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Brugada Syndrome. Clinical, Genetic, Molecular, Cellular and Ionic Aspects

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Abstract

The Brugada syndrome (BrS) is an inherited cardiac arrhythmia syndrome first described as a new clinical entity in 1992. Electrocardiographically characterized by distinct coved type ST segment elevation in the right precordial leads, the syndrome is associated with a high risk for sudden cardiac death in young adults, and less frequently in infants and children. The ECG manifestations of the BrS are often concealed and may be unmasked or aggravated by sodium channel blockers, a febrile state, vagotonic agents, as well as by tricyclic and tetracyclic antidepressants. An implantable cardioverter defibrillator (ICD) is the most widely accepted approach to therapy. Pharmacological therapy is designed to produce an inward shift in the balance of currents active during the early phases of the right ventricular action potential and can be used to abort electrical storms or as an adjunct or alternative to device therapy when use of an ICD is not possible. Isoproterenol, cilostazol and milrinone boost calcium channel current and drugs like quinidine, bepridil and the Chinese herb extract Wenxin Keli inhibit the transient outward current, acting to diminish the action potential (AP) notch and thus to suppress the substrate and trigger for VT/VF. Radiofrequency ablation of the right ventricular outflow tract epicardium of BrS patients has recently been shown to reduce arrhythmia-vulnerability and the ECG-manifestation of the disease, presumably by destroying the cells with more prominent AP notch. This review provides an overview of the clinical, genetic, molecular and cellular aspects of the BrS as well as the approach to therapy.

1. Clinical Characteristics and Diagnostic Criteria

The Brugada syndrome typically manifests in the third or fourth decade of life (average age of 41±15 years), although patients have been diagnosed with the syndrome at an age as young as 2 days and as old as 84 years. Prevalence of BrS ECG in the general population

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varies significantly among continents, countries and ethnic groups.[1–22] The prevalence of the disease is highest in Southeast Asia where the syndrome is endemic, estimated to be greater than 5 per 10,000 inhabitants.[23] In Japan, a Brugada syndrome ECG (Type 1) is observed in 12 per 10,000 inhabitants; Type 2 and 3 ECGs, which are not diagnostic of BrS, are much more prevalent, appearing in 58 per 10,000 inhabitants.[24] The true prevalence of the disease in the general population is difficult to estimate because the ECG pattern is often concealed.

Sudden unexplained nocturnal death syndrome (SUNDS also known as SUDS) and Brugada syndrome have been shown to be phenotypically, genetically and functionally the same disorder.[25] Most patients with a Brugada ECG are asymptomatic, usually diagnosed incidentally and they often remain asymptomatic for life. A small minority develop, nocturnal agonal breathing, syncope and/or palpitations, leading to ventricular tachycardia/fibrillation (VT/VF) or SCD. Approximately 20% of BrS patients also develop supraventricular arrhythmias, including atrial flutter, fibrillation, AV nodal reentry and pre-excitation syndromes such as WPW syndrome. Atrial fibrillation (AF) is reported in approximately 10–20% of cases. AV nodal reentrant tachycardia (AVNRT) and Wolf-Parkinson-White (WPW) syndrome have been described by Eckart et al. [26] Prolonged sinus node recovery time and sino-atrial conduction time [27] as well as slowed atrial conduction and atrial standstill have been reported in association with the syndrome. [28] Ventricular inducibility is positively correlated with a history of atrial arrhythmias [29]. The incidence of atrial arrhythmias is 27% in Brugada syndrome patients with an indication for ICD vs 13% in patients without an indication for ICD, suggesting a more advanced disease process in patients with spontaneous atrial arrhythmias. [29]

The Brugada syndrome is characterized by an ST segment elevation in the right precordial leads. Three types of ST segment elevation are generally recognized [30–32]. Type 1 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, polymorphic VT or VF, 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 criteria.[33] The diagnosis of BrS hinges exclusively on the presence of a Type 1 ST segment elevation in one or more right-precordial lead (V1–V3), [34] spontaneously or in the presence of provocative agents, regardless of presence or absence of symptoms. This is a major departure from the original recommendation of the 2002 and 2005 Consensus Conferences.[31, 32, 35] While this may serve to draw more attention to the syndrome, it disregards the fact that many subjects manifesting a Brugada pattern remain asymptomatic throughout life.

Patients with a Brugada Type 1 ECG have an approximate cardiac event-rate/year of 7.7% in patients with aborted SCD, 1.9% in patients with syncope, and 0.5% in asymptomatic patients.[36] Sodium channel blockers, including ajmaline, procainamide, flecainide, disopyramide, propafenone and pilsicainide are useful in the differential diagnosis when ST segment elevation is not diagnostic under baseline conditions.[37–41] However a negative I_{Na}-block test does not exclude a latent form of BrS (e.g. negative predictive value of flecainide-

testing is 36%).[40, 42] Ajmaline and pilsicainide seem to be more effective tools in unmasking BrS, compared to flecainide [43, 44] or procainamide[38]. The electrocardiographic manifestations of the Brugada syndrome when concealed can be also be unmasked by bradycardia, febrile state or with vagotonic agents. [37, 45–50]

Placement of the right precordial leads in a superior position (one or two intercostal space above normal) can increase the sensitivity of the ECG for detecting the Brugada phenotype in some patients, both in the presence or absence of a drug challenge. [51–5354–56]

There are several conditions that produce a Brugada-like ECG-morphology, which should be distinguished from Brugada syndrome. They can be divided into two main categories: acute and persistent conditions. The most commonly observed acute conditions are acute coronary events, pericarditis, myocarditis, pulmonary embolism, metabolic disorders, impaired ion-balance, dissecting aorta aneurism, thiamine deficiency, electric shock and certain pharmacologic agents (see below)[57]. These manifestations usually disappear with cessation of the provoking event. Most common permanent conditions producing right precordial ST-elevation are: left ventricular hypertrophy, athlete's heart, right bundle branch block (RBBB), pectus excavatum, septal hypertrophy, arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), autonomic nervous system abnormalities, Duchenne-dystrophy, Friedreich's ataxia, mediastinal tumor and Chagas disease[31, 58–60]. Some investigators have labelled these "phenocopies" indicating that they mimic the phenotype without a genetic predisposition. We would prefer to avoid this term because data as to a genetic predisposition is lacking in almost all cases.

Additionally, inappropriate settings of the recording device can be misleading. In some circumstances, highly-set low cut filters can lead to "false" ST-elevation or altered shape.[58, 61, 62]

Differentiating RBBB from BrS is not always easy, particularly because RBBB has been reported to mask BrS.[63, 64] 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 [58, 65, 66]. Thirty-eight consecutive patients with either Type 2 or Type 3 Brugada patterns that were referred for sodium block challenge were included in the study. Before administration of the provocative agent, α and β angles alone and in combination with QRS duration were measured from ECG leads V1 and/or V2 showing incomplete RBBB:

1. α angle was defined as the angle between a vertical line and the down slope of the r'-wave. Patients with BrS displayed wider α angles than patients with incomplete RBBB.
2. β angle was defined as the angle between the upslope of the S-wave and the down slope of the r'-wave. The mean β angle was significantly smaller in the 14 patients with incomplete RBBB than the 24 patients with BrS (positive response to sodium block) 36 ± 20° vs. 62 ± 20° ($p < 0.01$), respectively.

When the angles were combined with QRS duration, it improved discrimination. We must await further tests of the utility and validity of these diagnostic tools.

