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Recent advances in the treatment of Brugada syndrome

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Abstract

Introduction: Brugada syndrome (BrS) is an inherited cardiac arrhythmia syndrome characterized by ST-segment elevation in right precordial ECG leads and associated with sudden cardiac death in young adults. The ECG manifestations of BrS are often concealed but can be unmasked by sodium channel blockers and fever.

Areas covered: Implantation of a cardioverter defibrillator (ICD) is first-line therapy for BrS patients presenting with prior cardiac arrest or documented VT. A pharmacological approach to therapy is recommended in cases of electrical storm, as an adjunct to ICD and as preventative therapy. The goal of pharmacological therapy is to produce an inward shift to counter the genetically-induced outward shift of ion channel current flowing during the early phases of the ventricular epicardial action potential. This is accomplished by augmentation of I_{Ca} using β -adrenergic agents or phosphodiesterase III inhibitors or via inhibition of I_{to} . Radiofrequency ablation of the right ventricular outward flow tract epicardium is effective in suppressing arrhythmogenesis in BrS patients experiencing frequent appropriate ICD-shocks.

Expert commentary: Understanding of the pathophysiology and approach to therapy of BrS has advanced considerably in recent years, but there remains an urgent need for development of cardio-selective and ion-channel-specific drugs for treatment of BrS.

Keywords

Sudden cardiac death; J wave; cardiac arrhythmias; ventricular fibrillation; inherited cardiac arrhythmias syndrome

1. Clinical characteristics and diagnostic criteria

First described in 1992, Brugada syndrome (BrS) is an inherited cardiac arrhythmia syndrome associated with vulnerability to development of polymorphic ventricular

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Declaration of interest

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tachycardia (VT) and ventricular fibrillation (VF) leading to sudden cardiac death (SCD) in young adults with no apparent structural heart disease [1–4] and occasionally to sudden infant death syndrome (SIDS).[5–7]

The Brugada syndrome usually manifests during the third and fourth decade of life (average age of 42 ± 15 years), but some extreme cases have been diagnosed in patients as young as 2 days of age and as old as 87 years of age. [8]

The prevalence of BrS varies on the basis of geographic location. [9–18] In Southeast Asia, it is estimated to be at least 5 per 10,000 inhabitants and it is considered an endemic disease. [19–21] In Japan, a BrS type 1 ECG is observed in 12 per 10,000 inhabitants.[22–24] The real prevalence of the syndrome is difficult to estimate because it is often concealed.

Patients with a BrS ECG are often asymptomatic and may remain asymptomatic for life. [25] A small minority develop nocturnal agonal breathing, syncope or palpitations, leading to VT/VF or SCD. Approximately 20% of BrS patients also develop supraventricular arrhythmias, including atrial flutter, fibrillation, AV nodal reentry and pre-excitation syndromes.[26,27] Atrial fibrillation (AF) is reported in approximately 20% of cases. [28]

The clinical manifestation of BrS is characterized by an elevation of the ST segment in the right precordial leads of the ECG and there are three types of ST segment elevation typically recognized (Figure 1).[29,30] Type one is characterized by ST segment elevation ≥ 2 mm (0.2 mV) in ≥ 1 right precordial leads (V1–V3) positioned in the 4th, 3rd or 2nd intercostal space. When a Type 1 ST segment elevation is unmasked using sodium channel blockers, the diagnosis also requires that the patient presents with one of the following: ventricular fibrillation (VF) or polymorphic ventricular tachycardia (pVT), syncope of probable arrhythmic cause, a family history of SCD at <45 years old with negative autopsy, coved-type ECGs in family members, or nocturnal agonal respiration.[31] Data from the SABRUS registry shows that approximately 6% of the arrhythmic events in BrS were associated with fever with the highest proportion observed in the pediatric population (<16 years). [32]

A Type 2 (“saddle-back type”) or Type 3 ST segment elevation can be 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 one of the criteria specified above.[33] Type 2 is characterized by ST segment elevation of ≥ 0.5 mm (generally ≥ 2 mm in V2) in ≥ 1 right precordial lead (V1–V3), followed by a convex ST. The ST segment is followed by a positive T wave in V2 and variable morphology in V1. Type 3 is characterized by either a saddleback or coved appearance with an ST-segment elevation of <1 mm.[33] A proposed Diagnostic Score System for BrS, referred to as the Proposed Shanghai BrS Score, is presented in Table 1. When BrS is suspected in the absence of spontaneous type 1 ST segment elevation, a pharmacological challenge using a sodium channel blocker is recommended. A list of agents used for this purpose is presented in Table 2 (a complete list can be found at www.brugadadrugs.org).

There are also some conditions that can produce a Brugada-like ECG pattern. Currently, the terminology used in the literature to describe Brugada type 1 ECG pattern induced in patients without BrS is diverse. Some authors define Brugada phenocopies as clinical

entities that present and identical ECG patterns to that found in BrS but are elicited by other clinical circumstances.[34,35] Debate continues as to the appropriateness of this terminology given that it is very difficult to rule out a genetic predisposition, a prerequisite for designating the ECG manifestation as a phenocopy.[33] We prefer to refer to these as acquired forms of BrS or Brugada pattern.

The most commonly observed acute conditions producing a Brugada-like phenotype include acute coronary events, pericarditis, myocarditis, pulmonary embolism, metabolic disorders, impaired ion-balance, dissecting aorta aneurism, thiamine deficiency, electric shock and certain pharmacologic agents.[34] These acute manifestations often disappear with cessation of the provoking event. Some of the permanent conditions producing right precordial ST-elevation include left ventricular hypertrophy, athlete's heart, right bundle branch block (RBBB), pectus excavatum, septal hypertrophy and arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D).[29,36]

Another source of false positives in BrS is due to the inappropriate settings of the recording device. In some circumstances, highly-set low cut filters can lead to ST-elevation or altered shape.[37,38] Sodium block challenge using ajmaline has been shown to produce a false positive in 4.5% of those tested in a recent study by Hasdemir and co-workers.[39] Repeat ajmaline challenge after puberty unmasked Brugada syndrome in 23% of relatives with a previously negative drug test performed during childhood. [40] Ajmaline-induced BrS in children is commonly associated with male sex, sustained atrial arrhythmias, and sinus node dysfunction. Children also appear to be at higher risk for experiencing sustained ventricular arrhythmias (VA) during ajmaline challenge.[41] The development of VAs during ajmaline challenge occurs in approximately 1% of cases; these patients do not appear to be at higher risk of future arrhythmic events. [42,43].

