Brugada Syndrome: Recent Advances and Controversies

Charles Antzelevitch, PhD, and Eyal Nof, MD

Corresponding author
Charles Antzelevitch, PhD
Gordon K. Moe Scholar, Masonic Medical Research Laboratory,
2150 Bleecker Street, Utica, NY 13501, USA.
E-mail: ca@mmrl.edu

Current Cardiology Reports 2008, **10:**376–383
Current Medicine Group LLC ISSN 1523-3782

The Brugada syndrome, first described as a new clinical entity in 1992, is widely recognized today as a form of inherited sudden cardiac arrest. The past 16 years witnessed a progressive increase in the number of reported cases and a dramatic proliferation of articles serving to define the clinical, genetic, cellular, ionic, and molecular aspects of the disease. This article provides a brief overview of recent advances in our understanding of the clinical presentation and molecular and cellular mechanisms and an update of existing controversies.

Introduction

It has been 16 years since Pedro and Josep Brugada introduced the syndrome of ST-segment elevation and right bundle branch block associated with a high incidence of ventricular tachycardia/ventricular fibrillation (VT/VF) as a new clinical entity [1], and a bit longer since the introduction of the concept of phase 2 reentry induced by sodium channel block—the mechanism thought to trigger life-threatening arrhythmias in this clinical syndrome [2,3]. The entity—which came to be known as the Brugada syndrome in 1996 [4,5]—has attracted great interest because of its prevalence and association with high risk of sudden death, especially in men as they enter their third and fourth decade of life. A consensus report published in 2002 delineated diagnostic criteria for the syndrome [6]. A second consensus conference report published in 2005 focused on risk stratification schemes and approaches to therapy [7••]. This article provides a brief overview of recent advances in the genetic, clinical, molecular, and cellular aspects of the Brugada syndrome and an update of existing controversies.

Genetic Factors

Brugada syndrome is inherited as an autosomal-dominant trait. In 1998, it was linked to mutations in the *SCN5A* gene, encoding the α subunit of the cardiac sodium channel protein [8]. *SCN5A* mutations account for approximately 15% of probands. More than 100 mutations in *SCN5A* have been linked to the syndrome in recent years (http://www.fsm.it/cardmoc) [9]. Only a fraction of these mutations have been studied in expression systems and shown to result in loss of function due to 1) failure of the sodium channel to express; 2) a shift in the voltage dependence and time dependence of sodium channel current (I_{Na}) activation, inactivation, or reactivation; 3) entry of the sodium channel into an intermediate state of inactivation from which it recovers more slowly; or 4) accelerated inactivation of the sodium channel [10].

Hong et al. [11] provided the first report of a dysfunctional sodium channel created by an intronic mutation giving rise to cryptic splice site activation in *SCN5A* in a family with the Brugada syndrome. Deleting fragments of segments 2 and 3 of domain IV of *SCN5A* caused complete loss of function. Bezzina et al. [12] recently presented interesting evidence supporting the hypothesis that an *SCN5A* promoter polymorphism common in Asians modulates variability in cardiac conduction and may contribute to the high prevalence of Brugada syndrome in the Asian population. Sequencing of the *SCN5A* promoter identified a haplotype variant consisting of six polymorphisms in near-complete linkage disequilibrium that occurred at an allele frequency of 22% in Asian patients and was absent in whites and blacks. The study's results demonstrate that sodium channel transcription in the human heart may vary considerably among individuals and races and be associated with variable conduction velocity and arrhythmia susceptibility [12,13].