While most cases of BrS display prominent J waves, often appearing as ST segment elevation, limited to the right precordial leads, isolated cases of inferior lead [67] or left precordial lead [68] ST segment elevation have been reported in Brugada-like syndromes, in some cases associated with *SCN5A* mutations [69]. Coexistence of inferolateral early repolarization (ER) in BrS is not uncommon and is a recently identified risk factor for ventricular fibrillation.[7071, 72] 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).[73]

Minor prolongation of the QT-interval may accompany ST segment elevation in the Brugada syndrome .[41, 74, 75] The QT-interval is prolonged more in the right vs. left precordial leads, probably due to a preferential prolongation of action potential duration (APD) in RV epicardium secondary to accentuation of the action potential notch. [76, 77] Depolarization abnormalities including prolongation of P wave duration, PR- and QRS-intervals are frequently observed, particularly in patients linked to *SCN5A* mutations.[78] PR prolongation likely reflects HV conduction delay. [74]

Risk stratification in BrS

Because patients with BrS have a relatively low annual rate of cardiac events, risk stratification is critical in determination of appropriate therapy.

I. Commonly accepted risk factors

- Spontaneous Type 1 BrS ECG
- History of cardiac events or syncope likely due to VT/VF[33, 36, 79, 80]
- Aborted sudden cardiac death
- Documented VT/VF
- Nocturnal agonal respiration
- Late potentials on epicardial bipolar electrogram or SAECG [81–87]
- T wave amplitude variability [82]
- Short ventricular refractory period (VRP < 200 ms) [79]
- Fragmented QRS [79, 88]
- Prolonged QRS duration [89]
- Early repolarization pattern in the inferolateral leads. [71, 72]

II. 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.[36, 80, 90, 91]

Inducible VT/VF: Inducibility of VT/VF using programmed electrical stimulation (PES) was considered to be a reliable predictor of arrhythmic events in early studies, more recent

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, 79, 80, 90–94] It is noteworthy, that when PES is limited to one or two extrastimuli, the results are more prognostic than with triple extrastimuli.[95]

III. Promising new risk stratifiers

- Increased Tpeak-Tend interval as a marker of dispersion of repolarization [96–101]
- Decreased QT/RR-variability[102]
- Augmented ST-elevation during recovery from exercise[103]
- Early heart rate recovery after exercise testing [104]
- High daily fluctuation of ECG and SAECG parameters[105].

2. Genetic Basis

Inheritance of the Brugada syndrome is via an autosomal dominant mode of transmission. Mutations in 19 genes have been identified as associated with the Brugada phenotype (Table 1). These mutations cause either a decrease in inward sodium or calcium current or an increase in outward potassium currents resulting in an outward shift in the balance of current active during the early phases of the action potential.

1) Mutations causing a loss of function of sodium channel current

SCN5A—The first gene to be linked to the Brugada syndrome is ***SCN5A***, the gene encoding for the α-subunit of the voltage-gated cardiac sodium channel ($Na_v1.5$) [106]. To date more than 300 BrS-related mutations in SCN5A have been described [107–109], accounting for the vast majority of BrS genotype-positive cases but only 11 to 28% of total BrS probands.[110] Several of these mutations have been functionally expressed and shown to cause a loss-of-function of I_{Na}.

GPD1-L—More than a decade ago, Weiss et al. described a new BrS-associated locus, near to *SCN5A*.[111] The locus was later identified to be the ***GPD1-L*** gene, encoding the glycerol-3-phosphat dehydrogenase 1 -like protein[112], which has been found to be in close structural and functional association with $Na_V1.5$. [113]. Impaired enzymatic activity leads eventually to decreased I_{Na}, via *GPD1L*-dependent phosphorylation of $Na_v1.5$. [114]

SCN1B—BrS-related mutations in ***SCN1B*** gene, encoding the auxiliary $Na_{V\beta}1$ subunit of the voltage-gated cardiac sodium channel, was first identified to cause a loss function of peak I_{Na} by Watanabe et al. [115] In a subsequent study, co-expression of mutant **SCN1B** with WT-SCN5A and WT-*KCND3* (separately) induced a 55.6% decrease in peak I_{Na} and 70.6% gain of function in I_{to}, moreover, co-immunoprecipitation revealed structural association between $Na_V\beta1B$, $Na_V1.5$ and $K_V4.3$, suggesting that the elevated level of transient outward potassium current is predominantly responsible for pathogenesis in these cases of BrS.[116]

SCN3B—Hu et al. reproted missense mutations in ***SCN3B*** encoding the Navβ3 subunit of the cardiac sodium channel, which led to a decrease in peak sodium current density, accelerated inactivation, and slowed reactivation. The study revealed that the mutation in this subunit impaired the intracellular transport and cell surface expression of the cardiac sodium channel. [117] A further study by Ishikawa et al confirmed these findings. [118]

SCN2B—The ***SCN2B*** gene encodes the β2-subunit of the cardiac sodium channel. Mutation in the gene leads to a significant reduction in sodium current density due to a decreased $Na_v1.5$ cell surface expression[119].

SCN10A—Hu et al recently identified ***SCN10A*** as a major susceptibility gene for BrS. The gene encodes $Na_v1.8$, a neuronal sodium channel, which appears to play a role in the heart. The study showed that coexpression of *SCN5A*-WT with *SCN10A*-WT results in a gain of function in I_{Na}, whereas co-expression of *SCN5A*-WT with *SCN10A*-mutant leads to a major loss of function in I_{Na}, thus contributing to the manifestation of Brugada syndrome [110]. Previous studies (including genome-wide association studies) have associated *SCN10A* variants with BrS, although the prinipal loci were intronic. [120] Othere GWAS studies have idenitifed *SCN10A* variants with altered cardiac function and arrhythmogenesis, suggesting that $Na_v1.8$ plays an important role in the electrical function of the heart in both health and disease.[121–129] With the identification of *SCN10A* as BrS susceptibility gene in 16.7% of probands, potentially causative gene mutations can now be detected in more than 50% of BrS patients, further enhancing the impact of genotyping in risk stratification and in screening of family members.

HEY2—The trascriptional factor ***HEY2*** was also identified as associated with BrS in the GWAS study of Bezzina et al. [120, 130131]

FGF12 is another recently idetified BrS susceptibility gene. *FGF12* encodes for a fibroblast growth factor homologous factor (**FHF-1**). [132] FHFs exert modulatory effects on cardiac sodium -and calcium-channels.[133134] A Q7R missense mutation in *FGF12*, associated with BrS, has been shown to reduce I_{Na}. [132]

PKP2—Mutations in ***PKP2***, encoding the desmosomal protein plakophillin-2, a known susceptibility gene for arrhyhtmgenic right ventriccualr cardiomypathy (ARVC), has been associated with BrS. The disruption of desmosomes has been shown to result in loss of sodium channel function.[135]

RANGRF—Missense mutations in ***RANGRF***, encoding MOG1, a protein known to modulate $Na_V1.5$, have been associated with BrS and shown to reduce cardiac I_{Na} due to impaired trafficking of the sodium-channel.[136, 137]

SLMAP—Mutations in the sarcolemmal membrane-associated protein (**SLMAP**), a component of T-tubules and sarcoplasmic reticulum with unknown functional role, have been associated with BrS and shown to impair $Na_v1.5$ trafficking, thus causing a loss of function in I_{Na}. [138]

2) Mutations causing a loss of function of calcium channel current

CACNA1C—Loss of function mutations in ***CACNA1C***, encoding the α-subunit of the human L-type voltage-gated calcium channel, $Ca_V1.2$, have been associated with many cases of BrS.[139, 140]

