Clinical and Electrophysiologic Characteristics of Patients with Brugada Syndrome: Mid-term Follow-up

Majid Haghjoo, MD, Arash Arya, MD, Zahra Emkanjoo, MD, Farhad Sheikholeslami, MD, Ramezan Bakhshian, MD, M. R. Samieenasab, MD, Zahra Shamsali, MD and M. A. Sadr-Ameli, MD

Abstract

Background-The Brugada syndrome is a distinct form of idiopathic ventricular fibrillation that consists of ECG abnormalities at baseline or after provocation in the absence of documented structural heart disease. In this article, we present the clinical and electrophysiological data and follow-up of our patients with Brugada syndrome, which is the largest ever reported series in Iran.

Methods-We retrospectively studied the clinical, electrocardiographic and electrophysiologic characteristics of twenty consecutive patients with definitive diagnosis of Brugada syndrome that have been evaluated at our center from September 2001 to December 2003. We also searched for possible discriminate variable(s) between patients with vs. without inducible ventricular arrhythmia during programmed electrical stimulation.

Results- We studied 15 men and 5 women with mean age of 42±9 years. The typical ECG abnormality was recognized in five (25%) patients either after resuscitated cardiac arrest (2 patients) or syncopal episodes (3 patients). Fifteen patients (75%) were asymptomatic. The abnormal ECG was identified spontaneously in 6 (30%) patients and after pharmacological challenge with class IA or IC antiarrhythmic drugs in 14 (70%) patients. The mean values of PR interval, QT interval, and ST-segment elevation were similar in symptomatic and asymptomatic individuals (P=0.75, P=0.18, P=0.26, respectively) The PR interval was mildly longer in males compared to females (0.042) but the magnitude of ST-segment elevation was similar in both sexes (P=0.057). Electrophysiologic study was performed in 15 (75%) patients for further risk stratification. The HV interval was longer in males than females (P=0.047). Sustained ventricular arrhythmias were induced in 40% of asymptomatic patients. There was no statistically significant difference in mean age, sex, PR interval, ST elevation, and HV interval of inducible and non-inducible patients. An implantable cardioverter-defibrillator was implanted in 8 (40%) patients with aborted SCD, history of syncope or inducible sustained ventricular arrhythmias in programmed electrical stimulation. During 16±2 months follow-up, one patient had appropriate device therapy. None of the asymptomatic and non-inducible patients experienced any event.

Conclusions- The asymptomatic and non-inducible individuals with Brugada syndrome have a low risk of cardiac events. The baseline demographic (age, sex), and electrophysiologic (PR, ST elevation, HV) data have no role in predicting inducibility in programmed electrical stimulation ***Iranian Heart Journal 2004; 5(1,2):55-63).***

Key words: ■Brugada syndrome ■ fibrillation, ventricular ■electrocardiography ■ death, sudden

The Brugada syndrome is characterized by T-elevation in right precordial leads (V1-V3) that is unrelated to ischemia, electrolyte disturbances, or obvious

From the Department of Pacemaker and Electrophysiology, Shaheed Rajaie Cardiovascular Medical Center, Iran University of Medical Sciences, Tehran, Iran
Correspondence to: Majid Haghjoo MD, Department of Pacemaker and Electrophysiology, Shaheed Rajaie Cardiovascular Medical Center, Mellat Park, Vali-Asr Avenue, Tehran 1996911151, Iran
Fax: +9821-2048174 Phone: +9821-2192971 E-mail: haghjoo@rhc.ac.ir

structural heart disease.[1-3] This syndrome was initially described as a distinct clinical entity associated with a high risk of sudden cardiac death in 1992 by Brugada and Brugada.[1] The syndrome is genetically inherited as an autosomal dominant trait with incomplete penetrance and an incidence ranging between 5 and 66 per 10000.[4,5] In regions of Southeast Asia where it is endemic, the clinical presentation of Brugada syndrome is distinguished by a male predominance (male: female ratio of 8:1) and the appearance of arrhythmic events at an average age of 40 years (range: 1 to 77 years).[6,7] Electrophysiologically, the typical Brugada electrocardiogram (ECG) pattern includes ST segment elevation in the right precordial leads (V1-V3) associated with right bundle branch block, normal QT duration, and mild conduction defects with prolonged PR and HV intervals.[3] Although a number of candidate genes have been proposed for this syndrome, thus far the syndrome has been linked only to mutations of SCN5A, the gene encoding for α-subunit of cardiac sodium channel.[8-11]

