

ORIGINAL ARTICLE

Long-term follow-up in patients with Brugada Syndrome in South China

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Abstract

Objective: To evaluate the presence of Brugada electrocardiogram (ECG) pattern, clinical characteristics, treatment, and long-term prognosis of Brugada syndrome in southern Chinese population.

Methods: This prospective study consisted of a consecutive series of patients with diagnostic coved type I Brugada ECG pattern at baseline between January 2007 and February 2020. Histories of symptoms including ventricular tachycardia (VT)/ventricular fibrillation (VF) episode, syncope, and family history of Brugada Syndrome (BrS) or unexplained sudden cardiac death were collected. Electrophysiological study and implantable cardioverter-defibrillator (ICD) were performed. All patients included in this study were followed up in the outpatient department every 6 months after baseline evaluation. Occurrences of syncope, VF, and sudden death were independently analyzed by two cardiologists.

Results: 45 (56.3%) patients were diagnosed with BrS. During a mean follow-up of 7.9 ± 3.6 years, six patients had experienced documented VF/sudden cardiac death (SCD) or recurrent syncope. Two patients experienced episodes of syncope more than once. Two patients experienced onset of electrical storm with a total of 11 episodes of VF. There were 50% of these events occurring in fever status. One of patient with BrS died of SCD.

Conclusion: There was a very low prevalence of Brugada syndrome in southern Chinese population. The risk of arrhythmic events was low in asymptomatic patients. ICD was high effective in preventing SCD without adverse device outcome in long-term follow-up. Fever can lead to predispose to malignant arrhythmia, and aggressive treatment of febrile state in Brugada syndrome was recommended.

KEYWORDS

Brugada ECG pattern, Brugada syndrome, follow-up, southern Chinese population

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1 | INTRODUCTION

Brugada syndrome, first described by Pedro and Josep Brugada in 1992 Brugada and Brugada, (1992), is a lethal channelopathy disease characterized by typical ECG pattern in precordial lead in V1–V3 and predisposition to increase the risk of SCD caused by ventricular fibrillation in the absence of structural heart disease (Brugada et al., 1998). Mutations in SCN5A encoding the α -subunit of the sodium ion channel result in loss of function in the depolarizing I_{Na} current (Chen et al., 1998), which occurs in 15%–20% of BrS cases. There are three types of Brugada ECG patterns (Gussak et al., 1999). Only type 1 ECG pattern is essential to the diagnosis of BrS. Type 2 and 3 are suspected but not diagnostic (Antzelevitch et al., 2005).

Brugada syndrome is more prevalent in Southeast Asia Miyasaka et al., (2001). Large cohort population study has been conducted based most on European population (Benito, Sarkozy, et al., 2008; Hermida et al., 2000). However, data concerning the characteristics and long-term follow-up of Brugada syndrome in southern Chinese population are limited. Therefore, we performed a prospective clinical study to evaluate the presence of Brugada ECG pattern, clinical characteristics, treatment and long-term prognosis of Brugada syndrome in southern Chinese population.

2 | METHODS

2.1 | Study population

The prospective study consisted of a consecutive series of patients with diagnostic coved type I Brugada ECG pattern at baseline between January 2007 and February 2020 at the center of the First People's Hospital of Zhaoqing City and NanFang Hospital, Guangzhou, China. Surface twelve-lead ECG and echocardiography were routinely performed. Regardless of whether they are symptomatic or not, as long as the ECG examination shows the type I Brugada waveform in inpatient or outpatient, they are included in this study. Histories of symptoms, such as VT/VF episode, syncope, and family history of BrS or unexplained SCD, were collected. The presence of structural heart disease was excluded by echocardiographic study, cardiac magnetic resonance imaging, exercise testing, and coronary angiography.