A second locus on chromosome 3, close to but distinct from *SCN5A*, has been linked to the syndrome in a large pedigree in which the syndrome is associated with progressive conduction disease, a low sensitivity to procainamide, and a relatively good prognosis [14•]. The gene was identified as the glycerol-3-phosphate dehydrogenase 1-like gene (*GPD1L*). This *GPD1L* mutation has been shown to result in a partial reduction of I_{Na} due, at least in part, to a trafficking defect. *GPD1L* mutations causing loss of function of I_{Na} were recently linked to 3 of

Table 1. Genetic basis for the Brugada syndrome

Study	Type	Locus	Ion channel	Gene	Protein	Incidence, %
Chen et al. [8]	BrS1	3p21	I_{Na}	*SCN5A*	$Na_v1.5$	15*
London et al. [14•]	BrS2	3p24	I_{Na}	*GPD1L*	—	Rare
Antzelevitch et al. [17•]	BrS3	12p13.3	I_{Ca}	*CACNA1C*	$Ca_V1.2$	6.6*
Antzelevitch et al. [17•]	BrS4	10p12.33	I_{Ca}	*CACNB2b*	$Ca_v\beta_{2b}$	4.8*
Watanabe et al. [89]	BrS5	19q13.1	I_{Na}	*SCN1B*	$Na_v\beta1$	1.10%
Delpón et al. [90]	BrS6	11q13-q14	I_{to}	*KCNE3*	MiRP2	Rare

*Incidence values are updated to current values in our database consisting of 166 Brugada syndrome probands.

221 cases of sudden infant death syndrome (SIDS) [15]. In another case, a 19-day-old infant successfully resuscitated from VF was linked to a mutation in *SCN5A* [16]. These findings point to the Brugada syndrome as a cause of some SIDS cases.

The third and fourth genes associated with the Brugada syndrome were reported recently and shown to encode the α1 (*CACNA1C*) and β (*CACNB2b*) subunits of the L-type cardiac calcium channel. The mutations in the α1 and β_{2b} subunits of the cardiac calcium channel were often found to be associated with a familial sudden cardiac death (SCD) syndrome in which a Brugada syndrome phenotype is combined with shorter-than-normal QT secondary to a loss of function of the calcium channel current (I_{Ca}) [17•].

In the span of one decade, four genes were linked to the Brugada syndrome, with three identified over the past year (Table 1). The number of genetic defects responsible for Brugada syndrome will likely continue to grow as with the long QT syndrome, which is now up to 11 distinct genotypes.

As with other arrhythmogenic syndromes, variations in genotype-phenotype relationships in the Brugada syndrome are not uncommon. Modulatory effects of polymorphisms and compound mutations can account for such differences. Our group recently reported the additive effects of two heterozygous missense mutations in *SCN5A* [18]. A P336L mutation in *SCN5A* produced a reduction in I_{Na}, whereas the I1660V mutation abolished the current. Only the proband carrying both mutations displayed the Brugada syndrome phenotype, whereas neither mutation alone produced the clinical phenotype in the proband's parents or daughters. These data highlight the role of compound heterozygosity in the phenotypic expression of the Brugada syndrome.

Diagnostic Criteria

Brugada syndrome is diagnosed on the basis of a type 1 or coved-type ST-segment elevation in the right precordial leads plus one of the following conditions: documented VF or polymorphic VT, a family history of SCD at a young age (< 45 years) or a type 1 electrocardiogram (ECG) in family members, otherwise unexplained syncope, nocturnal agonal respiration, or inducibility of VT/VF with programmed electrical stimulation [6]. This ECG that is characteristic of Brugada syndrome is often dynamic. The ECG manifestations of the Brugada syndrome when concealed can be unmasked by sodium channel blockers, a febrile state, or vagotonic agents [19]. In the largest population of children affected by Brugada syndrome described to date, fever represented the most important precipitating factor for arrhythmic events [20]. Junttila et al. [21] recently found that patients who present with a type 1 ST-segment elevation in the right precordial leads during electrolyte abnormalities and after drug administration or fever are at high risk for SCD. In their series, 51% of patients manifesting this acquired phenotype had symptoms related to Brugada syndrome, including 38% who developed cardiac arrest. Therapeutic intervention with antipyretics or by termination of the culprit medication is warranted under these conditions. Type 1 and type 2 ST-segment elevation are not diagnostic of Brugada syndrome unless they are converted to type 1.