The Brugada syndrome is a newly recognized disease with many unknown aspects. Although, several studies were published about this syndrome, there has been no survey of these patients in our country. In this article, we present clinical and electrophysiological data and follow-up of our patients with this ECG abnormality which comprises the largest ever reported series of patients with Brugada syndrome in Iran.

Methods

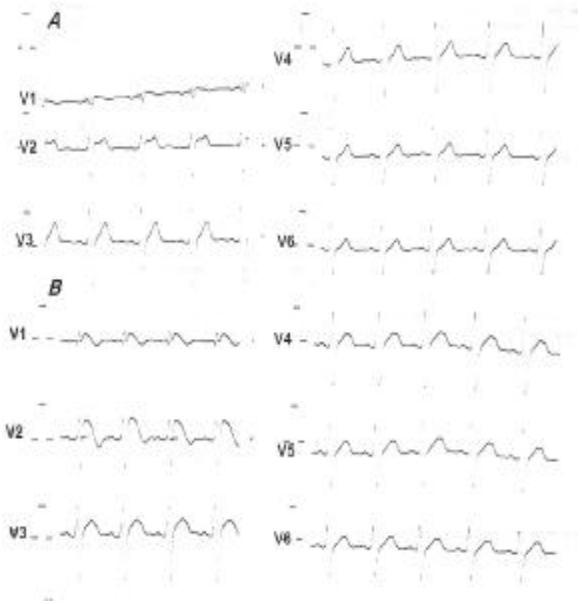
Study population Between September 2001 to December 2003, 20 consecutive patients (15 males; mean age, 42± 9 years) were included. All gave written informed consent for the procedure, and the local hospital ethics committee approved the study. Fourteen of 20 subjects referred to our center for a Brugada syndrome diagnostic work-up with a suspicious ECG underwent an antiarrhythmic challenge test with procainamide or flecainide; the remaining six had typical baseline ECGs. Among our cases, 14 were probands and the other 6 subjects (all asymptomatic) were detected during family screenings after diagnosis of Brugada syndrome in a family member. Structural heart disease was ruled out by means of non-invasive methods (echocardiography and exercise stress testing) and one patient also underwent coronary arteriography. The serum electrolyte levels were normal. Risk stratification was performed by electrophysiological study (EPS).

Definitions. *Symptomatic* patients refers to that group of patients presenting with aborted SCD or syncope and *asymptomatic* to patients presenting with non-specific symptoms or no symptom. *Proband* is defined as the first individual with Brugada syndrome within a family. *Sudden cardiac death* is defined as a sudden and unexpected death occurring within 1 hr after onset of symptoms**.**

Pharmacologic challenge test protocol An intravenous class IA or IC anti-arrhythmic drug was administered to 14 patients; intravenous flecainide at a dose of 2 mg/kg, max. 150 mg over a 10 min. period in 4 patients and intravenous procainamide at a dose of 10 mg/kg over a 10 min. period in 10 patients. ST segment was measured at the J points in leads V1, V2, and V3, and the difference between the ST levels before and after administration of flecainide or procainamide (ST segment elevation) was calculated. Subjects were continuously monitored for 30 minutes after completion of drug administration using a conventional bedside monitor (Zoll

M-series, Germany) equipped with an external defibrillator. A simultaneous 12-lead ECG (Hellige EK501, Germany) was recorded at a paper speed of 25 mm/s and amplitude of 10 mm/mV under basal conditions, two times (5th and 10th min.) during infusion and 5 mins. after the completion of flecainide or procainamide infusion. The ECGs were considered typical when they had a coved-type pattern: a terminal r' wave with a J-point elevation of ≥2 mm and a slowly descending ST segment in continuation with a flat or negative T wave in lead V1 to V3 (Fig. 1). A saddle-type pattern was not considered typical.