Although most cases of BrS display prominent J waves, appearing as ST segment elevation, limited to the right precordial leads, in some cases the J waves may also appear in the inferior or lateral leads.[44,45] Coexistence of infero-lateral early repolarization (ER) in BrS is not uncommon and is a recently identified risk factor for ventricular fibrillation.[46–48] However, in another interpretation, the presence of ER in inferior, lateral and anterior (right precordial) leads is referred to as global ER and designated as Type 3 early repolarization pattern (ERS3). [1]

2. Risk stratification

Risk stratification in BrS remains a clinical challenge because patients have a relatively low annual rate of cardiac events but, for most, the first symptom is cardiac arrest or sudden cardiac death. Several studies have demonstrated that a significant number of patients who presented arrhythmic events have been initially classified as low risk when following existing guidelines.[49,50] To avoid underscoring of BrS patients, some authors have proposed a multiparametric score model considering age, gender, ECG parameters, syncope and family history. These studies have demonstrated that patients with 2 or 3 risk factors experienced arrhythmic events more frequently than those with 0 or 1 risk factor.[51–54]

Several clinical, echocardiographic, electrocardiographic and electrophysiological markers that have been proposed as risk stratifiers are discussed below. [31,33]

2.1 Commonly accepted risk factors:

- Spontaneous Type 1 BrS ECG
- History of cardiac events or syncope likely due to VT/VF [25,31]
- Aborted sudden cardiac death
- Documented VT/VF
- Nocturnal agonal respiration
- Late potentials on epicardial bipolar electrogram or SAECG [55,56]
- T wave amplitude variability [57]
- Short ventricular refractory period (VRP < 200 ms) [58]
- Fragmented QRS [58,59]
- Prolonged QRS duration [60]
- Early repolarization pattern in the inferolateral leads. [47,48]
- High daily fluctuation of ECG and SAECG parameters [61]

2.2 Controversial risk stratifiers:

- Family history: There is currently no consensus regarding its prognostic value. The most recent studies have denied its usefulness in the prediction of major arrhythmic events.[62–65]. Family history of early SCD in first-degree relatives had an event incidence rate of 3.1% year as compared with 1.3% year if it was not present.[54] Genetic testing in probands and family members is an important source of information for applying the correct treatment and prevention of SCD.
- Inducible VT/VF: Inducibility of VT/VF using programmed electrical stimulation (PES) was a reliable predictor of arrhythmic events in early studies but recently more comprehensive clinical studies have discounted its value. Although the discrepancy between the different studies derives partly from the fact that there is no consensus protocol for PES in BrS, in the latest guidelines inducibility by PES is not considered to have a reliable prognostic value. [36,62–68] Sroubek and co-workers performed a systematic review and pooled analysis of prospective observational studies of Brugada syndrome patients without a history of sudden cardiac arrest who underwent PES. They concluded that arrhythmias induced using PES are associated with future ventricular arrhythmia risk, especially when induced with single or double extrastimuli. They also determined that lack of inducibility does not necessarily portend low ventricular arrhythmia risk particularly in patients with high-risk clinical features. [69]
- Age and gender: [25,70,71] Recent data from the Survey on Arrhythmic Events in Brugada Syndrome (SABRUS) study highlights the marked male

predominance of the syndrome (91.3%) with minor involvement of pediatric (4.3%) and elderly populations (1.5%) and the peak for arrhythmic events occurring at an average age of 42.[50] Based on these results, the authors suggest two age cutoffs (16 and 70 years) that may be important for decision-making. In a recent study, women comprised 42% of a cohort of 542 patients who presented with a spontaneous or drug-induced Brugada type 1 pattern on ECG.[72] Women with BrS present more benign clinical characteristics, less spontaneous type 1 ECG pattern, and are more likely to be asymptomatic. [73]

- Asymptomatic Patients: According to the multi-registry FINGER trial, approximately 67% of patients with BrS are asymptomatic. The annual incidence of arrhythmic events is 0.5%.[25] Clinical guidelines are limited for asymptomatic patients, making risk stratification challenging and sometimes controversial. Spontaneous type 1 ECG, inducible VAs and sinus node dysfunction can identify patients at a higher risk.[74]

2.3 New risk stratifiers:

- Increased Tpeak-Tend interval as a marker of dispersion of repolarization [75–78]
- Decreased QT/RR-variability [79]
- Augmented ST-elevation during recovery from exercise [80]
- Early heart rate recovery after exercise testing [81]
- Spatiotemporal characteristics of QRS complexes. [82]
- Presence of prominent S-wave in lead I. [83]

3. Genetic basis

Inheritance of the BrS is via an autosomal dominant mode of transmission. The syndrome has been associated with variants in 19 different genes (Table 3), but pathogenic mutations in these genes have been associated with only 30–35% of the patients.[84] Of them, 11 to 30% present genetic defects in the alpha subunit of the sodium voltage-gated channel (*SCN5A*) and, to date, more than 300 BrS-related variants in *SCN5A* have been described. [85–87]

Figure 2 illustrates the overlap between Brugada and other inherited cardiac arrhythmia syndromes related to genetic defects in the sodium, calcium and potassium channels. 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. [88–90]

Variants in *CACNA1C* (Cav1.2), *CACNB2b* (CavB2b) and *CACNA2D1* (Cav α 2 δ) have been reported in up to 13% of probands. [91–94] Mutations in glycerol-3-phosphate dehydrogenase 1- like enzyme gene (*GPD1L*), *SCN1B* (β 1-subunit of Na channel), *KCNE3* (MiRP2), *SCN3B* (β 3- subunit of Na channel), *KCNJ8* (Kir6.1), *KCND3* (Kv4.3),

RANGRF (MOG1), *SLMAP*, *ABCC9* (SUR2A), *SNC2B* (Navβ2), *PKP2* (Plakophilin-2), *FGF12* (FHAF1), *HEY2*, and *SEMA3A* (Semaphorin) are relatively rare.[95–106] An association of BrS with *SCN10A*, a neuronal sodium channel, was recently reported.[107,108]

New susceptibility genes proposed and awaiting confirmation include the Transient Receptor Potential Melastatin Protein 4 gene (*TRPM4*) 62 and the *KCND2* gene.[109,110] Variants in *KCNH2*, *KCNE5*, *SEMA3A*, while not causative, have been identified as capable of modulating the substrate for the development of BrS.[111–114] Loss-of-function mutations in *HCN4* that cause a reduction in pacemaker current, can unmask BrS by reducing heart rate.[115]

It is important to recognize that only a small fraction of identified genetic variants in genes associated with BrS have been studied using functional expression studies to establish their pathogenicity. Very few have been studied in genetically engineered mouse models, in native cardiac cells or in induced pluripotent stem cell-derived cardiac myocytes isolated from BrS patients.