Drugs used to unmask the syndrome for diagnostic purposes include ajmaline, flecainide, procainamide, and pilsicainide. Comparing intravenous ajmaline and flecainide in the same cohort of patients revealed that ajmaline is more effective in unmasking the syndrome [22]. A greater inhibition of I_{to} by flecainide is believed to underlie this difference. Drug-induced type 1 ECG is generally considered to be diagnostic of Brugada syndrome. However, controversy remains as to whether a positive drug challenge adds to the diagnostic accuracy of Brugada syndrome. Peters et al. [23] reported that 16% of patients with right ventricular cardiomyopathy also respond with an ST-segment elevation when challenged with a sodium channel blocker. Moreover, Priori and Napolitano [24] reported that some patients with intermittent type 1 ECG fail to demonstrate an ST-segment elevation in response to sodium channel block, whereas others have reported that some patients have a positive response in one test and a negative response in subsequent tests [25]. Accordingly, the results of a drug challenge should be interpreted with caution.

Placing the right precordial leads in a superior position (up to the second intercostal spaces) can increase the ECG's sensitivity for detecting the Brugada phenotype in some

Table 2. Other conditions leading to ST-segment elevation in the electrocardiogram

Common
Acute myocardial infarction [60]
Prinzmetal's angina [61]
Electrolyte disturbances, such as hyperkalemia [62,63]
Hypercalcemia [64,65]
Acute pericarditis, myocarditis [66]
Right bundle branch block
Electrocardiogram recorded after electrical cardioversion [67]
Less common
Arrhythmogenic right ventricular cardiomyopathy [68,69]
Autonomic nerve abnormalities [70,71]
Mechanical compression of the right ventricular outflow tract [72]

patients in the presence or absence of a drug challenge [26]. Miyamoto et al. [27] conducted a systematic study in which they obtained recording of V1 and V2 at elevated intercostal positions in 98 Brugada syndrome probands. They concluded that men with a spontaneous type 1 ECG recorded only at higher lead V1 and V2 positions show a prognosis similar to that of men with a type 1 ECG using standard V1-V2 leads. Because recordings of leads V1 and V2 at higher intercostal positions are easy and noninvasive, recording of leads V1 and V2 from a superior position was recommended as an alternative to sodium blocker drug challenge. A drug challenge should be considered only when this procedure's result is negative.

A recent study found that as many as 1.3% of normal Korean men displayed a type 2 (but not type 1) ST-segment elevation when right precordial leads were recorded from a superior position [28]. This study cautions against the use of a type 2 ECG to diagnose Brugada syndrome.

Some studies suggest that a type 1 ECG recorded using elevated right precordial leads may lead to overdiagnosis of Brugada syndrome. Priori and Napolitano [24] reported a family in which 25 of 63 displayed a type 1 ECG after upward displacement of the precordial leads; only 6 of these 25 individuals had the familial *SCN5A* mutation. In interpreting these results, we should keep in mind that *SCN5A* mutations account for only 15% of probands with Brugada syndrome.

Even when a clear Brugada syndrome-like ECG consisting of a greater than 2-mm J-point elevation followed by a downsloping ST segment and a negative T wave is apparent, other clinical conditions must be ruled out. This also includes those listed in Table 2.

Although other ECG characteristics are known to be associated with Brugada syndrome and in some cases are useful in risk stratification, these are generally not considered helpful in differential diagnosis of Brugada syndrome but may assist in identifying the genotype. Prolonged PR (due to His-ventricular prolongation) and QRS intervals are often observed in patients with *SCN5A* mutations [1,6].