2.2 | Brugada ECG pattern and diagnosis of BrS

Twelve-lead ECG data were recorded at a paper speed of 25 mm/s during sinus rhythm in the supine resting state. Type 1 ECG pattern was defined by a coved ST-segment elevation of 0.2 mV followed by a negative T wave showing on at least 2 right precordial leads (either spontaneously or after pharmacologic provocation with a sodium channel blocker). Type 2 pattern was defined by a 0.2 mm J point elevation and saddleback-type ST elevation with positive T wave. Sodium channel blockers used to confirm the diagnostic ECG pattern

was flecainide (2 mg/kg iv. in 10 min) in the current study. The test was considered to be positive if a type 1 Brugada ECG pattern was obtained. Electrocardiograms were analyzed by two investigators.

According to the second Brugada consensus statement (Antzelevitch et al., 2005), the diagnosis of BrS was made in presence of the type 1 Brugada ECG pattern with or without a sodium channel blocker challenge test in combination of one of the following clinical manifestations: history of spontaneous VT/VF episode or aborted SCD, family history of sudden death before the age of 45 or coved-type ECG, syncope or nocturnal agonal respiration, and inducibility of ventricular tachycardia with programmed electrical stimulation.

2.3 | Electrophysiologic study

Electrophysiologic study (EPS) was conducted in the fasting state with local anesthesia and after the signature of informed written consent. All antiarrhythmic drugs were discontinued at least 5 half-lives before the procedure. Surface ECG leads filtered at 30–500 Hz were recorded. Multielectrode catheters (Biosense-Webster, USA) were introduced percutaneously through the femoral veins. The EPS induction protocol was performed at right ventricular apex (RVA) and right ventricular outflow tract (RVOT) by 3 different basic pacing cycle lengths (600, 500, and 400 ms) with a minimum coupling interval of 200 ms for the last extra stimuli. The result of programmed stimulation was considered positive if ventricular arrhythmia requiring direct cardioversion or lasting over 30 s was induced.

2.4 | Implantable cardioverter-defibrillator

After written informed consent had been provided, the cardiologists and patients were both free to decide single versus dual-chamber ICD implantation and device manufacturer. Appropriate shocks were defined as shocks delivered for VT or VF. Electrical storm was defined as 3 or more episodes of treated VT/VF within 24 hr. Patients with ICD implanted were routinely examined at 3–6 months' intervals for outpatients' clinic review. In the condition of a shock or suspected device-related complications, patients were admission to hospitalization within 12 hr and device interrogated was required.

2.5 | Follow-up

All patients included in this study were followed up in the outpatient department every 6 months after baseline evaluation, or otherwise in case of arrhythmic events occurred. In patients with ICD, analysis of arrhythmias and shocks (appropriate or inappropriate) were also performed. Arrhythmic events, determined as an occurrence of syncope, VF or sudden death were independently analyzed by two cardiologists. The last follow-up was ended in April 2020.

2.6 | Statistical analysis

For normally distributed variables, data were described as mean \pm standard deviation. Significant differences between groups were evaluated with Student's *t* test or Mann-Whitney *U* test. Categorical variables were compared using Chi-square analysis or Fisher's exact test. All comparisons were conducted two sided and a value of $p < .05$ was considered statistically significant. The statistics were calculated using SPSS (version 13.0, SPSS Inc, Chicago, IL, USA).

3 | RESULTS

3.1 | Patient characteristics and diagnosis of BrS

A total of 86 patients with diagnostic coved type 1 ECG pattern were included in the study. 10 patients were excluded in further study for coronary artery disease ($n = 3$), aortic valve stenosis ($n = 2$), and hypertrophic cardiomyopathy ($n = 1$). Finally, 80 patients without structure heart diseases were analyzed. 96% of them were male, and the average age was 43.8 ± 13.6 years old at diagnosis, ranging from 17 to 73. The general characteristics of the study population

TABLE 1 Comparison of clinical characteristics between type 1 ECG pattern patients with and without baseline consensus clinical criteria