CACNB2B, a gene that encodes the β-subunit of $Ca_V1.2$, Cavβ2, is involved in regulation and intracellular trafficking of I_{CaL}.[141, 142] Several loss of function mutations in I_{CaL} function have been associated with BrS. [140, 143139, 140]

CACNA2D1 encodes the α2β-subunit of the voltage-dependent calcium channel and shares similar functional properties with Cavβ2[144]. Loss of function mutations in this gene are reported to contribute to SQTS, IVF, ERS and BrS. [139]

3) Mutations causing a gain of function of potassium channel currents

KCNE3—Gain of function mutations in *KCNE3* (MiRP2) have been asssocaited with BrS. The functional role of MiRP2 is modulation of several cardiac potassium currents, including I_{to} and I_{Ks}. Co-expression of KCNE3 mutations with WT-KCND3 leads to a gain-of-function and accelerated kinetics of I_{to}.[145]

KCND3—Gain of function mutation in ***KCND3*** has been also associated to BrS and shown to increase I_{to}. KCND3 encodes $K_v4.3$, the α-subunit of the I_{to} channel. [146]

SCN1B—As dicussed above, BrS-related mutations in ***SCN1B*** gene, encoding the auxiliary $Na_Vβ1$ subunit of the voltage-gated cardiac sodium channel, in addition to reducing I_{Na} can also increase I_{to} when co-expressed with WT-*KCND3.* [116]

KCNJ8—Mutations in ***KCNJ8***, encoding Kir6.1, have been reported to result in gain-of-function in $I_{K\text{-}ATP}$, a channel which, under normoxic conditons, is closed. This leads to accentuation of the action potenial notch as well as depression of the plateau, leading to BrS phenotype or SQTS phenotype due to abbreivation of action potential duration. [147–149]

ABCC9—Mutations in ***ABCC9***, encoding **SUR2A**, the ATP-binding cassette transporter of the $I_{K\text{-}ATP}$ channel, have been recently identified as causative of BrS.[150] Mutations in ABCC9 can reduce the ATP-sensitivity of the receptor-complex, resulting in a gain of function due to reduced tonic inhibitory effect of ATP.

4) Other candidate cenes

TRPM4—The transient receptor potential melastatin protein 4 gene (**TRPM4**), which encodes a calcium-activated non-selective cation channel has been proposed as a BrS-susceptibility gene. Mutations causing both a gain- and loss of function of the channel have been associated with BrS. The cellular basis as well its role in the pathophysiology of BrS requires further clarification. [151]

5) Genetic variants capable of modulating but not necessarily causing BrS

KCNE5—encodes one of the regulatory β-subunits of the I_{to} and I_{Ks} channels. Mutations in this gene can modualte expression of BrS by increasing I_{to}. [152] Evidence is currently insufficient to demonstrate causation.

KCNH2—Gain of function mutation in **KCNH2**, encoding the α-subunit of the rapid delayed rectifier potassium channel (hERG), results in increased I_{Kr} current, giving rise to SQTS and modulating the expression of BrS.[153] Evidence is currently insufficient to demsontrate causality.

HCN4—Loss of function mutations in **HCN4** encoding the hyperpolarization-activated cyclic nucleotide-gated channel 4 protein, the main monomer-isoform constituting the tetramer-complex of the human cardiac pacemaker channel (**I_f**), has been associated with BrS. [154–156] Reduction in I_f can lead to bradycardia, which is known to accentuate or unmask the BrS phenotype [107]. HCN4 (and HCN2) are mainly expressed in cells with high automaticity (SA-node > AV-node > His-Purkinje-system≫>working myocardium). [154, 157] Their very low expression level in ventricular myocardium argues against their direct invovlemet in causing BrS.

Role of Genetic Testing

Genetic testing is recommended for support of the clinical diagnosis, for early detection of relatives at potential risk, and particularly for the purpose of advancing research and consequently our understanding of genotype-phenotype relations. The role of genetic markers in risk stratification of BrS is a matter of debate. [158] According to the latest guidelines (HRS/EHRA consensus statement) [159], 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 [160] and other studies [156] suggest that a Type 1 BrS ECG alone should be enough of an indication (Class I recommendation) for genetic testing. In individuals expressing isolated Type 2 or 3 BrS pattern, genetic testing has a Class III recommendation. [159] 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 $I_{K\text{-}ATP}$ blockers in cases involving a gain of function of $I_{K\text{-}ATP}$ or use of I_{Kr} blockers in cases of I_{Kr} gain of function.

3. Cellular and Ionic Basis

An outward shift in the balance of currents active during phases 1 and 2 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 $I_{K\text{-}ATP}$), allows the already prominent I_{to} to accentuate phase 1 repolarization (Figs. 2 and 3). 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

plateau, predominantly in the right ventricular subepicardial cells where I_{to} is most prominent .

Conduction of the AP dome from epicardial sites at which it is maintained to sites at which it is lost results in the development of phase 2 reentry, giving rise to a very closely coupled extrasystole.[77] Interestingly, these repolarization abnormalities give rise to low voltage fractionated electrogram activity (Figure 4) and high frequency late potentials when a bipolar electrogram is recorded in the region of the RVOT (Figure 5).[161] 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.

The ability of the right ventricular action potential to lose its dome, giving rise to phase 2 reentry and other characteristics of the Brugada syndrome were identified in the early 1990's and evolved in parallel with the clinical syndrome. [162–165]

The development of prominent J waves, appearing as ST segment elevation, in the right precordial leads of BrS patients is believed to be due to accentuation of the right ventricular epicardial action potential notch secondary to the rebalancing of the currents active at the end of phase 1 (see [166] for references). A spike and dome morphology due to a prominent transient outward current (I_{to}), or notch, in ventricular epicardium, but not endocardium, generates a transmural voltage gradient that inscribes the electrocardiographic J wave in larger mammals and in man. The ST segment is typically isoelectric because of the absence of transmural voltage gradients at the level of the action potential plateau. Under pathophysiologic conditions such as those associated with BrS, accentuation of the right ventricular action potential notch leads to exaggeration of transmural voltage gradients and thus to accentuation of the J wave, causing an apparent ST segment elevation. [166] 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 leads to progressive inversion of the T wave.

Accentuation of the action potential notch in the right ventricular outflow tract (RVOT) can give rise to the typical Brugada ECG without creating an arrhythmogenic substrate, as illustrated in Figure 2B. The arrhythmogenic substrate could then arise with a further shift in the balance of currents causing loss of the action potential dome at some epicardial sites but not others. Disappearance 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 2C. 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 (P2R). The phase 2 reentrant extrasystole is often concealed because it is surrounded by refractory tissue. These concealed P2Rs are responsible for the appearance of high frequency late potentials (Figure 5) in epicardial electrograms recorded over these epicardial sites in patients with BrS.[161] When the P2R succeeds in propgating out of its protected focus and capturing the vulnerable window, it can trigger a circus movement

reentry, usually manifest as polymorphic VT/VF (Figure 2F). [167–169] The phase 2 reentrant beat fuses with the negative T wave of the basic response. Support for these hypotheses derives in part from experiments involving arterially perfused right ventricular wedge preparations as well as from studies such as those of Kurita et al. who obtained monophasic action potential (MAP) recordings form the epicardial and endocardial surfaces of the right ventricular outflow tract (RVOT) of patients with the Brugada syndrome.[164, 170] Figure 2E illustrates an example of programmed electrical stimulation-induced VT/VF under similar conditions.