The lack of functional or biological validation of the effects of the mutations remains a severe limitation of genetic test interpretation for BrS and other inherited cardiac syndromes.[116]

Collectively, these studies suggest the possibility that the susceptibility to VT/VF and SCD may not be due to a single genetic mutation (classical Mendelian view), but rather to inheritance of multiple BrS-susceptibility variants (oligogenic) acting in concert via one or more mechanistic pathways.[102] Moreover, the phenotype of the syndrome may be modulated by hormonal (testosterone,[102,117] thyroxine[118]), and other environmental factors, as well as structural changes such as fibrosis.[119]

Genetic testing, is helpful in the identification of family members possibly at risk but less so for risk stratification or prognosis.[120]

According to the recent guidelines (HRS/EHRA consensus statement), [89] genetic testing is recommended (Class I) for relatives of an index case with an identified BrS-causative mutation. Genetic testing can be useful (Class II) “for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient’s clinical history, family history and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype”. On the other hand, the latest CCS/CHRS joint position paper and other studies suggest that a Type 1 BrS ECG alone should be enough of an indication (Class I recommendation) for genetic testing. In individuals manifesting isolated Type 2 or 3 BrS pattern, genetic testing has a Class III recommendation.[121] Although identification of a genotype may not be helpful in the approach to therapy at present time, it could be argued that with additional evidence, some genotypes may offer innovative therapeutic strategies, e.g., use of I_{K-ATP} blockers in cases involving a gain of function of I_{K-ATP} or use of I_{K_r} blockers in cases of I_{K_r} gain of function.

4. Cellular and ionic basis

The cellular basis for BrS is thought to involve an outward shift of net transmembrane current active at the end of phase 1 of the right ventricular epicardial AP. I_{to} has been shown to be most prominent in RV, particularly in the region of the RVOT.[122] Such a shift can accentuate the AP notch and lead to all-or-none repolarization at the end of phase 1 (Figure 3). When phase 1 repolarizes 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. Induction of the AP dome from epicardial sites at which it is maintained to sites at which it is lost leads to the development of phase 2 reentry, giving rise to very closely coupled extrasystoles.[123–125]

The development of prominent J waves, appearing as ST segment elevation, in the right precordial leads of BrS patients is thought to be due to accentuation of the right ventricular epicardial AP notch secondary to an outward shift in the balance of currents active at the end of phase 1.[125] A spike and dome morphology due to a prominent transient outward current (I_{to}) in ventricular epicardium, but not endocardium, generates a transmural voltage gradient that results in the electrocardiographic J wave.[126]

The ST segment is normally isoelectric because of the absence of transmural voltage gradients during the action potential plateau. Pathophysiologic conditions such as those associated with accentuation of the right ventricular AP notch lead to amplification of transmural voltage gradients and thus to accentuation of the J wave, causing an apparent ST segment elevation.[125] The repolarization waves take on a saddleback or coved appearance depending on the timing of repolarization of epicardium relative to endocardium. A delay in epicardial activation and repolarization time results in T wave inversion.

The accentuation of the action potential notch in the right ventricular outflow tract (RVOT) can produce the typical Brugada ECG without creating an arrhythmogenic substrate, as illustrated in Figure 3B. The arrhythmogenic substrate could then arise with a further shift in the balance of currents causing loss of the AP dome at some epicardial sites but not others. The loss of the action potential dome in epicardium but not endocardium results in marked transmural dispersion of repolarization and refractoriness, which is responsible for the development of a vulnerable window, as illustrated in Figure 3C. Loss of the epicardial action potential dome is usually heterogeneous, leading to the development of epicardial dispersion of repolarization. Propagation of the action potential dome from RVOT sites at which it is maintained to sites at which it is lost can cause local re-excitation via a phase 2 reentry mechanism (Figure 3D) and polymorphic VT/VF (Figure 3E and F). The phase 2 reentrant extrasystole is often concealed because it is surrounded by refractory tissue. It resides within a protected focus.

Although the genetic mutations are equally distributed between genders, the clinical phenotype is 8–10 times more prevalent in males than in females. The basis for this sex-related distinction is due to a more prominent I_{to} in the right ventricular (RV) epicardium of males vs. females.[127] The more prominent I_{to} -mediated action potential notch causes the end of phase 1 of the RV epicardial action potential to repolarize to more negative potentials

in tissue and arterially perfused wedge preparations from males, facilitating loss of the action potential plateau and the development of phase 2 reentry and polymorphic VT.

The cellular mechanisms underlying BrS have long been a matter of debate.[128,129] Two principal hypotheses have been proposed: the **repolarization** hypothesis and the **depolarization** hypothesis. The repolarization hypothesis maintains that an outward shift in the balance of currents in right ventricular epicardium can lead to repolarization abnormalities resulting in the development of the substrate for reentrant activity as well as the development of phase 2 reentry, which generates closely-coupled premature beats capable of precipitating VT/VF. The depolarization hypothesis suggests that slow conduction in the RVOT, due to fibrosis, reduces Cx43 expression leading to discontinuities in conduction. Conduction slowing is not necessarily limited to the RVOT area.

