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STATE-OF-THE-ART PAPER

Atrial Fibrillation and Brugada Syndrome

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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. (J Am Coll Cardiol 2008;51:1149–53) © 2008 by the American College of Cardiology Foundation

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 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,

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Abbreviations and Acronyms

AF = atrial fibrillation
ECG = electrocardiogram
HV = His ventricular
ICD = implantable cardioverter-defibrillator
I_{Na} = sodium channel current

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).

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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