Journal of Arrhythmia 29 (2013) 211–216

Contents lists available at ScienceDirect

Journal of Arrhythmia

journal homepage: www.elsevier.com/locate/joa

Original Article

Brugada syndrome in the presence of coronary artery disease

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ARTICLE INFO

Article history:
Received 3 August 2012
Received in revised form
15 September 2012, 27 September 2012
Accepted 30 September 2012
Available online 4 January 2013

Keywords:
Brugada-type ECG
Coronary artery stenosis
Myocardial ischemia
Ventricular fibrillation
Electrophysiological study

ABSTRACT

Background: Brugada-type ECG changes have been described in association with various cardiac disease states including electrolyte abnormalities, myocardial pathologies, and mechanical cardiac abnormalities as well as drug therapies with particular medications. Such potential confounding factors make it difficult to diagnose Brugada syndrome on the basis of standard guidelines.
Methods: To investigate the incidence of significant coronary artery disease in patients with Brugada-type ECG, coronary angiography was performed in 55 patients with Brugada-type ECGs.
Results: Five of the 55 patients (9%) had significant coronary artery stenosis, and 3 out of these 5 were asymptomatic. Patients with coronary artery disease were older than in those without coronary artery disease (59.4 ± 7.2 years vs. 49.0 ± 13.8 years, $P=0.03$). An electrophysiological study was performed in 4 of the 5 patients, and ventricular fibrillation was induced in all 4.
Conclusions: We conclude that patients with Brugada-type ECGs should be evaluated for coronary artery disease, and this is especially important for patients in whom age could be a risk factor for the disease.

1. Introduction

Brugada syndrome is characterized by ST-segment elevation in the right precordial leads and sudden cardiac death (SCD) [1]. In general, the mean age of victims of SCD is approximately 40 years [2]. Brugada syndrome is believed to account for 4–12% of all cardiac deaths and at least 20% of deaths in patients with a structurally normal heart [2]. Thus, the timely diagnosis of Brugada syndrome is clinically imperative. However, myocardial ischemia can cause right ventricular ST-segment elevation similar to the Brugada ECG pattern [3–7], and the coexistence of Brugada syndrome with vasospastic angina has been reported [8–12]. In addition, Brugada syndrome has been reported to associate with individual cases of significant coronary artery stenosis [13–17]. Thus, Brugada syndrome cannot be diagnosed simply on the basis of standard guidelines if such potential confounding factors are present [2,7]. The present retrospective study was undertaken to evaluate the coexistence of Brugada syndrome and coronary artery disease in a single center.

2. Materials and methods

2.1. Patients

The subjects in this study included 55 consecutive patients with a spontaneous or drug-induced (pilsicainide 1 mg/kg) Brugada type 1 ECG pattern. The ECG diagnosis of Brugada syndrome was based on recommendations issued at the second consensus conference [2]. No patients with true right bundle branch block were included in the study. All 55 patients underwent transthoracic echocardiography, cardiac catheterization, coronary angiography, and left and right ventricular angiography, while 54 of the 55 patients also underwent an electrophysiological study. All study protocols (coronary angiography including coronary spasm induction by intracoronary administration of acetylcholine and electrophysiological studies) were approved by the Clinical Research Committee of Nihon University Hospital, and written informed consent was obtained from all patients.

Laboratory tests were performed at the outpatient clinic to exclude electrolyte or metabolic disturbances. The following clinical data were obtained from each patient's record: sex, age, symptom(s), family history of SCD (<45 years of age), ECG pattern (type 1, type 2, or type 3 before drug challenge test), and whether an implantable cardioverter-defibrillator (ICD)

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http://dx.doi.org/10.1016/j.joa.2012.09.008

was indicated. Patients with a history of syncope, presyncope, or aborted SCD were considered symptomatic. Those with established neurally mediated syncope were not considered symptomatic. Screening for mutations in the SCN5A gene was performed in 37 individuals after approval of the internal review board of the Nihon University School of Medicine and Nihon University Hospital.