Baseline characteristics	Patients with Type 1 pattern only	Patients with diagnostic BrS	<i>p</i> value
Number of patients (%)	35 (43.7%)	45 (56.3)	
Age (mean <i>SD</i>)	40.4 ± 8.1	44.2 ± 14.1	.185
Gender (male)	32	45	.182
Family history	0	12	.001
Clinical presentation			
asymptomatic	30	22	.001
Syncope	0	20	.001
Aborted SCD	0	3	.119
Palpitation and others	5	0	.009
Baseline ECG			
Type 1	31	34	.139
Type 2	4	11	.139
Unmask type 1 by fever	1	8	.036
ICD implantation	0	10	.003
EPS performed	3	7	.349
Induced VT/VF	0	4	.196
Syncope/VF/SCD during FU	0	5	.116

at baseline diagnosis were summarized (Table 1). A coved type 1 Brugada ECG pattern was found in 65 patients (81%) spontaneously (Figure 1a), five patients after a sodium channel blocker challenge (Figure 1b), and nine patients during fever. Interestingly, one patient with syncope episode had converted type 1 Brugada ECG pattern from type 2 after drinking strong tea. At diagnosis, 52 patients (65%) were asymptomatic, 20 patients (25%) had previously at least 1 episode of syncope, and 3 patients (3.75%) had been resuscitated from VF.

A total of 45 (56.3%) patients were diagnosed with BrS due to the following clinical manifestation: syncope without obvious extra-cardiogenic in 20 (25%) BrS patients, a family member with coved type I diagnostic ECG or SCD before 45 years old in 15 (18.7%) patients, inducible VT during EPS in 4 (5%) asymptomatic patients, documented non-sustained VT in seven (8.7%) patients and aborted SCD in 3 (3.7%) patients. In general, the symptoms of four patients met 2 clinical diagnostic criteria and of 41 patients met 1. In the remaining 35 patients with type 1 ECG at diagnosis, 30 patients were asymptomatic, and one patient had a palpitation. Comparisons were made between patients with type 1 Brugada ECG pattern only and patients with BrS. Compared with the type 1 ECG only patients, patients with BrS had more symptoms of syncope at baseline evaluation ($p < .001$). Unmask type 1 by fever was significantly manifested in BrS group ($p = .036$).

3.2 | EPS and ICD

EPS was performed in 10 patients, including four with family history, three with syncope, and three with asymptomatic. The remaining asymptomatic patients were proposed to receive EPS but refused. Sustained polymorphic VT or VF occurred in four patients (40%) including one syncope patient. ICDs were implanted in 10 of 45 BrS patients with a mean ICD follow-up period of 57.0 ± 32.3 months after implantation. Five patients (50%) had a Biotronik device (Biotronik Corporation, Berlin, Germany), three (30%) had a St Jude Medical device (St. Jude Medical Inc, St. Paul, Minneapolis, MN), and two patients had a Medtronic ICD (Medtronic Inc, Minneapolis, MN). All implanted devices were single-chamber. A total of 21 shocks in 4 patients were detected. The four patients who received shocks were all male, and there was no significant difference in baseline among the three groups compared with those with and without ICD or shocks. Inappropriate shock and device complication did not occur during ICD implantation and long-term follow-up.

3.3 | Follow-up and outcome

During a mean follow-up of 7.9 ± 3.6 years, documented VF/SCD or recurrent syncope occurred in six (13.3%) BrS patients while none occurred in type 1 pattern only subjects. Two patients suffered episodes of syncope more than once. Interestingly, 50% of these events happened in fever status. Two patients experienced onset of