Risk Stratification

Risk stratification—particularly of asymptomatic Brugada syndrome patients—remains a challenge and a matter of lively debate. It is widely accepted that Brugada syndrome patients who experience a life-threatening arrhythmia, aborted SCD, or nocturnal agonal respiration are at high risk for a recurrence and should receive an implantable cardioverter-defibrillator (ICD). Little argument exists that patients with a clinical picture of arrhythmia-mediated syncope and a type 1 ST-segment elevation should receive the protection of an ICD. However, the prognosis and treatment of asymptomatic Brugada syndrome patients continue to be debated.

In 1998, Brugada et al. [29] reported that 27% of previously asymptomatic patients experienced a first episode of VF or SCD. In 2005, Brugada et al. [30] reported that only 6% of asymptomatic patients displayed a first event during a mean follow-up of 42 ± 42 months, for a calculated event rate of 1.7%. The progressive decline in first event rate in previously asymptomatic patients most likely reflects a reduced severity of phenotypes referred to this registry in subsequent years. In 2005, Priori and Napolitano [24] reported that 3% of asymptomatic Brugada syndrome patients experienced a first event (4/132) over a 31-month follow-up period, for an event rate of 1%. The reason for this discrepancy is unclear. Brugada et al. [31] suggested that although their registry included only patients with type 1 ECG, the Priori and Napolitano [24] registry also included patients with type 2 and 3 ST-segment elevation, who may not have Brugada syndrome as defined by the consensus report [6]. Although this might serve as an explanation for the difference between these two databases, other studies that included only patients diagnosed on the basis of a type 1 ECG also failed to demonstrate that asymptomatic patients are at high risk for cardiac events. Eckardt et al. [32] recently reported that 1 of 123 asymptomatic individuals with a type 1 ECG (0.8%) had a first arrhythmic event during a 40- ± 50-month follow-up. This translates into a first event rate of 0.24% per year, considerably less than the other two registries.

Brugada et al. [29,30] reported that the risk for developing VT/VF is much greater in patients who are inducible during electrophysiologic study (EPS), whether or not a type 1 ST-segment elevation is spontaneously present and whether or not they are symptomatic. Using multivariate analysis in asymptomatic spontaneous type 1 ECG patients, they showed that the only predictor of arrhythmic events is inducibility during EPS. In sharp contrast, other studies [24,32–35] failed to find an association between inducibility and cardiac arrhythmic events. The incidence of VT/VF events during follow-up was too low

Table 3. Proposed risk factors for arrhythmic events in the Brugada syndrome

Width of the S wave and magnitude of ST-segment elevation [73]
Late potentials [74]
Prolonged QRS duration (> 102 ms) in lead V2 [40] or an r-J interval in lead V2 ≥ 90 ms [75]
Autonomic neuropathy [76]
Tp-e interval and Tp-e dispersion [77]
Corrected QT interval > 460 ms in lead V2 [77]
T-wave alternans, particularly after exposure to sodium channel blockers [78–86]
aVR sign (prominent R wave in lead aVR) [87]
Delay in onset of contraction between right and left ventricles [88]

(annual event rate of 0.8% to 1% [24,32]) to demonstrate any value for risk stratification based on EPS inducibility.

The last consensus conference published in 2005 [7••] recommended that asymptomatic patients displaying a type 1 ST-segment elevation (spontaneously or after sodium channel blockade) undergo EPS if a family history of SCD is suspected to be the result of Brugada syndrome. EPS was also considered justified with a negative family history but a spontaneous type 1 ST-segment elevation. If inducible for ventricular arrhythmia, implanting an ICD was recommended as a class IIa or IIb indication, meaning that conflicting evidence exists concerning usefulness and that the weight of evidence favors usefulness (class IIa) or usefulness is not well established (class IIb). The report also recommended that asymptomatic patients with no family history who develop a type 1 ST-segment elevation only after sodium channel blockade should be followed up closely. The large number of studies conducted since the appearance of the last consensus statement that have failed to demonstrate an association between inducibility and risk call into question the value or need for EPS in asymptomatic Brugada patients. The reason for the large disparity between the results of the Brugada brothers and those from other centers is not clear.

