inherited cardiac arrhythmia syndromes is to provide personalized therapy by combining genotyping and functional expression data, thus improving the safety and efficacy of pharmacologic treatment.

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Highlights

- Brugada syndrome (BrS) is characterized by the appearance of very prominent J waves appearing as coved type ST segment elevation in leads V1-V3 of the ECG.
- BrS has been associated for hundreds of mutations in 19 different genes causing a loss of function in inward currents as well as a gain of function in outward currents.
- ICD implantation is the mainstay of therapy.
- Pharmacologic therapy is aimed producing an inward shift in the balance of current active during the early phases of the epicardial action potential in the right ventricular outflow tract (RVOT).
- Radiofrequency ablation of the RVOT epicardium holds promise for long-term suppression of arrhythmias in patients with BrS.

Figure 1.

Twelve-lead electrocardiogram (ECG) tracings in an asymptomatic 26-year-old man with Brugada syndrome. **Left:** Baseline: Type 2 ECG (not diagnostic) displaying a “saddleback-type” ST segment elevation is observed in V2. **Center:** After intravenous administration of 750 mg procainamide, the Type 2 ECG is converted to the diagnostic Type 1 ECG consisting of a “coved-type” ST segment elevation. **Right:** A few days after oral administration of quinidine bisulfate (1,500 mg/day, serum quinidine level 2.6 mg/L), ST segment elevation is attenuated displaying a nonspecific abnormal pattern in the right precordial leads. VF could be induced during control and procainamide infusion, but not after quinidine. (Modified from ¹³³ with permission.)

Figure 2.

Cellular basis for electrocardiographic and arrhythmic manifestation of BrS. Each panel shows transmembrane action potentials from one endocardial (**top**) and two epicardial sites together with a transmural ECG recorded from a canine coronary-perfused right ventricular wedge preparation. **A:** Control (Basic cycle length (BCL) 400 msec). **B:** Combined sodium and calcium channel block with terfenadine (5 μ M) accentuates the epicardial action potential notch creating a transmural voltage gradient that manifests as an ST segment elevation or exaggerated J wave in the ECG. **C:** Continued exposure to terfenadine results in

all-or-none repolarization at the end of phase 1 at some epicardial sites but not others, creating a local epicardial dispersion of repolarization (EDR) as well as a transmural dispersion of repolarization (TDR). **D:** Phase 2 reentry occurs when the epicardial action potential dome propagates from a site where it is maintained to regions where it has been lost giving rise to a closely coupled extrasystole. **E:** Extrastimulus (S1-S2 = 250 msec) applied to epicardium triggers a polymorphic VT. **F:** Phase 2 reentrant extrasystole triggers a brief episode of polymorphic VT. (Modified from reference,¹⁰¹ with permission.)

Figure 3.

Heterogeneities in the appearance of the epicardial action potential second upstroke gives rise to fractionated epicardial electrogram (EG) activity in the setting of Brugada syndrome (BrS). **Left panel:** Shown are right precordial lead recordings, unipolar and bipolar EGs recorded from the right ventricular outflow tract of a BrS patient (from Nadamanee et al.³⁸, with permission). **Right panel:** ECG, action potentials from endocardium (Endo) and two epicardial (Epi) sites, and a bipolar epicardial EG (Bipolar EG) all simultaneously recorded from a coronary-perfused right ventricular wedge preparation treated with the I_{to} agonist NS5806 (5 μ M) and the calcium channel blocker verapamil (2 μ M) to induce the Brugada phenotype. Basic cycle length=1000 ms. (Reproduced from ⁹¹, with permission.)

Figure 4.

Concealed phase 2 reentry as the basis for late potential and fractionated bipolar epicardial (Epi) electrogram (Bipolar EG) activity in an experimental model of Brugada syndrome. Each panel shows (from top to bottom) a Bipolar EG, action potentials recorded from endocardium (Endo) and two Epi sites and an ECG all simultaneously recorded from a coronary-perfused right ventricular wedge preparation exposed to NS5806 (5 μ M) and verapamil (2 μ M) to induce the Brugada phenotype. Heterogeneous loss of the dome at epicardium caused local re-excitation via a 'concealed' phase 2 reentry mechanism, leading to the development of late potentials and fractionated bipolar epicardial EG activity. No major delays in conduction of the primary beat were ever observed. Each panel shows results from a different preparation. Basic cycle length=1000 ms. (Reproduced from ⁹¹, with permission.)

Figure 5.

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

now recorded from the deep subepicardium- midmyocardium (Mid1, Mid2) instead of the epicardial surface. Ablation markedly suppressed the BrS phenotype and abolished all arrhythmic activity.

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Figure 6.

Effects of I_{to} blockers 4-AP and quinidine on pinacidil-induced phase 2 reentry and VT in the arterially-perfused RV wedge preparation. In both examples, 2.5 μmol/L pinacidil produced heterogeneous loss of AP dome in epicardium, resulting in ST segment elevation, phase 2 reentry, and VT (left); 4-AP (A) and quinidine (B) restored epicardial AP dome, reduced both transmural and epicardial dispersion of repolarization, normalized the ST segment, and prevented phase 2 reentry and VT in continued presence of pinacidil. (From ¹⁰⁰, with permission.)