Some investigators have postulated that changes in ion channel current responsible for BrS, like loss of function I_{Na} and I_{Ca} or 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.[130] Others have argued that this is highly unlikely because conduction at critical junctions of current- to-load mismatch is exquisitely sensitive to acceleration of heart rate. The predicted behavior on the basis of this theory is opposite to that actually observed in patients with BrS; ST segment elevation typically diminished at faster heart rates. [33]

One of the arguments made in support of the depolarization hypothesis is that radiofrequency (RF) ablation of epicardial sites displaying fractionated bipolar electrograms (EGs) and late potentials in the RVOT of patients with BrS suppresses the electrocardiographic and arrhythmic manifestations of BrS. These authors concluded that the late potential and fractionated EG activity are due to conduction delays within the RVOT. [131,132] Similar conclusions were arrived at by Sacher and co-workers.[133] These authors are of the opinion that ablation of the sites of slow conduction is the basis for the ameliorative effect of ablation therapy. Szél and co-workers [134] provided a direct test of this hypothesis and using an experimental model of BrS showed that the electrophysiologic manifestation are due to a repolarization defect rather than a depolarization or conduction defect. They found that low-voltage fractionated electrogram activity similar to that observed in the RVOT of BrS patients develops as a consequence of the heterogeneous appearance of the second action potential upstroke, due to accentuation of the epicardial AP notch and not as a result of slow or delayed conduction. In addition, they showed that high frequency late potentials develop in RV epicardium due to delayed phase 2 upstroke and to concealed phase 2 reentry. Slow or delayed conduction of the primary beat was not observed in a wide variety of BrS models created by exposing canine right ventricular wedge preparations to drugs mimicking the effects of the genetic defects that have been associated with BrS. [134] These findings suggested a paradigm shift in our understanding of fractionated electrical activity, by revealing that in the setting of BrS fractionated electrograms and late potentials are due to repolarization rather than conduction defects. As we and others have often pointed out, It stands to reason that the repolarization and depolarization theories are not necessarily mutually exclusive and may indeed be synergistic. [135]

Leong and coworkers [136] recently reported a study in which the magnitude of ST elevation correlated with the degree of ajmaline-induced conduction delay in the RVOT of patients with Type I Brugada ECG, thus seemingly supporting the depolarization hypothesis. The study included 11 patients with concealed Type I BrS ECG and 2 healthy controls undergoing ECG imaging (ECGi) before and after ajmaline infusion. Activation maps and activation recovery intervals (ARI) were derived from electrograms recorded from the epicardial surface of the heart, including the right ventricle (RV), right ventricular outflow tract (RVOT), and left ventricle (LV). Conduction time was recorded from 3.5 cm segments within these regions of the heart before and after ajmaline and correlated with J point (ST segment) elevation observed in the surface ECGs. Ajmaline increased conduction delay by 5.4 ± 2.8 ms in the RVOT, 2.0 ± 2.8 ms in RV free wall and 1.1 ± 1.6 ms in LV free wall. Conduction delay in the RVOT, but not RV or LV, correlated with the degree of J point elevation in BrS-patients. The author's conclusion that the magnitude of J point (ST segment) elevation in patients with the Type I BrS pattern is attributable to conduction delay in the RVOT was challenged by Antzelevitch and Patocskaï, [137] who demonstrated that ajmaline can induce prominent ST segment elevation by accentuation the RV epicardial AP notch. They further pointed out that according to the depolarization hypothesis for ST segment elevation associated with BrS, RVOT activation delay, relative to activation of the RV, must be roughly equivalent to the duration of the ST segment elevation, typically > 200 ms [128] and that the 3.4 msec reported by Leong et al. falls far short of that requirement.

Interestingly, Elizari et al proposed another hypothesis: the neural crest hypothesis.[138] Their thesis is that the RVOT and its nearby structures come from different embryological origins from the rest of the heart expressing different physiological and anatomical characteristics. The abnormal expression of the neural crest cells would produce abnormal Cx43 expression, creating a depolarization delay and heterogeneity in the repolarization of the RVOT, producing the typical ECG observed in BrS.

5. Approach to therapy

Risk stratification analysis of patients with BrS is a crucial tool for the appropriate approach to therapy. Recommendations for the management of BrS from the recent expert consensus conference are presented in Table 4. [31]

5.1 Implantable cardioverter defibrillator

The implantation of an implantable cardioverter defibrillator (ICD) is accepted as first line therapy for prevention of SCD in high risk BrS. [139,140] It is important to recognize however, that ICDs can be associated with many complications, especially in young active individuals. [71,141,142] At 10 years post-implant, the rate of inappropriate shock and lead failure have been reported to be 37% and 29%, respectively. Remote monitoring can identify lead failure and avoid inappropriate shocks.[143] BrS patients with a first arrhythmic event documented after prophylactic ICD implantation exhibit their arrhythmic event at a later age with a higher incidence of positive family history of SCD and *SCN5A* mutations compared to those presenting with an aborted cardiac arrest. Subcutaneous ICDs (S-ICDs) are being

considered for this indication in that they are expected to be associated with fewer complications over a lifetime.[144, 145]

According to this 2016 HRS/APHRS/EHRA/SOLAECE consensus report, ICDs are considered 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, Jpeak amplitude) and patient's preference. Electrophysiologic study may be considered in asymptomatic individuals with spontaneous Type 1 Brugada pattern. If VT/VF is inducible, an ICD should be considered.[31] More recent studies argue in favor of using two or less extrastimuli to induce VT/VF.[69,146] Finally, the Task Force indicated that ICDs are not indicated in asymptomatic patients without any of the above characteristics (Figure 4).

5.2 Radiofrequency ablation therapy

The use of ablation to suppress focal arrhythmogenic substrates in BrS stems back more than a decade. Several studies reported on the effect of focal endocardial radiofrequency ablation (RFA) of sites generating monomorphic extrasystoles.[147,148–150]

A promising innovation in the treatment of BrS using RFA was reported by Nademanee et al. in 2011[131] The authors showed that RFA of epicardial sites displaying late potentials and fractionated bipolar electrograms (EGs) 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 non-inducible 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±6months) showed no recurrent VT/VF, with only 1 patient on medical therapy with amiodarone. Case reports have been published in support of these ameliorative effects of ablation.[149] Additional evidence in support of the effectiveness of epicardial substrate ablation was provided by Sacher et al. and Shah et al.[133,148]