In experimental models of the Brugada syndrome involving the coronary-perfused wedge preparation, polymorphic VT is readily inducible with a single ventricular extrastimulus, but only when applied on the epicardial surface [36–38]. Inducibility is not possible or much more difficult when extrastimulation is applied to the endocardial surface. Epicardium's shorter refractory period allows extrastimuli direct access to the vulnerable window across the ventricular wall, thus facilitating the induction of reentry. These relationships suggest that programmed electrical stimulation applied to the epicardium may provide a more accurate assessment of risk than the current clinical approach in which stimuli are applied to the endocardial surface. In support of this hypothesis, Carlsson et al. [39] reported that a Brugada syndrome patient with recurrent syncope due to polymorphic ventricular tachycardia could not be induced with right ventricular endocardial stimulation. However, epicardial stimulation from a left ventricular site through the coronary sinus led to polymorphic VT development. This approach may also be useful in inducing Brugada patients and might prove helpful in predicting future arrhythmic events. A percutaneous subxiphoid approach may also be useful for this purpose.

Additional risk factors are needed to help identify asymptomatic patients who would benefit from an ICD. Several risk factors identified in recent studies are presented in Table 3. A prolonged QRS duration has recently been suggested to serve as a noninvasive risk marker of vulnerability to life-threatening ventricular arrhythmias in Brugada syndrome [40]. S waves in leads II and III are significantly wider in patients with a positive sodium block challenge compared to those with a negative one [41]. The absence of an S wave in the left lateral leads with an ST-segment elevation in the right precordial leads may help preclude the presence of a true right ventricular conduction delay [6].

These risk factors have not been validated in prospective studies, and at present, their chief use is to identify patients requiring closer follow-up. It is not known whether specific genetic mutation carriers have a higher risk than others.

Treatment

The mainstay of therapy for Brugada syndrome is ICD implantation. Although this is the most effective approach to therapy, the rate of serious complications is high. In two recently reported studies, 28% to 36% of patients had serious complications [42,43]. Prominent among them are inappropriate shocks. When compared with other ICD-implanted populations, Brugada patients are much younger and more physically active. Because many are engaged in regular sport activities, inappropriate shocks may be due to episodes of sinus tachycardia [42]. Brugada patients are also known to have more supraventricular arrhythmias [44,45], and inappropriate shocks may be due to failure of the ICD to discriminate between atrial and ventricular arrhythmias. Brugada syndrome patients predisposed to life-threatening cardiac events have been reported to have the highest incidence of atrial fibrillation [46,47]. Although technically feasible, ICD therapy in children is challenging. The high risk of complications reported in adults is likely to be worse in children due to their smaller vessel diameter and cardiac size but also due to disruption of the leads that can occur as they grow [48]. ICD therapy is not an adequate solution for patients residing in regions of the world in which an ICD is unaffordable.

Other treatment options involve using pharmacologic agents, including I_{to} blockers such as quinidine [49–51]. The presence of a prominent I_{to} is fundamental to the mechanism underlying the Brugada syndrome. Consequently, the most prudent general approach to therapy, regardless of the

ionic or genetic basis for the disease, is to partially inhibit I_{to}. Cardioselective and I_{to}-specific blockers are currently not available. An agent currently on the US market and available in other regions of the world with significant I_{to}-blocking properties is quinidine, which was proposed for treating Brugada syndrome in 1999 [49]. Belhassen and Viskin [50] reported on quinidine's efficacy in a prospective study of 25 patients; 14 of these were high-risk, symptomatic patients (seven after an SCD event and seven with syncope). All 25 patients had inducible VF at baseline EPS. Quinidine prevented VF induction in 22 of the 25 patients (88%). After a follow-up period of 6 months to 22.2 years, all patients were alive. Of 19 patients treated with oral quinidine for 6 to 219 months (56 ± 67 months), none developed arrhythmic events. Quinidine's effectiveness has been demonstrated in a several studies [9], the most recent of which involves its use in children with Brugada syndrome [20]. Oral quinidine therapy appears to be a reasonable "bridge therapy" or adjunct to ICD therapy [48]. These data notwithstanding, a clear need exists for a large, randomized, controlled clinical trial to assess quinidine's effectiveness, preferably in patients with frequent events who have already received an ICD.

