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Atrial Fibrillation and Brugada Syndrome

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Abstract

Brugada syndrome is characterized by right bundle branch block pattern with ST-segment elevation in leads V_1 to V_3 and a propensity for sudden cardiac death due to ventricular arrhythmias. The arrhythmogenic substrate in Brugada syndrome may not be restricted to the ventricles, and atrial arrhythmias are being increasingly reported. Incidences of spontaneous atrial arrhythmias vary from 6% to 38% and those of inducible atrial arrhythmias from 3% to 100%. Atrial fibrillation (AF) is the most common atrial arrhythmia found in Brugada syndrome. Enhanced duration of atrial action potential and increased intra-atrial conduction time may contribute to the genesis of atrial arrhythmias in Brugada syndrome. Atrial arrhythmias are an important cause of inappropriate discharge of implantable defibrillators in patients with Brugada syndrome. Hence, implantation of dual-chamber defibrillators and careful programming of single-chamber devices have been recommended. Atrial fibrillation has been associated with mutations in both the sodium and calcium channels of the heart, as well as with cases of Brugada syndrome that could not genotyped to any of the known genes associated with the disease. This observation suggests that the substrate responsible for the development of ventricular arrhythmias also may contribute to arrhythmogenesis in the atria of the heart. The presence of a prominent transient outward current in atria and the observation that episodes of AF are triggered by closely coupled atrial extrasystoles point to the possibility that a substrate similar to that responsible for ventricular arrhythmogenesis underlies the development of AF in patients with Brugada syndrome.

Brugada syndrome is characterized by right bundle branch block pattern and ST-segment elevation in precordial leads V_1 to V_3 on electrocardiogram (ECG) and a propensity for sudden cardiac death (1). Several studies have linked the genetic basis of Brugada syndrome to mutations in the gene that encode the α subunit of the sodium channel (2). More recent studies have linked the syndrome to mutations in genes that encode the α and β subunits of the calcium channel (3) and the gene that encodes glycerol-3-phosphate dehydrogenase 1-like enzyme (GPD1L) (4). The 4 genes thus far identified are estimated to account for approximately 28% of Brugada syndrome probands. Accordingly, 72% of cases remain unaccounted for by genotype. Life-threatening ventricular arrhythmias are the hallmarks of Brugada syndrome. The arrhythmogenic substrate in Brugada syndrome may not be restricted to the ventricular level. Similar changes occur in the atria and could be the substrate for re-entrant atrial tachyarrhythmias. Atrial arrhythmias are being increasingly recognized in patients with Brugada syndrome. Incidences of spontaneous atrial arrhythmias between 6% and 38% have been reported. The inducibility of atrial arrhythmias has ranged from 3% to 100% (Table 1) (5–15). Bordachar et al. (9) have suggested that the disease process is more advanced in Brugada syndrome patients with atrial arrhythmias. One of the largest studies that has reported on atrial arrhythmias in Brugada syndrome is from Sacher et al. (11). Thirty-two of their 220

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patients had supraventricular arrhythmias, with 23 of them (10% of patients) having atrial fibrillation (AF). This was a retrospective evaluation of Brugada syndrome patients with an implantable cardioverter-defibrillator (ICD) from 14 centers.

Atrial fibrillation is the most common atrial arrhythmia found in Brugada syndrome, although a few cases of associated atrioventricular nodal re-entrant and atrioventricular re-entrant tachycardia with accessory pathway have also been noted (12). Some studies have reported prolongation of atrio His and His ventricular (HV) interval; these changes occur principally in patients with SCN5A mutations (16) and are consistent with a decreased excitability in the conduction system secondary to the loss of function of sodium channel activity. Vagal activity is believed to contribute to the ST-segment elevation and slower atrioventricular conduction in Brugada syndrome as well as in the initiation of paroxysmal AF (7). Bordachar et al. (9) noted that patients with an HV interval > 55 ms had significantly more atrial arrhythmias than those with a normal HV interval (66% vs. 8.5%; $p < 0.001$).

Clinical predictors of AF in Brugada syndrome

Bigi et al. (15) studied the clinical predictors of AF in Brugada syndrome. Of the 28 patients with Type 1 ST-segment elevation ECG pattern, 15 had paroxysmal AF. All of them had previous life-threatening cardiac events (8 had syncope, 2 had ventricular fibrillation, 4 had polymorphic ventricular tachycardia, and 1 had aborted sudden cardiac death). Multiple regression analysis did not show any correlation between various parameters such as left atrial size, age, and P-wave dispersion.