Fig.1. (*A*): Resting electrocardiogram of a patient presenting with recurrent syncope. Note that no significant abnormality was seen. (*B*): Marked ST segment elevation in V1-V3 after procainamide administration.



Electrophysiologic study

The electrophysiologic study was done in 15 patients (10 without any symptoms and 5 patients with nonspecific symptoms such as chest pain, palpitation, fatigue and dizziness), and induction of ventricular arrhythmia was attempted without the use of any anti-arrhythmic agents. The criterion for induction of ventricular arrhythmia was induction of sustained PMVT (Fig. 2) or monomorphic VT (MMVT) or VF by programmed electrical stimulation (PES) from the right ventricular apex (RVA). Although different protocols have been used for PES in the Brugada patients, our protocol included up to three extra stimuli (three basic cycle lengths of 600, 500, 400 ms) and minimum coupling interval of 200 ms delivered only from RVA (Ramon Brugada; personal communication).

Statistical analysis

The data analysis was done by SPSS 11.0 software; quantitative values were expressed as mean ± SD. Differences in characteristics between groups were assessed by unpaired t-test for continuous variables and chi-square statistics (or Fisher exact test if necessary) for discrete variables. A P value of <0.05 was considered statistically significant.

Results

Clinical Presentation

We identified 20 subjects (15 men, 5 women; mean age, 42±9 years) diagnosed as Brugada syndrome. In 5 (25%) patients, the abnormal ECG pattern was first identified after an episode of aborted SCD (n=2) or syncope of unknown origin (n=3) (symptomatic patients). In the remaining 15 (75%) patients, the abnormal ECG was recognized during evaluation for nonspecific symptoms (n=7), routine examinations (n=2), and screening of other family members (n=6) (asymptomatic patients) (Table I). Patients were not taking any drug when the abnormal ECG was identified. A family history of SCD was present in 4 of 20 (20%) patients (all asymptomatic). Physical examination was normal in all patients. During 16±2 months

follow-up, none of the asymptomatic patients developed symptoms (SCD or syncope).

Table I. Summary of demographic, clinical, and electrophysiological characteristics.

Case	Age	Sex	Family	Symptom	Baseline ST Morphology	EPS
1	51	F	N	Syncope	Saddle back	NA
2	44	M	N	Asymptomatic	Coved	PMVT
3	44	M	Y	Asymptomatic	Saddle back	VF
4	43	M	N	Asymptomatic	Coved	PMVT
5	45	F	N	Asymptomatic	Saddle back	Non-inducible
6	38	F	N	Asymptomatic	Saddle back	Non-inducible
7	32	M	N	Asymptomatic	Saddle back	Non-inducible
8	53	F	N	Asymptomatic	Saddle back	PMVT
9	43	M	N	Asymptomatic	Saddle back	PMVT
10	50	M	Y	Asymptomatic	coved	Non-inducible
11	39	M	N	Syncope	Saddle back	NA
12	38	M	N	Asymptomatic	Saddle back	Non-inducible
13	42	M	N	Asymptomatic	Saddle back	Non-inducible
14	27	M	N	Asymptomatic	Saddle backe	No n-inducibl
15	28	M	N	Aborted SCD	Saddle back	NA
16	49	M	N	Aborted SCD	Saddle back	NA
17	62	M	N	Asymptomatic	Coved	Non-inducible
18	42	M	N	Syncope	Coved	NA
19	34	F	Y	Asymptomatic	Saddle back	Non-inducible
20	29	M	Y	Asymptomatic	Coved	VF

F=female; M=male; Y=yes; N=no; EPS=electrophysiologic study; NA=not assessed; PMVT=polymorphic ventricular tachycardia; VF=ventricular fibrillation