Using a canine coronary-perfused right ventricular wedge model, Patocskaï et al. tested the hypothesis that ablation suppresses the electrocardiographic and arrhythmic manifestations of BrS by destroying sites of abnormal conduction. Epicardial regions displaying fractionated electrograms and late potentials in the experimental models of BrS were ablated. Ablation of the RV epicardium suppressed the manifestation of J waves and ST segment elevation and abolished all arrhythmic activity (Figure 5). These findings did not provide support for the depolarization hypothesis but demonstrated that RFA provides an ameliorative effect by destroying the cells with the most prominent I_{to} -mediated notch, thus eliminating the source of repolarization abnormalities responsible for phase 2 reentry and VT/VF [135]

Brugada and co-workers used substrate epicardial mapping in order to identify areas of abnormal electrograms as target of RFA. Epicardial low voltage areas were identified and quantified during sinus rhythm before and after flecainide, and abnormal electrograms inside these areas were tagged for RFA delivery. Abnormal electrograms were defined as those with amplitude <1.5 mV or associated wide duration (>80 ms), multiple (>3), or delayed

components extending beyond the end of the QRS complex. Flecainide was used to identify functional epicardial substrates. Treatment with RFA eliminated abnormal bipolar electrograms, normalized ST segment elevation on right precordial leads of ECG, and decreased VT/VF inducibility in all patients.[132]

Ablation therapy can be life-saving 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.

5.3 Pharmacologic approach to therapy

A pharmacologic approach to therapy is recommended in the case of electrical storms, as an adjunct to ICD and as preventative therapy for asymptomatic patients at risk for the development of life-threatening arrhythmic events.[33] Because the arrhythmogenic substrate in BrS develops as a consequence of an outward shift in the balance of current during phase 1 of the epicardial action potential, the principal goal of therapy is to produce an inward shift in the balance of currents. This can be accomplished either by boosting inward calcium current using β -adrenergic agents or phosphodiesterase III inhibitors or by reducing outward currents including the transient outward current (I_{to}) using agents such as quinidine.[151] **Table 5** lists the various pharmacologic agents investigated in recent years. Amiodarone and β -blockers have been shown to be ineffective; whereas Class IC antiarrhythmic drugs, such as flecainide and propafenone, and class IA agents, such as procainamide, are contraindicated because of their effects to unmask BrS and to induce life-threatening arrhythmias (see www.brugadadrugs.org). Disopyramide, a class IA antiarrhythmic, has been shown to normalize ST segment elevation in some BrS patients while it unmasks the syndrome in others. [152]

5.3.1 Transient Outward Current Blockers—Because a prominent I_{to} -mediated notch is central to the mechanism underlying BrS, the most rationale approach to therapy, regardless of the ionic or genetic basis for the disease, is to partially inhibit I_{to} . Unfortunately, cardio-selective and I_{to} -specific blockers are not currently available. 4-aminopyridine (4-AP), although relatively selective for I_{to} in the ventricles of the heart, is not cardio-selective because it inhibits I_{to} throughout the nervous system. It is very effective in suppressing arrhythmogenesis in experimental models of the Brugada syndrome,[153] but is unlikely to be of clinical benefit because of neurally-mediated and other side effects.

5.3.2 Quinidine—The only drug currently on the market 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. Experimental studies have shown that quinidine is effective in restoring the epicardial action potential dome and normalizing the ST segment, thus preventing the development of phase 2 reentry and polymorphic VT, regardless of which pharmacologic agents were used to mimic the BrS-phenotype.

Recent experimental studies suggest that quinidine has a protective effect against hypothermia-induced VT/VF in a J wave syndrome model.[154] Many studies support the effectiveness of quinidine in normalizing ST segment elevation and preventing arrhythmic events in patients with the BrS. [155–160] Belhassen and coworkers examined the effects of

quinidine to prevent inducible and spontaneous VT/VF, all 25 patients enrolled had inducible VF at baseline. Relatively high doses of quinidine (1483 ± 240 mg) were used and shown to prevent VF induction in 22 of the 25 patients (88%). With a follow-up period of 6 months to 22.2 years, all patients survived. Of 19 patients treated with oral quinidine for 6 to 219 months (56 ± 67 months), none developed any arrhythmic events. The main side effect, diarrhea, occurred in 36% of patients administered quinidine and was readily reversed after drug discontinuation. The study concluded that quinidine effectively suppresses spontaneous as well as inducible VT/VF 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 undesirable or not feasible. These results are consistent with those reported the same group in prior years [161,162] and subsequently by other investigators.[163] Hermida et al. reported 76 % efficacy in prevention of VF induced by PES.[164] In a more recent trial conducted at two French centers, 44 asymptomatic BrS patients with inducible VT/VF were enrolled (47 ± 10 years, 95% male). Of these, 34 (77%) were no longer inducible while treated with 600 mg/day hydroquinidine (HQ) for 6.2 ± 3 years. Among the 10 other patients (22%), who remained inducible and received ICD (Group PVS+), none received appropriate shocks during a mean follow-up of 7.7 ± 2 years. The overall annual rate of arrhythmic events was 1.04%, without significant difference between inducibility under HQ. One-third of patients experienced device-related complications. [164]

After evaluating the clinical history of symptomatic patients with recurrent arrhythmias and frequent ICD discharges, Marquez et al. evaluated reported that low doses of quinidine, as adjunctive therapy, completely prevented arrhythmias in 85 % of the patients (median follow-up of 4years).[159] The recent HRS/EHRA/APHRS expert consensus statement, gave quinidine a Class IIa recommendation in BrS patients who are qualified for an ICD but in whom hindering factors are present, Class IIa in ICD-patients with electrical storms, and Class IIb recommendation in asymptomatic BrS-patients displaying a spontaneous Type I ECG.[31] The development of a more cardio-selective and Ito-specific blocker would be a most welcome addition to the limited therapeutic armamentarium currently available to combat this disease.

Figure 6 illustrates the effect of quinidine on the BrS phenotype induced in a coronary-perfused canine right ventricular wedge preparation. Quinidine ($10 \mu\text{M}$) via its effect to inhibit I_{to} reversed the repolarization defects, restored action potential homogeneity, normalized the ECG and abolished phase 2 reentry and associated late potentials evident on the bipolar electrogram.