Noninvasive evaluation

The atrial arrhythmias are triggered by atrial premature beats as observed on Holter recordings of the arrhythmia. The prematurity and P-on-T morphology of these beats also suggest a pulmonary vein focus (9) or phase 2 re-entry mechanism. The presence of atrial arrhythmias has been correlated with inducible ventricular arrhythmias in patients with Brugada syndrome. Patients with a spontaneous Brugada-type ECG are more likely to have atrial arrhythmias than those who manifest the pattern only on challenge with drugs like flecainide. Greater incidences of atrial arrhythmias have also been noted in patients with ICDs than those without, presumably because the former were implanted ICDs because of risk factors for sudden cardiac death and more severe form of Brugada syndrome (9).

Signal-averaged ECG has been used to assess the vulnerability to AF. The filtered P-wave duration is prolonged in patients with Brugada syndrome. In one study (9), the mean filtered P-wave duration was 143.2 ± 12.9 ms in patients with Brugada syndrome and 129.6 ± 10.1 ms in controls ($p < 0.01$). Similar findings were reported by Osaka et al. (17) in their study; mean filtered P-wave duration was 143.7 ± 10.3 ms in patients versus 122.3 ± 9.9 ms in controls ($p < 0.0001$).

Invasive electrophysiologic evaluation

Atrial vulnerability is enhanced in Brugada syndrome, as documented by electrophysiologic studies. The duration of atrial action potential is prolonged (80.3 ± 18.0 ms in patients vs. in controls 59.3 ± 9.2 ms, $p < 0.001$) (12). As discussed herein, although an association between prolonged atrial action potentials and AF seems counterintuitive, the increased vulnerability of the atrium may be secondary to a concomitant increase in dispersion of repolarization and refractoriness, as occurs in the ventricular myocardium. This hypothesis is among many that remain to be tested. Increased intra-atrial conduction time also may contribute to the genesis of atrial arrhythmias. Morita et al. (7) reported that right atrial effective refractory period is not

prolonged in Brugada syndrome but that intra-atrial conduction time is significantly increased (168.4 ± 17.5 ms vs. 131.8 ± 13.0 ms, $p < 0.001$).

Induction of AF with programmed extrastimulation of the atria in patients without the spontaneous clinical arrhythmia also has been noted. All 11 patients studied by Yamada et al. (12) had AF induced by a protocol using up to 2 extrastimuli from the high right atrium. The mean right atrial refractory period at a cycle length of 600 ms was 196.6 ± 28.3 (160 to 240) ms in these patients, which was not significantly different from controls (206.6 ± 22.3 [170 to 245] ms). Other studies using single extrastimuli reported a much lower rate of induction of AF. Eckardt et al. (5) could induce AF in only one of the 35 patients studied, though 9 others developed other supraventricular arrhythmias with a single atrial extra stimulus. In the series reported by Morita et al. (7), AF was induced in 8 of 14 patients (57%) with single extrastimuli. In both of these series, patients displayed clinical episodes of AF. Moriata et al. (7) reported 8 patients with inducible AF; 6 did not have spontaneous AF, and 1 of the 7 patients with spontaneous AF did not have inducible AF. They defined inducible AF as one that was precipitated with programmed electrical stimulation and persisted for at least 30 s. In one of their patients, AF also was induced by isoproterenol infusion. An important limitation of these studies is that induced AF is a weak surrogate for the clinical arrhythmia.

Significance of AF in Brugada syndrome patients receiving an ICD

Atrial arrhythmias are an important cause of inappropriate ICD shocks in patients with Brugada syndrome. In one study, the number of inappropriate shocks (14%) exceeded the number of appropriate shocks (10.5%) (8). Dual-chamber ICDs are useful in preventing such inappropriate shocks in patients with paroxysmal AF, but this has to be weighed against the increased complication rate associated with the atrial lead placement. Another, less invasive and, at times, simpler option is the use of rate-lowering drugs. Careful programming of single-chamber ICDs also is recommended to avoid inappropriate shocks in those without documented AF. Kharazi et al. (13) reported similar findings. In their study, 41% had inappropriate shocks whereas 17% had appropriate shocks. Of the 5 patients who had inappropriate shocks, 2 had AF. Sacher et al. (11) also found that inappropriate shocks were 2.5 times more common than appropriate ones. In their study, supraventricular arrhythmia was the reason for shock only in 9 of the 45 patients who received inappropriate shocks. One hundred ninety-six of their patients have received single-chamber ICD and 24 received dual-chamber devices.