Although the genetic mutations are equally distributed between the sexes, the clinical phenotype is 8 to 10 times more prevalent in males than in females. The basis for this sex-related distinction was shown to be due to a more prominent I_{to}-mediated action potential notch in the right ventricular (RV) epicardium of males vs. females.[171] The more prominent I_{to} 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 dome and the development of phase 2 reentry and polymorphic VT. The gender distinction is not seen in all families; some authors described families without a male predominance of the Brugada phenotype.[172]

Available data support the hypothesis that the Brugada syndrome is the result of amplification of heterogeneities intrinsic to the early phases of the action potential among the different transmural cell types. This is due to a rebalancing of currents active during phases 1 and 2 of the acion potential secondary to a decrease in I_{Na} or I_{Ca} or augmentation of outward currents including IKr, I_{Ks}, $I_{Cl(Ca)}$ or I_{to} (Figure 3). The accentuation of the action potential notch leads to elevation of the ST segment, eventually leading to loss of the action potential dome in right ventricular epicardium, where I_{to} is most prominent. Loss of the dome causes a transmural as well as epicardial dispersion of repolarization. The transmural dispersion contributes to development of ST segment elevation and the generation of a vulnerable window across the ventricular wall, whereas the epicardial dispersion leads to development of phase 2 reentry, thus providing a closely coupled extrasystole that captures the vulnerable window and precipitates VT/VF. The polymorphic VT generated resembles a rapid form of Torsade de Pointes (Figures 2F and 3).

The cellular mechanisms underlying Brugada syndrome have long been a matter of debate [173, 174]. 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.

To date, the most compelling evidence in support of the depolarization hypothesis was the demonstration by Nademanee et al.[83] of late potentials and fractionated electrogram (EGs)

recorded from the right ventricular outflow tract (RVOT) of BrS using bipolar electrograms. They further demonstrated that radiofrequency (RF) ablation these epicardial sites significantly reduced the arrhythmia-vulnerability and ECG-manifestation of the disease. These authors concluded that the high frequency late potential (LP) and low voltage 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[83]. In a direct test of this hypothesis, our group recently suggested an alternative cellular electrophysiological mechanism as the basis for late potentials and fractionated electrogram activity in the setting of BrS.[161] Using the coronary-perfused wedge model of BrS, Szel et al. [161] demonstrated that the high frequency late potentials are due to concealed phase 2 reentry and that the low-voltage fractionated electrogram activity recorded from the RV epicardium is due to different timing of the second upstroke of the action potential secondary to accentuation of the epicardial action potential notch (Figures 4 and 5).

If late potentials and fractionated electrogram activity recorded from the RVOT do not reflect depolarization and conduction abnormalities, what is the basis for the ameliorative effect of RVOT ablation? As we will discuss below, our preliminary data strongly support the hypothesis that ablation destroys the cells with the most prominent action potential notch, thus eliminating the cells responsible for the repolarization abnormalities that give rise to phase 2 reentry and VT/VF (Figure 6).

Factors that Modulate ECG and Arrhythmic Manifestations of the Brugada Syndrome

ST segment elevation in the Brugada syndrome is often dynamic. The Brugada ECG is often concealed and can be unmasked or modulated by sodium channel blockers, a febrile state, vagotonic agents, α adrenergic agonists, β adrenergic blockers, tricyclic or tetracyclic antidepressants, a combination of glucose and insulin, hyperkalemia, hypokalemia, hypercalcemia, and by alcohol and cocaine toxicity [37, 45, 46, 175–181]. A number of precipitants for ventricular arrhythmias have been reported and should be addressed acutely. These agents may also induce acquired forms of the Brugada syndrome (Table 2). All patients should be promptly treated for fevers and avoid drugs that unmask or aggravate BrS. A definitive list of agents to avoid in the Brugada syndrome can be found in the website www.brugadadrugs.org , and are briefly summarized in Table 2.

Acute ischemia or myocardial infarction due to vasospasm involving the RVOT mimics ST segment elevation similar to that in Brugada syndrome. This effect is secondary to the depression of I_{Ca} and the activation of $I_{K\text{-}ATP}$ during ischemia, and suggests that patients with congenital and possibly acquired forms of Brugada syndrome may be at a higher risk for ischemia-related sudden cardiac death. [182]

VF and sudden death in the Brugada syndrome usually occur at rest and at night. Circadian variation of sympatho-vagal balance, hormones and other metabolic factors likely contribute this circadian pattern. Bradycardia, due to altered symaptho-vagal balance or other factors, may contribute to arrhythmia initiation. [183–185] Abnormal ^{123}I-MIBG uptake in 8 (17%) of the 17 Brugada syndrome patients but none in the control group was demonstrated by Wichter et al.[186] There was segmental reduction of ^{123}I-MIBG in the inferior and the septal left ventricular wall indicating presynaptic sympathetic dysfunction. Of note, imaging of the

right ventricle, particularly the RVOT, is difficult with this technique, so insufficient information is available concerning sympathetic function in the regions known to harbor the arrhythmogenic substrate. Moreover, it remains unclear what role the reduced uptake function plays in the arrhythmogenesis of the Brugada syndrome. If indeed the RVOT is similarly affected, this defect may alter the symaptho-vagal balance in favor of the development of an arrhythmogenic substrate.[168, 187]

Kies and coworkers [188] assessed autonomic nervous system function noninvasively in patients with the Brugada syndrome, quantifying myocardial presynaptic and postsynaptic sympathetic function by means of positron emission tomography with the norepinephrine analogue 11C-Hydroxyephedrine (11C-HED) and the nonselective beta-blocker 11C-CGP 12177 (11C-CGP). Presynaptic sympathetic norepinephrine recycling, assessed by 11C-HED, was found to be globally increased in patients with Brugada syndrome compared with a group of age-matched healthy control subjects, whereas postsynaptic β adrenoceptor density, assessed by 11C-CGP, was similar in patients and control. This study provides further evidence in support of an autonomic dysfunction in Brugada syndrome.

Hypokalemia has been implicated as a contributing cause for the high prevalence of SUDS in the Northeastern region of Thailand where potassium deficiency is endemic.[189180] Serum potassium in the Northeastern population is significantly lower than that of the population in Bangkok, which lies in the central part of Thailand, where potassium is abundant in the food. A recent case report highlights the ability of hypokalemia to induce VF in a 60 year old man who had asymptomatic Brugada syndrome, without a family history of sudden cardiac death.[180] This patient was initially treated for asthma by steroids, which lowered serum potassium from 3.8 mmol/L on admission to 3.4 and 2.9 mmol/L on the 7th day and 8th day of admission, respectively. Both were associated with unconsciousness. VF was documented during the last episode, which reverted spontaneously to sinus rhythm.

Accelerated inactivation of the sodium channel in *SCN5A* mutations associated with the Brugada syndrome has been shown to be accentuated at higher temperatures [190], suggesting that a febrile state may unmask the Brugada syndrome by causing loss of function secondary to premature inactivation of I_{Na}. Indeed, numerous case reports have emerged since 1999 demonstrating that febrile illness could reveal the Brugada ECG and precipitate VF.[47, 191–197] Anecdotal reports point to hot baths as a possible precipitating factor. Of note, the Northeastern part of Thailand, where the Brugada syndrome is most prevalent, is known for its very hot climate.

Oxidative stress has recently been added to the list of modulating factors. Tanaka et al. reported that elevated oxidative stress can modulate the development of VF in SCN5A-negative BrS patients.[198] There was no evidence of histological structural changes in this cohort.

5. Approach to Therapy

Table 3 lists device and pharmacologic therapies suggested on the basis of clinical experience or experimental stduies.