5.3.3 Wenxin Keli—Wenxin Keli, a traditional Chinese medicine (TCM), in addition to its actions to suppress atrial fibrillation by atrial-selective inhibition of I_{Na} -dependent parameters, [165] has been shown to inhibit I_{to} and thus to suppress VT/VF in experimental models of BrS when combined with low concentrations of quinidine ($5 \mu\text{M}$). Wenxin Keli has also been reported to suppress ischemia- induced VAs.[166]

5.3.4 Bepridil—Bepridil has been reported to suppress VT/VF in patients with BrS.[167–170] Bepridil's action is thought to be mediated by: 1) inhibition of I_{to} ; 2) augmentation of

I_{Na} via up-regulation of the sodium channels[171]; and 3) prolongation of QT interval at slow rates, thus increasing the QT/RR slope.[167,170]

5.3.5 Acacetin—The natural flavone acacetin has been demonstrated to inhibit transient outward potassium current (I_{to}) in human atrial myocytes in a frequency-dependent manner. [172] The ameliorative effect of this agent in the setting of BrS has not been reported as yet and is being investigated by our group.

5.3.6 Calcium channel current agonists

5.3.6.1 β adrenergic agonists: Agents that augment the L-type calcium channel current, such as β adrenergic agonists like isoproterenol, denopamine or orciprenaline, are effective as well.[125,153,168,173–175] Isoproterenol, sometimes in combination with quinidine, has been reported to successfully suppress VF storms and to normalize the ST elevation, particularly in children. [155,162,163,176–178] Spontaneous VF in patients with BrS is often mediated by an increase in vagal tone and is amenable to treatment by an increase of sympathetic tone via the administration of isoproterenol. In the latest HRS/EHRA/APHRS consensus document, isoproterenol is a Class IIa indication for BrS patients presenting with electrical storms (Figure 4).[31]

5.3.6.2 Phosphodiesterase III inhibitors: The phosphodiesterase III inhibitor cilostazol has been proposed as another promising therapy for BrS.[168,173,179] Cilostazol has been shown to normalize ST segment elevation, most likely by augmenting calcium current (I_{Ca}) as well as by reducing I_{to} secondary to an increase in cAMP and heart rate.[179] Other effects of cilostazol, such as inhibition of adenosine uptake [180] may contribute as well. Shinohara et al. [181] report that phosphodiesterase III inhibition in combination with bepridil prevents VF-episodes in BrS. It is noteworthy that failure of cilostazol in the treatment of a BrS-patient has been reported in a single case report.[182] Milrinone, another phosphodiesterase III inhibitor, was identified as a more potent alternative to cilostazol in suppressing ST elevation and arrhythmogenesis in an experimental model of BrS.[183] No clinical reports have appeared as yet.

Figure 7 shows the effect of milrinone and cilostazol to suppress phase 2 reentry-induced polymorphic ventricular tachycardia (VT) in a right ventricular wedge model of Brugada syndrome. Milrinone (2.5 μ M, upper panel) and cilostazol (10 μ M, lower panel) reduced the magnitude of the epicardial AP notch, restored the AP dome and suppressed phase 2 reentry and polymorphic VT. [183]

5.3.7 Agents that augment I_{Na}

5.3.7.1 Dimethyl lithospermate B: Agents that augment I_{Na} active during the early phases of the action potential, such as dimethyl lithospermate B (dmLSB), have also been suggested to be of value in the pharmacologic approach to therapy of BrS. Figure 8 shows an example of the effectiveness of dmLSB to suppress VT/VF in experimental models of BrS.

As discussed above, the action of bepridil is in part due to augmentation of peak I_{Na} via up-regulation of the sodium channels. [171]

5.3.8 Anti-androgen therapy—Despite equal genetic transmission, the clinical phenotype of BrS is 8 to 10 times more prevalent in males than in females.[125] The basis for this sex-related distinction is still unknown, but there is evidence that the predominance of the BrS in the male population may have a hormonal basis. The reversion of the phenotype in two patients with prostate cancer after surgical castration points to the role of androgens in the development of the disease.[184] Moreover, male patients with BrS have been reported to have higher testosterone levels than age-matched normal controls.[185] Other studies showed augmentation of the ST segment elevation at night, when the serum testosterone levels are high.[186] Previous studies demonstrated that anti-androgen therapy lowered the ST elevation in leads V₂ and V₃ matching control females.[186]

The hypothesis that testosterone modulates ion currents underlying the epicardial action potential notch requires further investigation. Our group is currently testing the hypothesis that testosterone modulates the expression of I_{to} and that anti-androgen therapy exerts an ameliorative effect in BrS by reducing expression of I_{to}.

6. Conclusion

The pathophysiology of Brugada syndrome has advanced considerably in recent years. Like other inherited cardiac arrhythmia syndromes, the development of the BrS phenotype is thought to be multifactorial, the result of a combination of genetic and environmental factors that can differ considerably from one patient to another. The implantation of an implantable cardioverter defibrillator (ICD) is accepted as first line therapy for prevention of SCD in high risk patients. Epicardial radiofrequency ablation is useful in select cases, particularly in patients who experience repeated appropriate ICD shocks. A pharmacologic approach to therapy is important as an adjunct to ICD therapy or as an alternative when ICD implantation is not an appropriate solution, particularly for treatment of infants and young children. The pharmacologic approach to therapy is geared to producing an inward shift in the balance of current flowing during the early phases of the epicardial action potential, particularly in the RVOT. This can be achieved by inhibition of I_{to} or augmentation of I_{Ca} or I_{Na} or by a combination of these effects. There is a dire need for development of cardio-selective and ion-channel-specific I_{to} blockers for treatment of BrS as well as other syndromes, including early repolarization syndrome. Because I_{to} expression is modulated by hormonal factors, anti-androgens may prove helpful in severe cases, pending further clinical evidence in support of this approach

7. Expert commentary

Since BrS was first described in 1992, major advances have been realized with respect to diagnosis and management of the disease. The 2016 HRS/EHRA/APHRS/SOLAECE J-Wave Syndrome Consensus Report proposed a scoring system to facilitate diagnosis of Brugada syndrome (BrS) taking into account electrocardiographic recordings, genetic results, clinical characteristics and family history. Recent studies have validated this approach. ICD implantation is considered the most effective means of preventing SCD in patients with BrS. Recently, Subcutaneous ICDs (S-ICDs) are being implemented and are expected to be associated with fewer complications over a lifetime, especially in younger

more active individuals. The important strides in the pharmacologic approach to therapy notwithstanding, there remains an urgent need for development of cardio-selective and ion-channel-specific I_{to} blockers for treatment of BrS. A reduction in I_{to} with or without a parallel augmentation of inward current secondary to an increase in I_{Ca} or slowed inactivation of I_{Na} are important targets for drug development. These pharmacological solutions are also expected to be of benefit in other J wave syndromes, including the early repolarization syndrome (ERS). Our group is currently evaluating the effectiveness of natural flavone acacetin and its congeners as safe and effective therapy of both BrS and ERS. Because I_{to} expression is modulated by hormonal factors, anti-androgen therapy may prove helpful in severe cases, pending further clinical evidence in support of this approach. We and others are currently evaluating the effectiveness of anti-androgen therapy in experimental models of BrS.