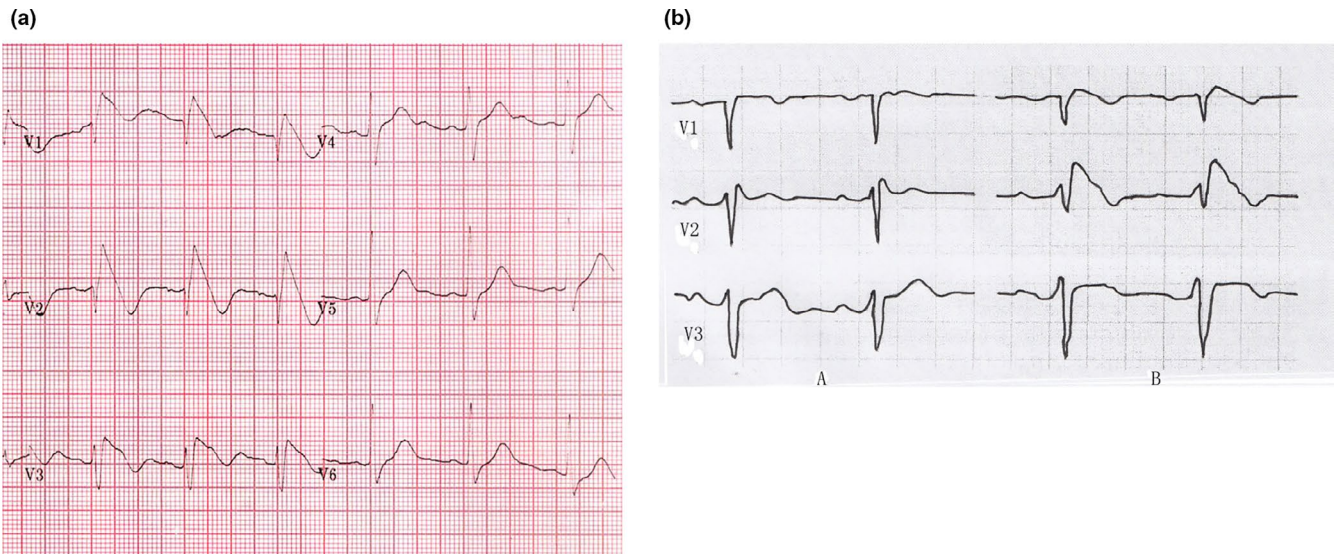


FIGURE 1 The covered type 1 Brugada ECG pattern in (A) 65 patients spontaneously (B) 5 patients after a sodium channel blocker challenge