Device Therapy

Implantable cardioverter defibrillator (ICD)—Implantation of an ICD is first line therapy for patients presenting with aborted SCD or documented VT/VF with or without syncope. [199, 200] The HRS/EHRA/APHRS expert consensus statement [33] recommendations for ICD implantation are illustrated in Table 3 and summarized as follows:

1. **Recommended (Class I):**

   Symptomatic patients presenting with a Type 1 Brugada ECG (spontaneously or after sodium channel blockade) and aborted sudden death or documented VTT/VF should receive an ICD as a Class I indication. 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 I pattern, in whom syncope is presumed to be likely caused by VT/VF.

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

   The annual rate of arrhythmic events in asymptomatic patients is relatively low (0.5% vs. 7.7–10.2% in patients with VF and 0.6–1.2% in patients with syncope). This warrants careful consideration for ICDs in asymptomatic patients[36, 158].

4. **ICDs are not indicated (Class III) in asymptomatic patients**[33].

The validity of HRS/EHRA/APHRS (Class II) recommendation for patients with a history of syncope and spontaneous Type 1 ECG was confirmed by Takagi et al in a multicenter large-cohort study in the Japanese population.[201] These authors reported that in patients with Class II indication, a history of syncope in combination with a 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 preventing sudden cardiac death was 100% in a multicenter trial in which 258 patients diagnosed with Brugada syndrome. 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 initially asymptomatic patients, appropriate ICD shocks were delivered in 4%, 6%, 9%, 17% and 37% at 1, 2, 3, 4, and 5 years of follow-up, respectively. Subsequent long-term follow-up studies have confirmed the safety and effectiveness of this approach.[202, 203]

Pacemaker therapy—Despite the fact that life-threatening arrhythmias generally occur during sleep or at rest and associated with slow heart rates, a potential therapeutic role for cardiac pacing remains largely unexplored[204] and limited to a few case reports.[205, 206]

BrS patients who suffer from electrical storms leading to numerous appropriate ICD discharges highlight the need for adjunctive therapy. Before the development of ablation techniques (see below)[83] , a heart transplantation was the only option for these patients.[207]

Ablation therapy—The idea of using ablation to suppress focal arrhythmogenic substrates in BrS stems back to the turn of the century. Several studies reported on the effect of focal **endocardial** radiofrequency ablation of sites generating monomorphic extrasystoles.[208–211]

A promising innovation in the treatment of BrS using radiofrequency (RF) ablation was recently reported by Nademanee et al.[83] The authors showed that RF ablation of **epicardial** sites displaying late potentials and fractionated bipolar electrograms (EGs) in the RVOT of BrS patients significantly reduced arrhythmia-vulnerability and ECG-manifestation of the disease. Ablation at these sites was able to render VT/VF non-inducible and to normalize the Brugada ECG pattern in the majority of patients over a period of weeks or months. No recurrent VT/VF was observed over a 20+6 month follow-up, with only 1 patient on medical therapy with amiodarone. Subsequent case reports have been published in support of these effects.[212] Ablation therapy may be life-saving in uncontrollable cases, or BrS cases in which ICD therapy is impractical (e.g. contraindications or financial hardship in developing countries). RF ablation was assigned a **Class IIb** indication in the recent HRS/EHRA/APHRS expert consensus guidelines for BrS-patients with frequent appropriate ICD-shocks due to recurrent electrical storms.[33]

The cellular basis for the ameliorative effect of epicardial ablation in BrS is a matter of debate. Szel et al.[161] showed that late potentials and fractionated electrogram activity are due to concealed phase 2 reentry and dysnchrony in the emergence of the second action potetnial upstroke secondary to heterogeneous accentuation of the epicardial action potential notch (Figure 4 and 5). We hypothesized that RF ablation of the RVOT would eliminate these sites of abnormal repolarization and thus suppress the substrate for developmet of arrhyhtmias. Employing the canine right ventricular wedge model of BrS, we recently conducted studies to provide evidence in support of this hypothesis. As ilustrated in Figure 6, epicardial ablation is observed to destroy the cells with the most prominent action potential notch, thus annihilating the cells responsible for the repolarization abnormalities that give rise to phase 2 reentry and VT/VF[213].

Pharmacologic approach to therapy

A pharmacologic approach to therapy has been sought because 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. Pharmacologic-mediated therapy aimed at rebalancing the currents active during the early phases of the epicardial action potential in the RVOT so as to reduce the magnitude of the action potential notch and/or restore the action potential dome, has been the focus of much basic and clinical research. Table 3 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. Disopyramide, a class IA antiarrhythmic, has been shown to normalize ST segment elevation in some BrS patients but to unmask the syndrome in others. [214]

Because a prominent transient outward current, I_{to}, 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}. Regrettably, cardio-selective and I_{to}-specific blockers are not currently available. 4-aminopyridine (4-AP), although selective of I_{to} at low concentrations, is not cardio-selective because it inhibits I_{to} in the nervous system. It is very effective in suppressing arrhythmogenesis in wedge models of the Brugada syndrome, [168] but is unlikely to be of clinical benefit because of neurally-mediated and other side effects.

The only drug available in the United States and other part of 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. Experimental studies have shown quinidine to be effective in restoring the epicardial action potential dome, thus normalizing the ST segment and preventing the development of phase 2 reentry and polymorphic VT, regardless of which pharmacologic agents were used to mimic the BrS-phenotype. [161, 168, 215, 216] Interestingly, a recent experimental study suggests that quinidine exerts a protective effect against hypothermia-induced VT/VF in a J wave syndrome model.[217]

Clinical evidence of the effectiveness of quinidine in normalizing ST segment elevation and preventing arrhythmic events in patients with the BrS is abundant. [218203, 218–230] The first prospective study to examine the effects of quinidine to prevent inducible and spontaneous VT/VF was reported by Belhassen and coworkers. 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 nineteen 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 [219, 231] and subsequently by other investigators [232, 233]. 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.[232]

Quinidine may has been proposed as a preventative meassure in asymptomatic patients, however this has not been evaluated in large double-blinded clinical trials[221]. 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.[234]

A prospective registry of empiric quinidine for asymptomatic Brugada syndrome has been established. The study appears at the National Institutes of Health website (ClinicalTrials.gov) and can be accessed at http://clinicaltrials.gov/ct2/show/NCT00789165?term_brugada&rank_2. Doses between 600 and 900 mg are recommended, if tolerated. [221]

Because of the GI side effects of high dose quinidine, low-dose quinidine (<600mg) has been investigated as a therapeutic option. Marquez et al. evaluated the clinical history of symptomatic patients with recurrent arrhythmias and frequent ICD discharges and reported that relatively low dose quinidine, as adjunctive therapy, completely prevented arrhythmias in 85 % of the patients (median follow-up of 4years).[223]

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, IIa in ICD-patients with electrical storms, and IIb recommendation in asymptomatic BrS-patients displaying a spontaneous Type I ECG. [33]

The development of a more cardio-selective and I_{to}-specific blocker would be a most welcome addition to the limited therapeutic armamentarium currently available to combat this disease.

Agents that augment the L-type calcium channel current, such as β adrenergic agents like isoproterenol, denopamine or orciprenaline have been shown to be useful [166, 168, 226, 230, 235, 236]. Isoproterenol, sometimes in combination with quinidine, has been utilized successfully to suppress electrical storms and to normalize ST elevation particularly in children [51, 218, 219, 230, 233, 237–24346, 224, 244–247]. The occurrence of spontaneous VF in patients with Brugada syndrome is often related to an increase 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.[33]

Administration of the phosphodiesterase III inhibitor cilostazol has been proposed as another promising approach to therapy of BrS.[230, 235, 248] 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.[249] Other effects of cilostazol may contribute as well. (e.g.: adenosine uptake inhibition [250]) Its efficacy in combination with bepridil in preventing VF-episodes was recently reported by Shinohara et al.[251] It is noteworthy that failure of cilostazol in the treatment of a BrS-patient has been reported in a single case report[252].