Genetic basis

The past decade has witnessed steady progress in our ability to elucidate the genetic basis of the Brugada syndrome. *SCN5A*, the gene that encodes the α subunit of the cardiac sodium channel, was the first gene linked to Brugada syndrome. (2) More than one-hundred mutations in SCN5A have been linked to the syndrome in recent years (18). Some of these mutations have been studied in expression systems and shown to result in loss of function due either to: 1) failure of the sodium channel to express; 2) a shift in the voltage- 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. Mutations in the *SCN5A* gene account for approximately 15% of Brugada syndrome probands (3,19,20). A greater incidence of *SCN5A* mutations has been reported in familial than in sporadic cases (20). Negative *SCN5A* results do not rule out causal gene mutations, because the promoter region, cryptic splicing mutations or presence of gross rearrangements are generally not part of routine investigation. Hong et al. (21) 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. The deletion of fragments of segments 2 and 3 of domain IV of SCN5A

caused complete loss of function. Bezzina et al. (22) recently provided interesting evidence in support of the hypothesis that SCN5A promoter polymorphism common in Asians modulate 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 6 polymorphisms in near-complete linkage disequilibrium that occurred at an allele frequency of 22% in Asian subjects and was absent in white and black patients. The results of the study 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. A second locus on chromosome 3, close to but distinct from SCN5A, has recently been linked to the syndrome (23) in a large pedigree in which the syndrome is associated with progressive conduction disease, a low sensitivity to procainamide, and a relatively good prognosis. The gene recently was identified as the GPD1L. A mutation in GPD1L has been shown to result in a reduction of I_{Na} (4). The third and fourth genes associated with the Brugada syndrome were reported earlier this year and shown to encode the α1 (CACNA1C) and β (CACNB2b) subunits of the L-type cardiac calcium channel. Mutations in the α and βsubunits of the calcium channel can also lead to a shorter than normal QT interval, creating a new clinical entity consisting of a combined Brugada/short-QT syndrome (3). Because the genetic basis of all cases of Brugada syndrome have not been identified in approximately 72% of probands, defects other than sodium channel, calcium channel, or GPD1L also could cause Brugada syndrome.

Atrial fibrillation has been associated with mutations in both the sodium and calcium channels of the heart, as well as with cases of Brugada syndrome that could not be genotyped to any of the known genes associated with the disease (3,24). This observation suggests that the substrate responsible for the development of ventricular arrhythmias also may contribute to arrhythmogenesis in the atria of the heart.

Cellular and ionic mechanisms

The available data support the hypothesis that the electrocardiographic and ventricular arrhythmic manifestations of Brugada syndrome result from amplification of heterogeneities intrinsic to the early phases of the action potential among the different ventricular cell types. The amplification is secondary to a rebalancing of currents active during phase 1, including a decrease in I_{Na} or calcium channel current or augmentation of any one of a number of outward currents. ST-segment elevation similar to that observed in patients with the Brugada syndrome occurs as a consequence of the accentuation of the action potential notch, eventually leading to loss of the action potential dome in right ventricular epicardium, where transient outward current (I_{to}) is most prominent. Loss of the dome gives rise to both a transmural as well as epicardial dispersion of repolarization. The transmural dispersion is responsible for the development of ST-segment elevation and the creation of a vulnerable window across the ventricular wall, whereas the epicardial dispersion give to phase 2 re-entry, which provides the closely coupled extra-systole that captures the vulnerable window, thus precipitating ventricular tachycardia/ventricular fibrillation. The presence of a prominent I_{to} appears to be a prerequisite for these mechanisms to evolve and presence of a prominent I_{to} in the right ventricular epicardium forms the basis for why the Brugada syndrome is a right ventricular disease (25).