Figure 7.

Effect of milrinone to reverse the repolarization defects responsible for the electrocardiographic and arrhythmic manifestations of Brugada syndrome in a coronary-perfused right ventricular wedge model pharmacologically mimicking loss of function of I_{Ca} in the setting of a prominent I_{to} . Recordings obtained at a basic cycle length of 1000 ms. Each grouping represents the transmembrane action potentials (APs) recorded from 2 epicardial (Epi) sites and 1 endocardial (Endo) site together with an electrocardiogram (ECG), all simultaneously recorded. The I_{to} agonist NS5806 increases notch and J wave parameters but does not induce arrhythmic activity. The addition of verapamil leads to marked accentuation of the Epi AP notch, giving rise to a prominent J wave, appearing as an ST segment elevation. Loss of the dome at Epi 2 results in development of phase 2 reentry. Milrinone reverses these repolarization defects, restoring AP duration homogeneity, normalizing the ECG and abolishing all arrhythmic activity. The Brugada phenotype promptly reappears after washout of milrinone. The top trace is a stimulus marker. (Reproduced from ¹⁷⁴, with permission.)

Table 1

Brugada Syndrome Susceptibility Genes.

	Locus	Gene	Ion Channel	% of Probands
BrS1	3p21	<i>SCN5A</i> , <i>Na_v1.5</i>	↓ I _{Na}	11–28%
BrS2	3p24	<i>GPD1L</i>	↓ I _{Na}	Rare
BrS3	12p13.3	<i>CACNA1C</i> , <i>Ca_v1.2</i>	↓ I _{Ca}	6.6%
BrS4	10p12.33	<i>CACNB2b</i> , <i>Ca_vβ2b</i>	↓ I _{Ca}	4.8%
BrS5	19q13.1	<i>SCN1B</i> , <i>Na_vβ1</i>	↓ I _{Na}	1.1%
BrS6	11q13–14	<i>KCNE3</i> , <i>MiRP2</i>	↑ I _{to}	Rare
BrS7	11q23.3	<i>SCN3B</i> , <i>Na_vβ3</i>	↓ I _{Na}	Rare
BrS8	12p11.23	<i>KCNJ8</i> , <i>Kir6.1</i>	↑ I _{K-ATP}	2%
BrS9	7q21.11	<i>CACNA2D1</i> , <i>Ca_vα2δ</i>	↓ I _{Ca}	1.8%
BrS10	1p13.2	<i>KCND3</i> , <i>K_v4.3</i>	↑ I _{to}	Rare
BrS11	17p13.1	<i>RANGRF</i> , <i>MOG1</i>	↓ I _{Na}	Rare
BrS12	3p21.2–p14.3	<i>SLMAP</i>	↓ I _{Na}	Rare
BrS13	12p12.1	<i>ABCC9</i> , <i>SUR2A</i>	↑ I _{K-ATP}	Rare
BrS14	11q23	<i>SCN2B</i> , <i>Na_vβ2</i>	↓ I _{Na}	Rare
BrS15	12p11	<i>PKP2</i> , <i>Plakophilin-2</i>	↓ I _{Na}	Rare
BrS16	3q28	<i>FGF12</i> , <i>FHAF1</i>	↓ I _{Na}	Rare
BrS17	3p22.2	<i>SCN10A</i> , <i>Na_v1.8</i>	↓ I _{Na}	16.7%
BrS18	6q	<i>HEY2</i> (transcriptional factor)	↑ I _{Na}	Rare
BrS19	7p12.1	<i>SEMA3A</i> , <i>Semaphorin</i>	↑ I _{to}	Rare

Table 2**Device and Pharmacologic Approach to Therapy of Brugada Syndrome**

Devices and Ablation
ICD ¹⁰³
Radiofrequency Ablation ^{38, 120–124}
? Pacemaker ^{116–118}
Pharmacologic Approach to Therapy
<i>Ineffective or Proarrhythmic</i>
Amiodarone ¹²⁶
β Blockers ¹²⁶
Class IC antiarrhythmics
Flecainide ¹⁰
Propafenone ¹⁸⁴
? Disopyramide ¹²⁷
Class IA antiarrhythmics
Procainamide ⁹
<i>Effective for Treatment of Electrical Storms</i>
β Adrenergic agonists – isoproterenol ^{16, 162} , denopamine ¹⁴⁴ , orciprenaline ^{140, 156}
Phosphodiesterase III Inhibitors cilostazol ¹⁵⁵
<i>Effective General Therapy</i>
Quinidine ^{100, 132–134, 145–147}
Bepidil (I_{to} -blocking and I_{Na} -gaining effect?) ¹⁷⁷
Cilostazol combined with bepidil ¹⁷²
<i>Experimental Therapy</i>
I_{to} Blockers - cardioselective and ion channel specific
Quinidine ¹⁰⁰
4-aminopyridine ¹⁰⁰
Tedisamil ¹⁵⁰
AVE0118 ¹⁵⁴
PDE-III-inhibitors
Cilostazol – Increases I_{CaL} and inhibits I_{to} ^{174, 185}
Milrinone - I_{CaL} -boosting ^{174, 185}
Herbal extracts
Wenxin Keli - combined I_{to} -blocking and tyramine-like effect ¹³⁰