Milrinone is another phosphodiesterase III inhibitor recently identified as a more potent alternative to cilostazol in suppressing ST elevation and arrhythmogenesis in an experimental model of BrS[161, 253]. No clinical reports have appeared as yet.

Wenxin Keli, a traditional Chinese medicine (TCM), in addition to its actions to suppress atrial fibrillation by atrial-selective inhibition of I_{Na}-dependent parameters[254], 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 μM). [216] A recent study has also reported the effect of Wenxin Keli to suppress ischemia-induced ventricular arrhythmias.[255]

Agents that augment I_{Na} active during the early phases of the action potential, including bepridil and dimethyl lithospermate B (dmLSB), have also been suggested to be of value in the pharmacologic approach to therapy of BrS. Several studies have reported an effect of bepridil to suppress VT/VF in patients with BrS.[230, 256–258] The drug's action are thought to be mediated by: 1) inhibition of $I_{to;}$ 2) augmentation of I_{Na} via upregulation of the channels[259]; and 3) prolongation of QT interval at slow rates thus increasing the QT/RR slope.[256, 258] Dimethyl lithospermate B, an extract of Danshen, a traditional Chinese herbal remedy, has been shown to slow inactivation of I_{Na} thus increasing inward current during the early phases of the action potential (AP) and to be effective in suppressing arrhythmogenesis in experimental models of BrS.[260]

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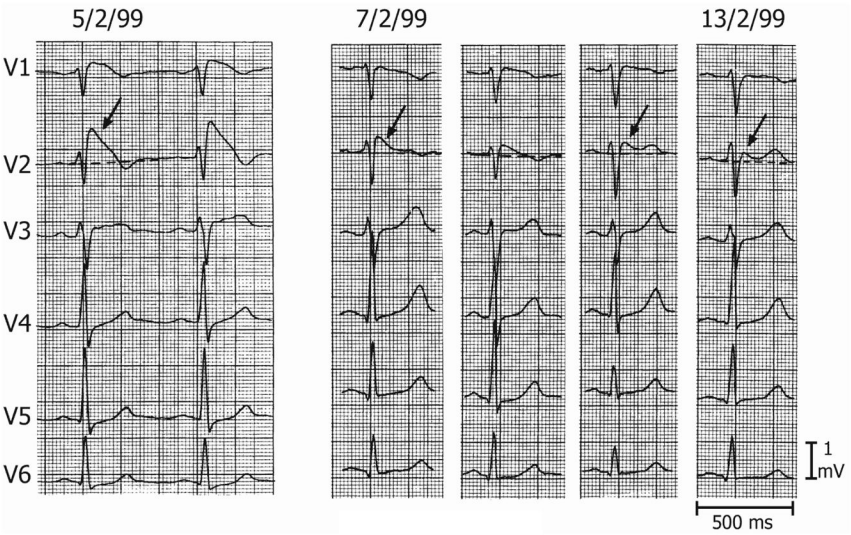

Figure 1.

Three Types of ST segment elevation generally observed in patients with the Brugada syndrome. Shown are precordial leads recorded from a patient diagnosed with the Brugada syndrome. Note the dynamic ECG changes occurring over a period of a week. The left panel shows a clear Type 1 ECG, which is diagnostic of the Brugada syndrome. A saddleback ST segment elevation (Type 2) is observed a day later. The ST segment is further normalized a week later, showing a Type 3 ECG. Modified from [31], with permission.

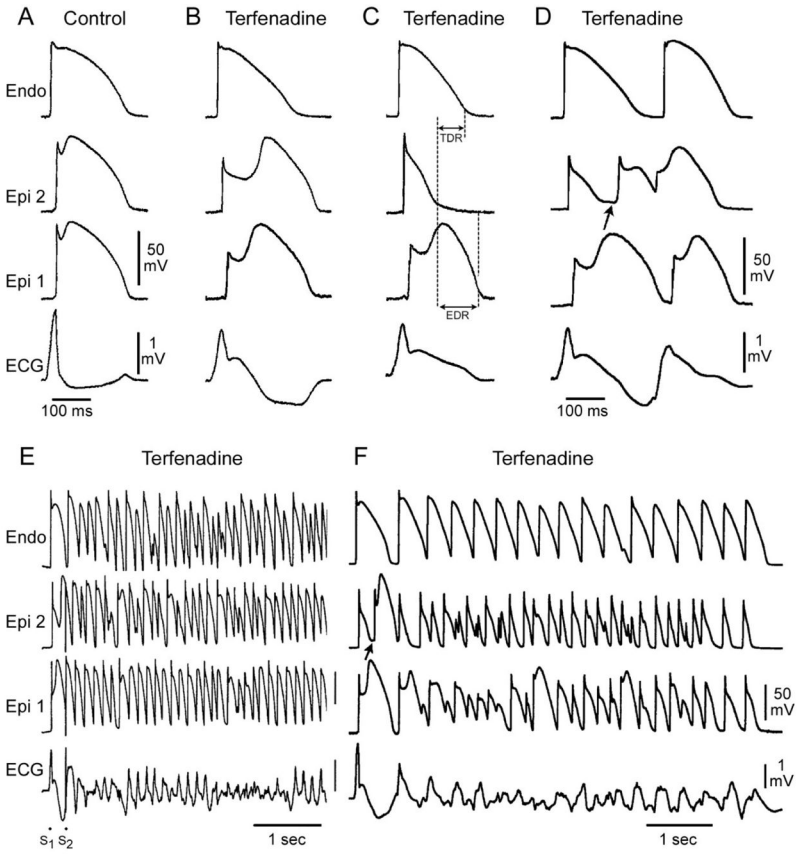

Figure 2.

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 μM) 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[169], with permission)

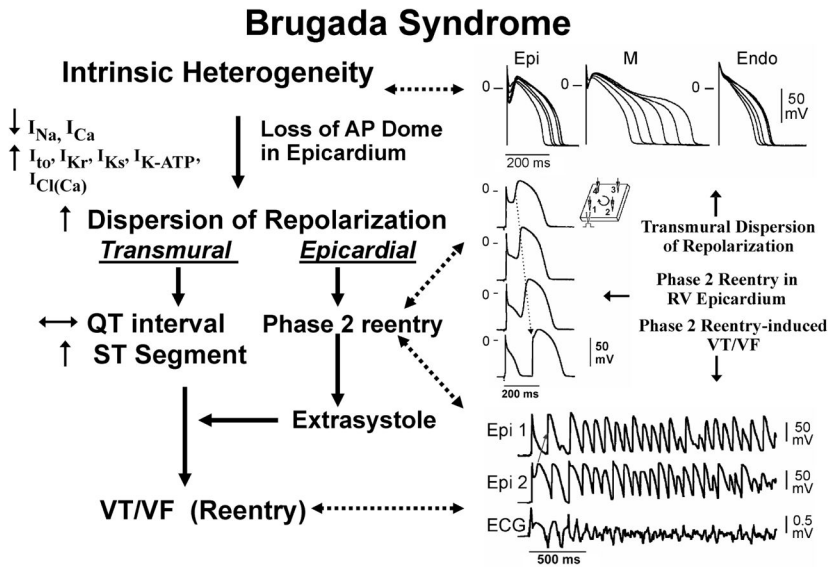

Figure 3.