The presence of a prominent I_{to} in atria and the observation that episodes of AF are triggered by closely coupled atrial extrasystoles point to the possibility that a substrate similar to that responsible for ventricular arrhythmogenesis underlies the development of AF in patients with Brugada syndrome. Additional research is clearly needed to examine the validity of this hypothesis. Relevant to this issue is a recent report demonstrating a major difference in the electrophysiology of atrial and ventricular sodium channels in the canine heart. These studies

indicate that steady-state inactivation $V_{0.5}$ is 16 mV more negative in atrial than in ventricular cells, rendering a large fraction of sodium channels unavailable at the normal resting membrane potential (26,27). An intrinsically more positive resting membrane potential in atria (approximately −83 mV) versus ventricles (approximately −87 mV) contributes to the atrioventricular difference in sodium channel availability. These findings suggest that the impact of some *SCN5A* mutations may be greater in the atria than in the ventricles, and thus may predispose to the development of AF more readily than to ventricular arrhythmias.

Although genetic mutations responsible for the Brugada syndrome are equally distributed between men and women, the Brugada phenotype is generally 8 to 10 times more prevalent in men than in women. The basis for this gender-related distinction has been shown to be due to a more prominent I_{to}, giving rise to a more prominent action potential notch in the right ventricular epicardium of men versus women (28). It is not clear whether this gender distinction extends also to the prevalence of AF. Studies in which an association of AF with Brugada syndrome has been evaluated have involved mostly males. All patients in the series reported by Morita et al. (7) and Yamada et al. (12), both with and without AF, were men. The vast majority of Brugada patients in the series reported by Itoh et al. (6), and Park et al. (8) also were men.

The extent to which *SCN5A* mutations apparently unrelated to Brugada syndrome may be associated with AF is not well defined. It is noteworthy that mutations in *SCN5A* associated with AF have been reported in relatives of probands with idiopathic dilated cardiomyopathy. In the study of Olson et al. (29), among family members with *SCN5A* mutations, 38% had dilated cardiomyopathy (mean age at diagnosis was 47.9 years) and 43% had AF (mean age at diagnosis was 27.8 years). It would be of interest to conduct a similar study with families of probands with Brugada syndrome.

Study limitations

Many of the large series of patients with Brugada syndrome do not report the incidence or characteristics of atrial arrhythmias, for example, Brugada et al. (30), 547 patients; Eckardt et al. (31), 212 patients; Priori et al. (32), 200 patients. The only large study that reported on atrial arrhythmia was the retrospective analysis by Sacher et al. (11) of 220 Brugada syndrome patients with an implantable defibrillator. Because of the retrospective nature of the study, no electrophysiological data on AF are available from this study. Hence, larger studies with prospective and detailed evaluation of AF and other atrial arrhythmias in Brugada syndrome are needed to establish the link between the two. Another limitation is that AF often occurs without symptoms, even in “symptomatic” patients and it is likely that there is an underestimation of the “true” AF rate.

The degree to which AF is inducible in patients with Brugada syndrome also may be underestimated because symptomatic patients with Brugada syndrome as a general rule do not undergo electrophysiological testing. The second consensus report published in 2005 recommended electrophysiological testing of symptomatic patients for the express purpose of assessing the potential for supraventricular arrhythmias (25,33).

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Abbreviations and Acronyms

AF

atrial fibrillation

ECG

electrocardiogram

HV

His ventricular

ICD

implantable cardioverter-defibrillator

I_{Na}

sodium channel current

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Table 1

Incidence of Atrial Arrhythmias in Brugada Syndrome

Author	Year	No. of Patients	Incidence of Atrial Arrhythmias		
			Total	Atrial Fibrillation	
				Spontaneous	Inducible
Eckardt et al. (5)	2001	35	29%	—	3% (1/35)
Itoh et al. (6)	2001	30	30%	30% (9/30)	—
Morita et al. (7)	2002	18	—	39% (7/18)	57% (8/14)
Park et al. (8)	2003	15	40%	27% (4/15)	8% (1/13)
Bordachar et al. (9)	2004	59	20%	17% (12/59)	—
Junttila et al. (10)	2004	18	6%	6% (1/18)	—
Sacher et al. (11)	2006	220	15%	10% (23/220)	—
Yamada et al. (12)	2006	11	100%	0	100% (11/11)
Kharazi et al. (13)	2007	12	17%	17% (2/12)	—
Miyamoto et al. (14)	2007	98	20%	20% (20/98)	—
Bigi et al. (15)	2007	28	53%	53% (15/28)	—

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