ECG characteristics

Analysis of ST-segment morphology, QT interval, and PR interval was performed in all patients. A spontaneous pattern was present in at least one of the recorded ECGs of 6 (30%) patients. In the remaining 14 (70%) patients, typical Brugada ECG pattern was unmasked by intravenous infusion of class IA or IC drugs (Table I). The morphology of ST-segment elevation (coved versus saddle-back pattern) was similarly distributed between aborted SCD and syncope victims and other patients (P=0.35). The mean ST-segment elevation was 2.28±0.42 mm in symptomatic and 2.7±0.77 mm in asymptomatic patients (P=0.26). The mean value of ST-segment elevation was similar in both sexes (2.7±0.78 mm in men, 2.24±0.26 mm in women, P=0.15). The QT interval was normal in all patients. The mean value of PR interval was 188±18 ms in symptomatic and 184±24 ms in asymptomatic patients (P=0.75). The mean PR interval was longer in men (191±21 ms) than women (168±18 ms, P=0.042).

Electrophysiological study

EPS was done in 15 (75%) asymptomatic patients who provided informed consent. The stimulation protocol was identical in all patients: a maximum of three extra stimuli were delivered from RVA unless PMVT, MMVT, or VF was induced in a previous step. In 6 of 15 patients (40 %), VF or sustained PMVT was induced (5 males) with 1 extra stimulus (n=1), 2 extra stimuli (n=2), and 3 extra stimuli (n=3) (Table I). The mean age was 42.7±7.7 years in inducible patients and 40.9±10 years in non-inducible patients (P=0.33). There is no difference in inducibility between male (45%) and female (25%; P=0.10) patients.The HV intervals were mildly prolonged for the total study population (46-60 ms; mean, 55.5±5 ms). The mean HV interval was 57±4 ms in men and 50±4 ms in women (P=0.047). The HV interval was comparable between

inducible (57±2.5 ms) and non-inducible individuals (54±5.7 ms; P=0.55).

Echocardiography, exercise stress testing, and coronary arteriography

No echocardiographic evidence for structural heart disease was found in the 20 patients. Ischemia was excluded by exercise stress testing (6 patients) and coronary arteriography (1 patient) in 7 patients with atypical chest pain.

Management and follow-up data

ICD implantation was recommended in 11 high-risk patients (5 symptomatic patients, 6 inducible patients in EPS) and ICD was implanted in 8 patients (7 males and 1 female, P=0.63). The remaining 3 candidate patients rejected this recommendation. The remaining low-risk patients (asymptomatic and non-inducible in PES) were followed clinically. In the ICD group, 2 patients have had inappropriate therapy for sinus tachycardia and 1 patient appropriate discharge for fast VT. One patient in the ICD group developed left arm thrombophlebitis which was managed successfully by intravenous and oral anticoagulants. In this patient, near normal ECG on admission converted to a typical coved-type ECG following a rise of body temperature to 39°C. This patient had no ventricular arrhythmia during the febrile state. In the non-ICD group, no patient has had any event during a mean follow-up of 16±2 months.

Discussion

This study reports the clinical, electrophysiological, management and mid-term follow-up data in a cohort of both symptomatic and asymptomatic patients with Brugada syndrome.

Clinical profile of patients

We evaluated 20 consecutive patients with the diagnosis of Brugada syndrome to define their clinical, electrophysiologic, management and follow-up profiles. In accord with previous studies,[1,6,8] the ECG diagnosis was predominantly seen among males (75%), and 80% of major events (syncope and sudden cardiac arrest) occurred in males after the third decade of life. In most of patients (75%), this ECG diagnosis was made for the first time during evaluation for non-specific complaints, routine evaluations, or screening of family members and only one-fourth of the patients were detected after major events. A family history of SCD was present in 20% of patients (all asymptomatic). This difference may be related to the fact that a significant proportion of asymptomatic patients was detected during family screening. As mentioned above, many Brugada patients were diagnosed after atypical chest pain. Until now, no acceptable explanation was found for this presentation (Ramon Brugada; personal communication).