Proposed mechanism for the Brugada syndrome. An outward shift in the balance of currents serves to amplify existing heterogeneities by causing loss of the action potential dome at some epicardial, but not endocardial sites. A vulnerable window develops as a result of the dispersion of repolarization and refractoriness within epicardium as well as across the wall. Epicardial dispersion leads to the development of phase 2 reentry, which provides the extrasystole that captures the vulnerable window and initiates VT/VF via a circus movement reentry mechanism. Modified from [261], with permission.

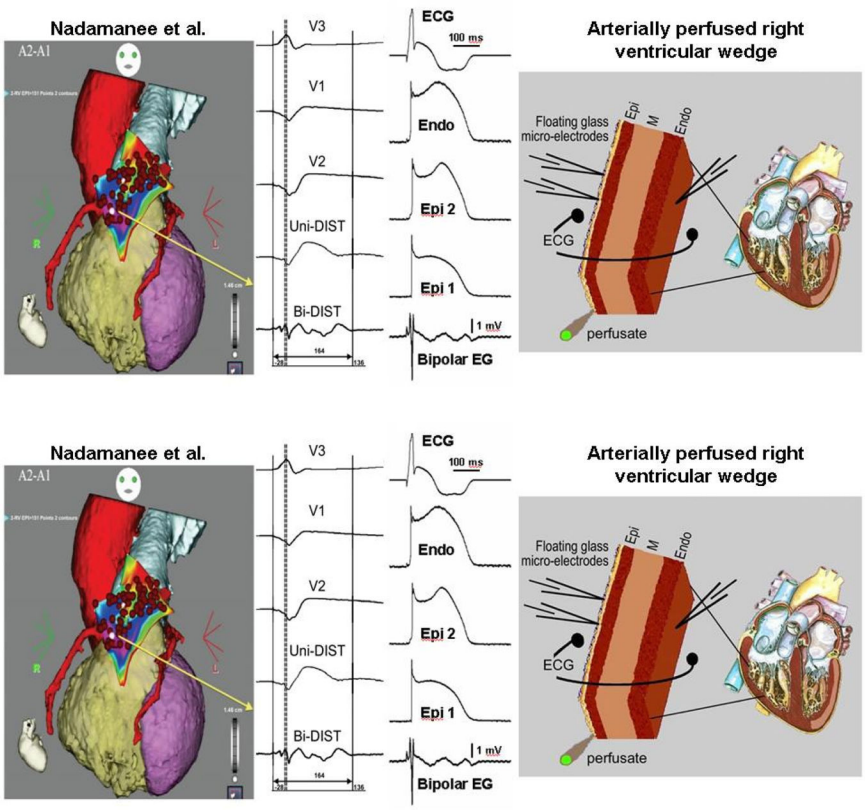

Figure 4.

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 and unipolar and bipolar EGs recorded form the right ventricular outflow tract of a BrS patient (from Nademanee et al. [83]). **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 μM) and the calcium channel blocker verapamil (2 μM) to induce the Brugada phenotype. Basic cycle length=1000 ms. Reproduced from[161], with permission.

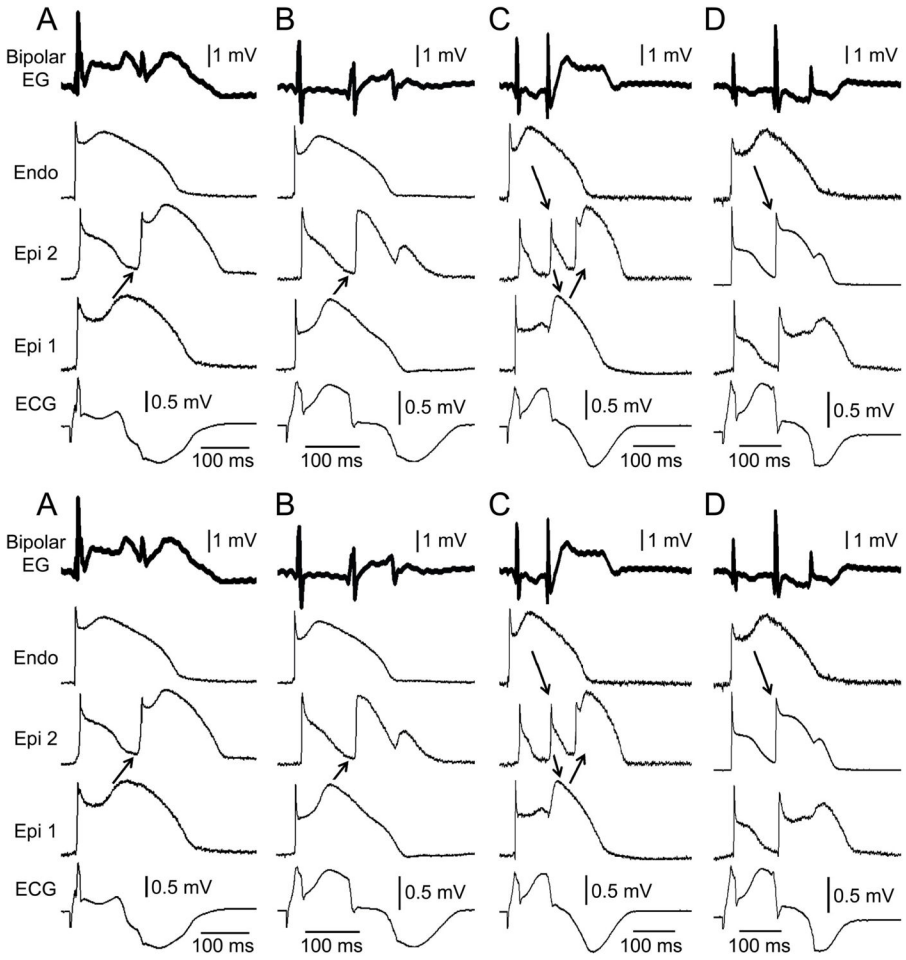

Figure 5.

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 μM) and verapamil (2 μM) to induce the Brugada phenotype. Heterogeneous loss of the dome at epicardium caused local re-excitation via a 'concealed' phase 2 re-entry 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 [161], with permission.

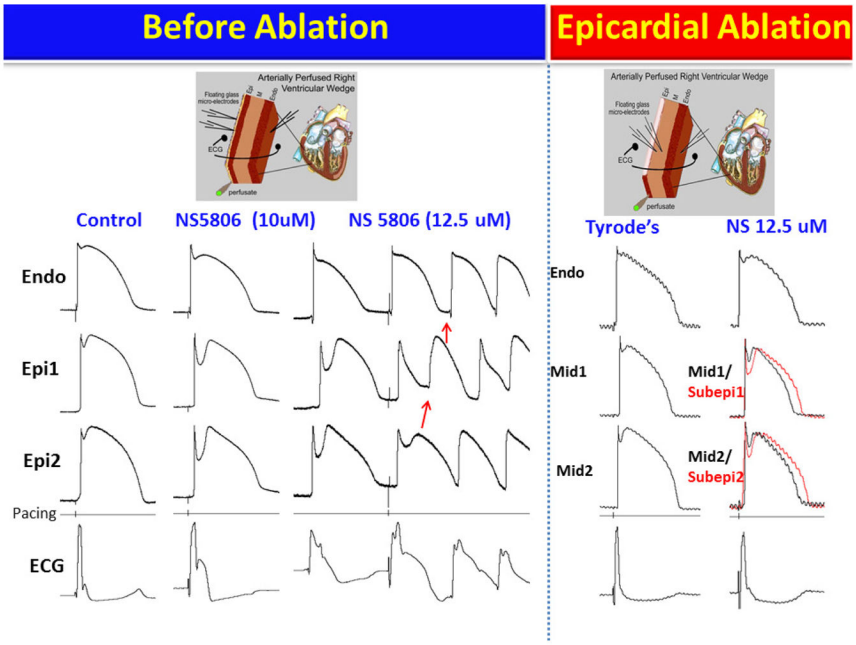

Figure 6.