8. Five-year view

Our hope is that within the next five years the implementation of routine genetic screening will uncover many of the missing genetic causes and modulators of BrS, enabling better identification of family members at risk. Moreover, clinical and basic science research will identify additional electrocardiographic, structural imaging, and other risk factors enabling better risk stratification of the disease. We expect, that safe and effective ion channel-specific and cardio-selective transient outward current blockers will be identified enabling a major advance in the pharmacological approach to therapy together with greater implementation of S-ICD will resulting in fewer long-term complications.

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* of interest

** of considerable interest

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Key issues:

- The pathophysiology of Brugada syndrome has advanced considerably in recent years, yet the genetic basis for the syndrome remains unknown in greater than 65% of cases, risk stratification of patients at risk for SCD is not optimal and many of the pharmacological approaches to therapy remain to be studied in randomized double blind clinical trials. Like other inherited cardiac arrhythmia syndromes, including the long QT syndromes, the development of the BrS phenotype is multifactorial, involving a combination of genetic and environmental factors.
- Additional genome wide association studies (GWAS), Whole genome (WGS) and whole exome (WES) studies as well as targeted Next Generation Studies (NGS) are desirable to uncover the missing genetic causes of BrS.
- The implantation of an ICD is first line therapy for prevention of SCD in high risk patients. Epicardial radiofrequency ablation is useful in select cases, particularly in patients who experience repeated appropriate ICD shocks. Long term outcomes of epicardial ablation for BrS remains to be determined.
- A pharmacologic approach to therapy is important in treating electrical storms, as an adjunct to ICD therapy or as an alternative when ICD implantation is not an appropriate solution, particularly for treatment of infants and young children.
- The pharmacologic approach to therapy is geared to producing an inward shift in the balance of current flowing during the early phases of the epicardial action potential, particularly in the RVOT. This can be achieved by inhibition of Ito or augmentation of ICa or INa or by a combination of these effects.

Figure 1.

Three types of ST segment elevation associated with Brugada syndrome. Type one is characterized by ST segment elevation ≥ 2 mm (0.2 mV) in ≥ 1 right precordial leads (V1-V3) positioned in the 4th, 3rd or 2nd intercostal space. Type 2 is characterized by ST segment elevation of ≥ 0.5 mm (generally ≥ 2 mm in V2) in ≥ 1 right precordial lead (V1-V3), followed by a convex ST. The ST segment is followed by a positive T wave in V2 and variable morphology V1. Type 3 is characterized by either a saddleback or coved appearance with an ST-segment elevation of <1 mm. Only Type 1 is diagnostic of BrS. (Modified from [33], with permission)

Figure 2.

Schematic showing the three categories of overlap syndromes resulting from genetic defects and loss of function of sodium (I_{Na}) and/or calcium (I_{Ca}) channel currents. In the absence of I_{to} or I_{K-ATP} , loss-of-function mutations in the inward currents result in various manifestations of conduction disease. In the presence of prominent I_{to} or I_{K-ATP} , loss-of-function mutations in inward currents cause conduction disease as well as the J wave syndromes (Brugada and Early Repolarization Syndromes). The genetic defects that contribute to BrS and ERS can also contribute to the development of long QT and conduction system disease. (Modified from [33], with permission)

Figure 3.

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 as well as a transmural dispersion of repolarization. **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 [213], with permission)

Figure 4.

Indications for therapy of patients with Brugada syndrome. ES, extrastimuli at RV apex; ICD, implantable cardioverter defibrillator; ILR, Implantable loop recorder; NAR, nocturnal agonal respiration; pVT, polymorphic VT; SCD, sudden cardiac death; VT, ventricular tachycardia. (Modified from [33], with permission)

Figure 5.

Radiofrequency ablation of **epicardium** (Epi) suppresses the electrocardiographic and arrhythmic manifestations of Brugada syndrome in coronary-perfused canine RV wedge model generated using a combination of the I_{to} agonist **NS5806** and calcium channel blocker **verapamil**. Each column shows action potentials (AP) simultaneously recorded from an endocardial (Endo) and 2 epicardial (Epi1 and Epi2) sites together with a bipolar epicardial electrogram (Bipol. Epi EG) and an ECG recorded across the bath. **A:** Control. **B,C,D:** The addition of NS5806 7µM and verapamil 2µM to the perfusate induced pronounced J waves and phase 2 reentry depicting as abnormal electrogram activity when concealed, and giving rise to ventricular fibrillation when it succeeds in propagating out. **E, F:** Recovery period of the preparation after epicardial ablation. Note the normalization of ST-elevation after 70 min. Action potential recordings were obtained from midmyocardial (Mid) and subepicardial layers due to inactivation of the epicardium. **G:** With superficially ablated epicardium, the re-administration of the provocative agents (in the same concentration as before) did not produce pronounced J waves or arrhythmic activity. **H:** Photo of wedge preparation after epicardial ablation to a depth of 1–2 mm, taken at the end of the experiment. (Reproduced from [135], with permission).

Figure 6.

Effect of quinidine (10 μ M) to reverse the repolarization defects responsible for phase 2 reentry and associated late potentials and fractionated epicardial (Epi) electrogram (EG) activity. 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 the I_{to} agonist NS5806 (5 μ M) and the calcium channel blocker verapamil (2 μ M) to induce the Brugada phenotype. The addition of quinidine (10 μ M) to the coronary perfusate reversed the repolarization

defects, restored action potential homogeneity, normalized the ECG and abolished phase 2 reentry and associated late potentials on the bipolar electrogram (Bipolar EG). Endo: endocardium. Reproduced with permission from [134].