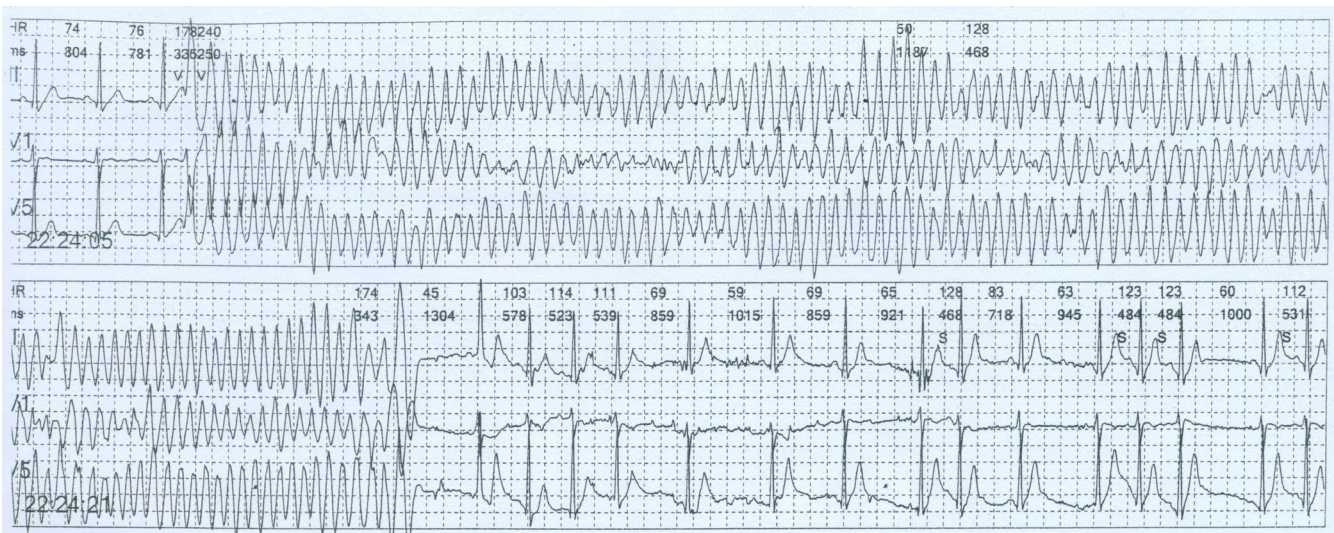


FIGURE 2 The electrical storm with a total of 11 episode of VF within 24 hr in patients with fever

electrical storm with a total of 11 episode of VF within 24 hr, which were also during febrile state (Figure 2). One of BrS patients died of SCD. Four of 10 patients with ICD implanted had appropriate ICD shocks for VF, including one patient with 8 electrical storms, which were terminated appropriately by the ICD. VF events were detected by Home monitor (Lumax300VR-T, Biotronik, Germany) and EGM was transmitted soon after onset of the VF (Figure 3). No inappropriate shock was observed in these ten patients.

4 | DISCUSSION

The prevalence of Brugada-type ECG findings (type 1 and 2) in the general population has been reported ranging between 0.01% and 6.1%, which is higher in Asia (0.36%) than Europe (0.25%) (Mizusawa

& Wilde, 2012). However, the prevalence of BrS is unknown in Chinese population. Sidik et al., (2009) reported a much higher prevalence of both Brugada sign and syndrome in a hospital-based population in Singapore, of which 76.8% patients were Chinese. In our present study, based on the great amount of outpatients visits at the Nanfang Hospital over a more than 10-year period from 2007 to 2020 for more than 2 million visits annually, the prevalence was much lower than the other Asian countries reported with rates of 25.9 and 26.3 per 100 000 in Thailand (Tatsanavivat et al., 1992) and the Philippines (Munger & Booton, 1998), respectively.

BS is not constant in some patients, which may fluctuate with modulating factors. Autonomic nervous system (Miyazaki et al., 1996), electrolyte disturbance (Benito et al., 2008b), and body temperature (Antzelevitch & Brugada, 2002) sometimes unmask the BrS ECG pattern or even cause malignant arrhythmias. We found