Pharmacological challenge

The major value of this test is its ability to establish a diagnosis in individuals with a suspicious ECG. Two different ECG patterns have been included in our study: the "coved-type" ECG (Fig. 3) and the "saddle-back" ECG (Fig. 4). We would not diagnose Brugada syndrome in an individual with a "saddle-back" ECG without inducing a "coved-type" ECG pattern with a pharmacological challenge test. All symptomatic and asymptomatic individuals included in this study had a spontaneous or drug-induced "coved-type" ECG morphology. The accentuation of ST elevation by class IA or IC antiarrhythmic drugs was reported to be one of the characteristics of Brugada syndrome.[12] The class IA or IC drugs were used to unmask the concealed or intermittent forms of Brugada syndrome, as ST elevation of

symptomatic patients fluctuate periodically.[13-15] Krishnan and Antzelevitch[16,17] reported that strong sodium channel current inhibition in the epicardium led to loss of the action potential dome in the epicardium but not in the endocardium, inducing dispersion of repolarization accompanied by prominent conduction delay, which resulted in local re-excitation (phase 2 reentry).

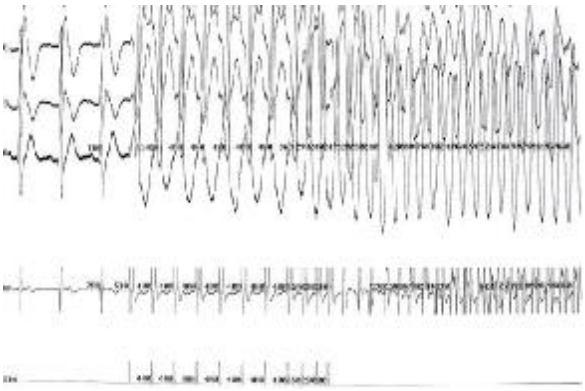


Fig. 2. Electrophysiologic tracing of an asymptomatic Brugada patient. Polymorphic ventricular tachycardia was induced with S1-500, S2-290 ms from the right ventricular apex.

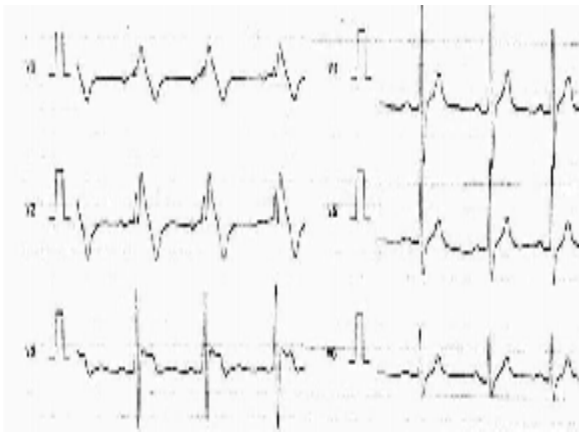


Fig.3. Resting electrocardiogram of an asymptomatic patient with Brugada syndrome. Typical Brugada ECG pattern including incomplete right bundle branch block and coved-type ST segment elevation in V1-V3 was observed.

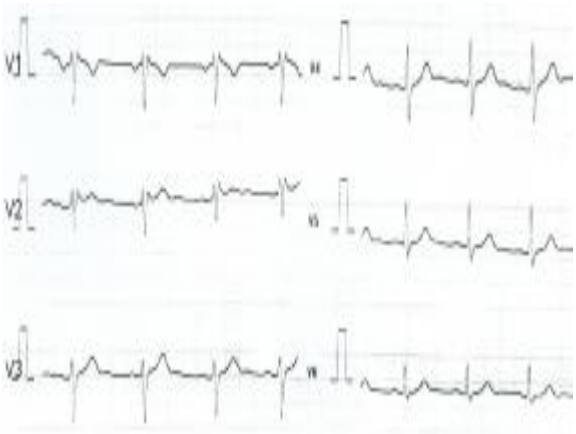


Fig. 4. Resting electrocardiogram of a patient with aborted sudden cardiac death. Note that incomplete right bundle branch block and saddle-back ST-segment elevation was seen.