Disadvantages of oral quinidine include gastrointestinal side effects, particularly at the high doses needed to achieve I_{to} block. The effect of quinidine to block the rapidly and slowly activating delayed rectifier currents, I_{Kr} and I_{Ks}, can predispose to the development of acquired long QT syndrome. Quinidine's effect is minimized at high plasma levels because at these concentrations, quinidine also blocks the inward sodium channel current, I_{Na}, which serves to counter the effects of I_{Kr} and I_{Ks} block to increase spatial dispersion of repolarization and triggered activity, the substrate and trigger for the development of torsade de pointes arrhythmias [52,53].

Other potential pharmacologic approaches to therapy of Brugada syndrome include a reduction of vagal tone, an increase in early sodium or calcium currents, and block of potassium currents designed to prolong the action potential duration and thus prevent phase 2 reentry. Isoproterenol has been reported to be effective in acute and chronic treatment of patients with VF storms [51,54]. This drug reduces vagal tone and increases heart rate, which contributes to reducing the I_{to} current. Furthermore, by increasing calcium currents, it restores the action potential dome [54]. Cilostazol, a phosphodiesterase III inhibitor, was reported to normalize the ST segment and prevent VF in Brugada syndrome in one report [55], most likely by augmenting calcium current (I_{Ca}) and by reducing I_{to} secondary to an increase in heart rate [56]. Cilostazol failed to suppress VF in another reported use in Brugada syndrome [57].

Another pharmacologic approach is to augment a component of I_{Na} that is active during phase 1 of the epicardial action potential. Dimethyl lithospermate B is an extract of Danshen, a traditional Chinese herbal remedy that slows inactivation of I_{Na}, leading to increased inward current during the early phases of the action potential. This drug was shown to be effective in eliminating the arrhythmogenic substrate responsible for the Brugada syndrome in the canine arterially perfused right ventricular wedge model of Brugada syndrome [58].

Alternative approaches to therapy include cardiac pacing to prevent slow heart rates at which arrhythmias typically develop, or focal radiofrequency ablation aimed at eliminating the ventricular premature beats that trigger VT/VF [59]. These options remain largely unexplored at present.

Conclusions

In the span of 16 years, the Brugada syndrome has rapidly gained recognition as a major cause of SCD throughout the world, particularly in Southeast Asia. Although we have made great strides in our understanding of the syndrome, substantial controversies persist, particularly with respect to risk stratification of asymptomatic patients. We look forward to the availability of data from prospective trials to further refine our approach to diagnosing and treating the Brugada syndrome and related diseases.

Two additional genes have very recently been associated with the Brugada syndrome. Watanabe et al. [89] reported mutations in *SCN1B* causing defects in the β1 and β1b subunits of the sodium channel, leading to a loss of function in I_{Na}, in three kindreds manifesting Brugada syndrome and conduction disease. Our group reported the sixth gene *KCNE3* [90]. A defect in *MiRP2*, the gene product of *KCNE3*, was shown to cause a gain of function in I_{to}. I_{to} has long been thought to play a pivotal role in electrocardiographic and arrhythmic manifestations of the Brugada syndrome. This is the first demonstration of the involvement of an I_{to}-related gene.

Disclosures

This article was supported by grant HL47678 from the National Heart, Lung, and Blood Institute and New York State and Florida Grand Lodges F. & A. M. Eyal Nof was supported by fellowship grants from Biotronik and the American Physicians Fellowship for Medicine in Israel. No other potential conflicts of interest relevant to this article were reported.

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