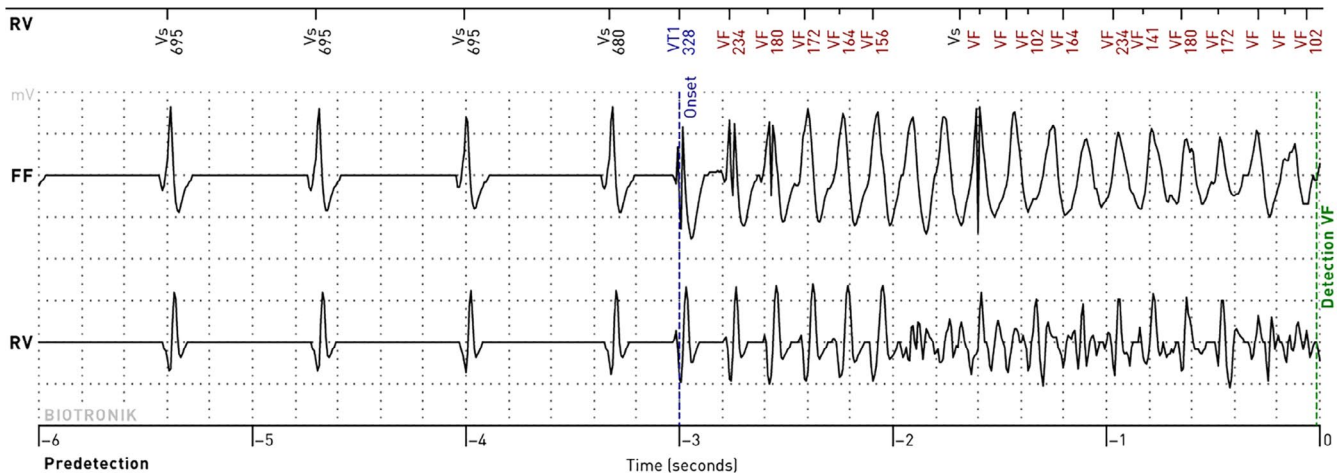


FIGURE 3 The VF events detected by Home monitor and the transmitting of EGM soon after onset of the VF

that drinking strong tea might be one possible precipitating factor for recurrent syncope in one patient, which was seldom reported. For the lack of large ECG screen for Brugada ECG pattern in a large community-based population, or even without the situation, the presence of intermittent manifestation of Brugada ECG made the diagnosis difficult in some cases. For example, five out of our patients unmasked type 1 ECG pattern using drug challenge. So the diagnostic type 1 pattern ECG was definitely lower than the real prevalence. Benito, Sarkozy, et al. (2008) reported a series of 384 BrS patients of whom 301 (78.3%) were asymptomatic. Probst et al., (2010) found 64% asymptomatic patients in the FINGER registry study. However, in our study, 23 out of 45 patients with Brugada Syndrome presented syncope or aborted SCD as first manifestation of the disease. It is possible that sudden death may be the first manifestation of the disease in a previously asymptomatic individual before diagnosis was made. We believed that the awareness of the severity of the disease was not fully aroused before adverse outcome happened in Chinese community, where patients were not routinely to carry out an ECG examination, making the diagnosis even difficult. Due to the above reasons, the true incidence of the disease in China was likely underestimated.

EPS remains controversial as a method of stratification (Brugada et al., 2003; Priori et al., 2002, 2012). In this study, we only performed EPS in 10 of the 80 patients and 4 had a positive outcome. So it had little value in identifying patients at high risk of future cardiac events due to the small sample. The implantation of an ICD is the only proven effective treatment for the prevention of SCD (Antzelevitch et al., 2005; Nademanee et al., 2003; Steven et al., 2011). In the study group, most refused to receive EPS and ICD implanted due to the low social economic status. In spite of the small size of our patients with implanted ICD, there were 13 appropriate shocks in 4 BrS patients and no inappropriate shock or device complication during the long-term follow-up, implicating the high efficacy and safety of protection of SCD. A series of literatures have reported a high long-term complication rate of Brugada patients with ICD implanted (Rosso et al., 2008), especially in low-risk patients. Sacher et al., (2006) reported significant risk of device-related complications

(8.9%/year). Additionally, inappropriate shocks were 2.5 times more frequent than appropriate ones. Sarkozy et al., (2007) studied 47 patients with BS, who underwent primary prophylactic ICD implantation. They found that 17 patients received inappropriate shocks. In a study conducted by Steven et al., (2011), adverse effects of an ICD occurred in 24% of patients, and ICD-related adverse effects in patients without a previous history of SCD exceeded the frequency of ventricular arrhythmias. These data emphasize balancing the benefit and risk using ICDs in asymptomatic BS patient, especially in active and younger patients.