The arrhythmia in Brugada syndrome has been interpreted as to be due to this mechanism.

In the present study, all patients with "saddle-back" ECG showed accentuation of ST-segment elevation by procainamide or flecainide, which was one of the inclusion criteria in this study. However, there was no correlation between the degree of increase in ST-segment elevation and inducibility in PES (Table II). Thus, pharmacological challenge probably has no role in predicting of PMVT/VF induction in asymptomatic patients with Brugada syndrome.

Table II. Correlation of demographic and electrophysiologic findings with inducibility in EPS

Parameter	Inducible in PES	Non-inducible in PES	P value
Age	42.67±7.7	40.89±10	0.73
Sex	M: 5 F: 1	M: 6 F: 3	0.60
PR interval	181.67±24	186.67±26	0.7
ST elevation	2.5±0.4	2.8±0.9	0.56
HV interval	56.67±2.5	54.50±5.7	0.55

PES=programmed electrical stimulation; M=male; F-female

Programmed electrical stimulation
Brugada et al.[6] reported that the incidence of PMVT or VF induction during PES is very high in symptomatic Brugada patients (78%). They found that inducibility of PMVT or VF by PES in asymptomatic patients also was very high (85%). We did not find such a high inducibility rate in our asymptomatic patients (40%) despite the presence of a family history of SCD in 27% of this group of patients. Our results were more compatible with the findings of Morita et al.[18] (VF was induced in 33% of asymptomatic patients). This difference in inducibility of asymptomatic patients can be explained by the use of different PES protocols. Like other studies,[6,18] PMVT or VF induction was done mostly by two or three extra stimuli (5/6 of patients) in our study (see above, Ramon Brugada; personal communication) In the present study, we did not find any correlation between demographic (age, sex), clinical (family history of SCD), electrocardiographic (PR interval, degree of ST-segment elevation, spontaneous or provoked type) data, HV interval and inducibility in PES. In the study of Brugada et al.[19] males were more frequently inducible than females. Although there was a trend toward higher inducibility in male (45%) compared to female (25%) patients in our cohort, it failed to reach to statistical significance. They also found that inducible individuals had a longer HV interval than non-inducible patients. These differences may relate to either our smaller sample size and hence lower statistical power or to differences between study populations. Our new findings were absence of correlation between age, family history, and ECG characteristics and inducibility in PES. We also found that HV interval was longer in males than females. This fact may be related to the ionic and cellular differences of male and female patients with Brugada syndrome.

Treatment and clinical follow-up
According to the published recommendations,[3,20] 11 patients became candidates for ICD implantation because of a history of aborted SCD or syncope or PMVT/VF induction in EPS. The nine asymptomatic and non-inducible patients were followed clinically. An ICD was implanted in 8 patients and the remaining three patients (all asymptomatic and inducible in EPS) did not give consent for this procedure. In the ICD group, 2 patients had inappropriate therapy for sinus tachycardia and one patient appropriate therapy for fast VT (this patient had a history of recurrent syncope). Another important finding was unmasking of a typical Brugada-type ECG in one of our patients after a febrile state of left arm thrombophlebitis. This important feature of Brugada syndrome was reported in several newly published case reports.[21,22] The underlying mechanism of this phenomenon is temperature-dependency of sodium channels responsible for Brugada syndrome.[23] In the non-ICD group, no drug was administered and patients were followed clinically. We have shown that asymptomatic and non-inducible patients remain as such after a mean follow-up of 16 months, but we cannot exclude that these patients might have cardiac events at a later time in life. In three patients who rejected ICD implantation, we recommended quinidine on the basis of recent studies which showed a beneficial effect of this drug in these patients.[24]
Our follow-up data confirmed the relatively benign course of asymptomatic and non-inducible Brugada patients and recurrence of arrhythmic events in symptomatic patients.[19,25,26]

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