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Figure 7.

Effect of milrinone and cilostazol to suppress phase 2 reentry-induced polymorphic ventricular tachycardia (VT) in a right ventricular wedge model of Brugada syndrome. The combination of NS5806 (5 μ M) and verapamil (2 μ M) induces heterogeneous loss of the epicardial (Epi) action potential dome. Phase 2 reentry occurs as the dome propagates from Epi 1 to Epi 2, triggering an episode of polymorphic VT. Addition of 2.5 μ M milrinone (upper panel) or 10 μ M cilostazol (lower panel) abolishes phase 2 reentry and polymorphic

VT. ECG = electrocardiogram; Epi=epicardium; Endo = endocardial. Reproduced with permission from [183].

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Figure 8.

Effect of dimethyl lithospermate B (dmLSB), an extract of Danshen, on phase 2 reentry induced in three different experimental models of BrS created using canine right ventricular wedge preparations. Terfenadine (5 μ M, **A.**), verapamil (5 μ M, **B.**), or pinacidil (6 μ M, **C.**) induced accentuation of the epicardial action potential notch and heterogeneous loss of the epicardial action potential dome, leading to the development of prominent J waves appearing as ST segment elevation. Phase 2 reentry developed as the dome is propagated from Epi 1 to Epi 2, triggering either a closely coupled extrasystole or polymorphic ventricular

tachycardia. In all 3 models, addition of dmLSB (10 μ M) normalized the ST segment and abolished phase 2 reentry and resultant arrhythmias. . Reproduced with permission from [214].

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Table 1.

Proposed Shanghai Score System for Diagnosis of Brugada Syndrome.

<u>I. ECG (12-Lead/Ambulatory)</u>	Points
A. Spontaneous type 1 Brugada ECG pattern at nominal or high	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 w/ provocative drug challenge	2
*Only award points once for highest score within this category. One item from this category must apply.	
<u>II. Clinical History*</u>	
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
*Only award points once for highest score within this category	
<u>III. Family History</u>	
A. 1st or 2nd degree relative with definite BrS	2
B. Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a 1st or 2nd degree relative	1
C. Unexplained SCD < 45 years in first/second degree relative with negative autopsy	0.5
*Only award points once for highest score within this category	
<u>IV. Genetic Test Result</u>	
A. Probable pathogenic mutation in BrS-susceptibility gene	0.5
<u>SCORE (Requires at least 1 ECG finding)</u>	
> 3.5 points - Probable/Definite BrS	
2 – 3 points - Possible BrS	
< 2 points - Non-Diagnostic	

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Table 2.

Drugs used to unmask the Brugada Syndrome phenotype.

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

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Table 3.

Genes associated with Brugada Syndrome

	Locus	Gene/Protein	Ion Channel	% of Probands	Reference
BrS 1	3p21	SCN5A/Nav1.5	↓ INa	11–28%	[87,187]
BrS 2	3p24	GPD1L	↓ INa	Rare	[188,189]
BrS 3	12p13.3	CACNA1C/Cav1.2	↓ ICa	6.6%	[93,189]
BrS 4	10p12.33	CACNB2b/Cavβ2b	↓ ICa	4.8%	[93,189]
BrS 5	19q13.1	SCN1B/Navβ1	↓ INa	1.1%	[190]
BrS 6	11q13–14	KCNE3/MiRP2	↑ Ito	Rare	[98]
BrS 7	11q23.3	SCN3B/Navβ3	↓ INa	Rare	[191]
BrS 8	12p11.23	KCNJ8/Kir6.1	↑ IK-ATP	2%	[95,192]
BrS 9	7q21.11	CACNA2D1/Cavα2δ1	↓ Ica	1.8%	[91]
BrS 10	1p13.2	KCND3/Kv4.3	↑ Ito	Rare	[193]
BrS 11	17p13.1	RANGRF/MOG1	↓ INa	Rare	[194]
BrS 12	3p21.2-p14.3	SLMAP	↓ INa	Rare	[195]
BrS 13	12p12.1	ABCC9/SUR2A	↑ IK-ATP	Rare	[196]
BrS 14	11q23	SCN2B/Navβ2	↓ INa	Rare	[97]
BrS 15	12p11	PKP2/Plakophilin-2	↓ INa	Rare	[100]
BrS 16	3q28	FGF12/FHAF1	↓ INa	Rare	[101]
BrS 17	3p22.2	SCN10A/Nav1.8	↓ INa	5–16.7%	[102,107,108,197]
BrS 18	6q	HEY2 (transcriptional factor)	↑ INa	Rare	[102,198]
BrS 19	7p12.1	SEMA3A, Semaphorin	↑ Ito	Rare	[114]

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Table 4.

Device and Pharmacologic Approach to Therapy of the Brugada Syndrome.

Devices and Ablation	
ICD [139,142]	
Radiofrequency Ablation [131,132,135,199,200]	
? Pacemaker [201,202]	
Pharmacologic Approach to Therapy	
<i>Ineffective or Proarrhythmic</i>	
Amiodarone[203]	
β Blockers[203]	
<i>Class IC antiarrhythmics</i>	
Flecainide[204]	
Propafenone[205]	
? Disopyramide[152]	
<i>Class IA antiarrhythmics</i>	
Procainamide[206]	
<i>Effective for Treatment of Electrical Storms</i>	
β adrenergic agonists – isoproterenol[207-209], denopamine[168], orciprenaline [174,175]	
Phosphodiesterase III Inhibitors-cilostazol [173,179,183]	
<i>Effective General Therapy</i>	
Quinidine [153,155-160,207]	
Bepridil - Ito-inhibition and INa augmentation [170]	
Cilostazol combined with bepridil [181]	
<i>Experimental Therapy</i>	
Ito Blockers - cardioselective and ion channel specific	
Quinidine[153]	
4-aminopyridine[153]	
Tedisamil[210]	
AVE0118[211]	
Acacetin[172]	
PDE-3-inhibitors	
Cilostazol – Increase in ICa and inhibition of Ito [154]	
Milrinone – ICa augmentation [154]	
Traditional Chinese Medicine	
Dimethyl lithospermate B – Increase in INa due to slow inactivation	
Wenxin Keli - combined Ito-block and tyramine-like effect [212]	