During the long-term follow-up, six patients experienced recurrent syncope and documented VF, of whom 3 had a history of symptom before. At baseline, patients with Brugada syndrome were more prone to develop syncope than patients with type 1 ECG pattern only ($p < .001$), but the long-term survival rate was not significantly different ($p = .116$). It is less controversial that a previous episode of SCD and syncope is markers of future life-threatening arrhythmia events (Zipes et al., 2006). However, there are controversial in risk stratification of asymptomatic patients. Recently, a large cohort of BrS patients in FINGER registry data showed that asymptomatic patients seemed to be at low risk (Probst et al., 2010). Eckardt et al., (2005) reported a recurrent arrhythmic event in only 0.8% asymptomatic patients after a mean follow-up of 40 months. Similar to the previous studies, asymptomatic patients in this study showed no cardiac event (VF or death), predicting the relatively good long-term prognosis. However, Brugada et al., (2003) reported a significantly high risk of asymptomatic patients suffering SCD or documented VF during follow-up. In our present study, no arrhythmic events were observed in the coved type 1 ECG only patients during long-term follow-up, thus none of them change diagnostic category from idiopathic Brugada ECG pattern to Brugada syndrome. Consistent with the previous report, patients with coved type 1 ECG only were at low risk of adverse outcome (Delise et al., 2011).

The relationship between electrical storm and BrS is seldom reported. In this study, we encountered 2 out of 45 (4.4%) BrS patients developed electrical storm during follow-up, who both were implanted with ICD. One patient suffered from diarrhea and

developed fever and low serum potassium. The other patient had fever only. Low serum potassium level or fever is suggested to be a predisposing factor for VF in patients with Brugada syndrome (Antzelevitch & Brugada, 2002; Benito, Brugada, et al., 2008). Ohgo et al., (2007) compared patients with and without history of electrical storm. They reported that no specifically clinical, laboratory, electrocardiographic, and electrophysiological characteristics were recognized in patients with Brugada syndrome associated with electrical storm of VF. In 9 of 80 patients, Brugada-type ECG developed during a febrile episode. Similar to our study, Junttila et al., (2008) also reported the role of fever in triggering malignant arrhythmias in their population. Due to the lack of large cohort study, it is unknown whether fever is a risk factor in patients with a Brugada-type ECG induced by fever. There may be a possible increased risk in those with SCN5A mutations (Keller et al., 2006). Genetic and molecular basis of electrical mechanisms have been proposed to explain the pathophysiology of fever-induced BrS or onset of VF. Dumaine et al., (1999) described an accelerated inactivation of the T1620M mutant sodium channels using patch-clamp studies in vitro. They first reported temperature-dependent dysfunction of cardiac sodium channels. In the following study, Mok et al., (2003) identified that H681P-SCN5A mutant reduced window current during hyperthermia. Morita et al., (2007) had also shown that hyperthermia can abbreviate action potentials and facilitate reentry in canine tissue models. However, gene analysis was not performed in the two ES patients in this study. These mutant genes are temperature-sensitive responsible for accelerating inactivation of the sodium channel. Further impairment of cardiac sodium channel during thermal state makes it more predominance of outward ionic current (I_{to}) at the end of phase 1 of the action potential causing a transmural dispersion of repolarization (Samani et al., 2009), which might predispose some Brugada patients to arrhythmias during the febrile state.

Clinical management of ES in Brugada syndrome primarily relies on reported cases owing to its low prevalence. Isoproterenol (which increases the I-CaL current) and quinidine (a Class Ia AAD with I_{to} and I-Kr blocker effects) have proved to be useful for treating electrical storm in acute and long-term setting in BS (Aiba et al., 2006; Maury et al., 2005; Ohgo et al., 2007; Schweizer et al., 2010). However, quinidine is not available in China. In our hospital, electrical storm in two patients was stabilized electric activity by cooling down the body temperature with cooling maneuvers and normalizing electrolyte disturbance by infusion of potassium magnesium aspartate. It is helpful to advise such patients to avoid and promptly treat febrile states for prevention of malignant arrhythmia.

5 | CONCLUSIONS

In this prospective study, Brugada syndrome has a very low prevalence in southern Chinese population and is probably under-recognized. A total of 51.1% of the patients had symptoms. The risk of arrhythmic events is low in asymptomatic patients. ICD is high effective in preventing SCD without adverse device outcome in long-term

follow-up. Fever in the setting of Brugada syndrome can lead to predispose to malignant arrhythmia. We recommend the aggressive treatment of febrile state in Brugada syndrome.

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