Epicardial radiofrequency ablation abolishes the electrographic and arrhythmic manifestations of Brugada syndrome (BrS) in coronary-perfused canine right ventricular wedge-model. Transmembrane action potentials (AP) were simultaneously recorded from one endocardial (Endo) and two epicardial (Epi) sites together with a transmural pseudo-ECG. (The model is schematically illustrated in the top panels). Stimulus marker (pacing) is indicated in the 4th row. All recordings were obtained at 1000 ms basic cycle length. **Column 1:** Control. **Column 2:** Recorded 20 min after the addition of the I_{to}-agonist NS5806 (10μM) to the coronary perfusate. The much greater accentuation of the Epicardial (Epi) vs. Endocardial (Endo) AP notch was associated with accentuation of the J wave in the ECG. **Column 3:** Recorded 15 min after increasing the concentration of NS5806 to 12.5 μM. A stimulated premature beat induced VT (later VF) via a phase 2 reentry (P2R) mechanism. The abbreviated cycle length caused loss of the AP dome in Epi1 due to use-dependent block of I_{Na} by NS5806. In the Endo and Epi2 sites the dome is maintained and the notch is slightly reduced because slow recovery of I_{to} overwhelmed the use-dependent inhibition of I_{Na}. The pronounced epicardial and transmural dispersion of repolarization created the substrate for P2R and VT/VF. **Column 4:** Recorded after washout of NS5806 and 70 min after RF ablation of the epicardial surface. APs were recorded from the subepicardial layer (Subepi) just below the ablation border and from the midmyocardium (Mid) because the Epi layer was destroyed. **Column 5: Recorded** 45 min after re-introduction of NS5806 (12.5μM) to the coronary perfusate. After ablation of epicardium, NS5806 was no longer able to induce the ECG or arrhythmic manifestations of BrS.

Table 1

Brugada Syndrome Susceptibility Genes.

	Locus	Gene	Ion Channel	% of Probands
BrS1	3p21	*SCN5A, $Na_v1.5$*	↓ I_{Na}	11–28%
BrS2	3p24	*GPD1L*	↓ I_{Na}	Rare
BrS3	12p13.3	*CACNA1C, $Ca_v1.2$*	↓ I_{Ca}	6.6%
BrS4	10p12.33	*CACNB2b, $Ca_v\beta 2b$*	↓ I_{Ca}	4.8%
BrS5	19q13.1	*SCN1B, $Na_v\beta 1$*	↓ I_{Na}	1.1%
BrS6	11q13–14	*KCNE3, MiRP2*	↑ I_{to}	Rare
BrS7	11q23.3	*SCN3B, $Na_v\beta 3$*	↓ I_{Na}	Rare
BrS8	12p11.23	*KCNJ8, Kir6.1*	↑ $I_{K\text{-}ATP}$	2%
BrS9	7q21.11	*CACNA2D1, $Ca_v a2\delta$*	↓ I_{Ca}	1.8%
BrS10	1p13.2	*KCND3, $K_v4.3$*	↑ I_{to}	Rare
BrS11	17p13.1	*RANGRF, MOG1*	↓ I_{Na}	Rare
BrS12	3p21.2-p14.3	*SLMAP*	↓ I_{Na}	Rare
BrS13	12p12.1	*ABCC9, SUR2A*	↑ $I_{K\text{-}ATP}$	Rare
BrS14	11q23	*SCN2B, $Na_v\beta 2$*	↓ I_{Na}	Rare
BrS15	12p11	*PKP2, Plakophillin-2*	↓ I_{Na}	Rare
BrS16	3q28	*FGF12, FHAF1*	↓ I_{Na}	Rare
BrS17	3p22.2	*SCN10A, $Na_v1.8$*	↓ I_{Na}	16.7%
BrS18	6q	*HEY2 (transcriptional factor)*	↓ I_{Na}	Rare
BrS19	7p12.1	*SEMA3A, Semaphorin*	↑ I_{to}	Rare

Table 2

Drug-induced Brugada-like ECG Patterns

I. Antiarrhythmic drugs

1. Na^+ channel blockers

   Class IC drugs (Flecainide [37, 38, 262–264], Pilsicainide [265, 266], Propafenone [267])

   Class IA drugs (Ajmaline [37, 268], Procainamide [37, 46], Disopyramide [31, 46], Cibenzoline [269])

2. Ca^{2+} channel blockers

   Verapamil

II. Antianginal drugs

1. Ca^{2+} channel blockers

   Nifedipine, Diltiazem.

2. Nitrate

   Isosorbide dinitrate, Nitroglycerine [270].

3. K^+ channel openers

   Nicorandil.

III. Psychotropic drugs

1. Tricyclic antidepressants

   Amitriptyline[271, 272], Nortriptyline [177], Desipramine [175], Clomipramine [176].

2. Tetracyclic antidepressants

   Maprotiline [271].

3. Phenothiazine

   Perphenazine [271], Cyamemazine., Trifluoperazine[272]

4. Other antipsychotics

   Loxapin [272],

5. Selective serotonin reuptake inhibitors

   Fluoxetine [272].

6. Anticonvulsives

   Oxcarbazepine [273]

IV.Anesthetic and analgesics

1. Bupivacaine[274275]

2. Procaine [276]

3. Propofol[277–279]

V. Other drugs

1. Histaminic H1 receptor antagonists

   Dimenhydrinate [181].

2. Cocaine intoxication [178, 280]

3. Alcohol Intoxication

4. Cannabis [281]

5. Ergonovine [182]

6. Acetilcholine[46, 182]

Modified from[44], with permission

Table 3

Device and Pharmacologic Approach to Therapy of the Brugada Syndrome

Devices and Ablation
ICD [199]
Radiofrequency Ablation [83, 208–212]
? Pacemaker [204–206]
Pharmacologic Approach to Therapy
Ineffective or Proarrhythmic
Amiodarone [282]
β Blockers [282]
Class IC antiarrhythmics
Flecainide [38]
Propafenone [267]
? Disopyramide [214]
Class IA antiarrhythmics
Procainamide[37]
Effective for Treatment of Electrical Storms
β Adrenergic agonists – isoproterenol [46, 51], denopamine[230], orciprenaline [226, 236]
Phosphodiesterase III Inhibitors-cilostazol [235]
Effective General Therapy
Quinidine [168, 218–220, 231–233]
Bepridil - I_{to}-inhibition and I_{Na} augmentation[258]
Cilostazol combined with bepridil [251]
Experimental Therapy
I_{to} Blockers - cardioselective and ion channel specific
Quinidine [168]
4-aminopyridine [168]
Tedisamil [283]
AVE0118 [284]
PDE-3-inhibitors
Cilostazol – Increase in I_{Ca} and inhibition of I_{to} [253, 285]
Milrinone - I_{Ca} augmentation [253, 285]
Traditional Chinese Medicine
Dimethyl lithospermate B – Increase in I_{Na} due to slowed inactivation
Wenxin Keli - combined I_{to}-block and tyramine-like effect[216]