2.2. Signal-averaged electrocardiogram

A ventricular signal-averaged electrocardiogram (ART 1200 EPX signal-averaged ECG apparatus, Arrhythmia Research Technology Inc., Austin, TX, USA; noise level < 0.3 μV, bidirectional 4-pole Butterworth high pass filter setting of 40 Hz) was recorded in 52 patients. A positive late potential is defined at our institution as the root mean square voltage of the last 40 ms < 20 μV [18].

2.3. Electrophysiological study

A comprehensive electrophysiological study was performed on 54 patients in a fasting, drug-free, and non-sedated state. In patients who underwent coronary artery stent implantation, a programmed ventricular stimulation (PVS) study was performed for 1 month. After access to the right femoral vein was obtained at 4 sites, 1 quadripolar catheter (Biosense-Webster, Diamond Bar, CA, USA) was positioned at the right atrial appendage, 1 octapolar catheter (Biosense-Webster) was positioned at the His bundle electrogram recording site, and 2 steerable quadripolar catheters (6F) with an interelectrode distance of 2-5-2 mm (Biosense-Webster) were positioned in the right ventricular apex and outflow tract. The endocardial potentials were filtered to recording frequencies of 30–500 Hz and recorded on a BARD computer system (BARD Lab Pro, BARD Electrophysiology, Lowell, MA, USA). Programmed electrical stimulation from the right ventricular apex and right ventricular outflow tract was performed at strength of twice the diastolic threshold, and a 2-ms pulse was applied with a pulse generator (BD-02, Fukuda Denshi Co., Tokyo, Japan). An S_1-S_2 interval was applied after 8 beats of drive pacing (S_1) at basic cycle lengths of 600 ms and 400 ms. The S_1-S_2 interval was decreased in 10-ms steps until the effective refractory period of the right ventricle was reached. When ventricular fibrillation (VF) that lasted > 5 s and required direct current (DC) shock was not induced with a single premature beat, 3 extrastimuli (S_2 until the effective refractory period was reached, S_3 and S_4 to 180 ms) were delivered.

2.4. Follow-up

In general, patients were followed up at 4- to 5-month intervals in our outpatient clinic. Each examination included an assessment of subjective symptoms, 12-lead ECG, and device interrogation if necessary in the event of symptom onset or device discharge. The follow-up period ranged from 6 to 194 months (mean, 81.0 ± 47.5 months; median, 77 months).

2.5. Statistical analysis

Continuous clinical and electrophysiological values are shown as mean ± SD. Between-group differences in these values were analyzed by the Mann–Whitney U test. Categorical data were analyzed by Fisher's exact probability test. A P value of < 0.05 was considered statistically significant. StatView 5.0 software (SAS Institute, Cary, NC, USA) was used for analysis.

3. Results

The male/female sex ratio in the study group was 53/2, and the mean age was 50.4 ± 13.8 years (range, 24–79 years). Brugada syndrome ECG patterns were spontaneous type 1 ($n=31$) and drug-induced type 1 ($n=24$; type 2 = 14, type 3 = 10). The clinical, genetic, electrocardiographic, and electrophysiological characteristics of the study patients are shown in Table 1. Eleven patients were symptomatic (3 with history of syncope, 2 with presyncope, and 6 with aborted SCD), and 5 patients had a positive family history of SCD. An SCN5A gene mutation was found in 2 patients (5.4%). The left ventriculogram was normal with an ejection fraction of 69.2% ± 9.0% (55–89%) in 55 patients who had undergone left ventricular angiography. The coronary angiogram, although normal in 49 patients, revealed significant coronary artery disease in 5 patients. Risk factors in patients with coronary artery disease are listed in Table 2. Patients with coronary artery disease were older than those without coronary artery disease (59.4 ± 7.2 years vs. 49.0 ± 13.8 years, $P=0.03$) (Table 1). Two of the 5 patients (Patients 2 and 4) exhibited symptoms related to coronary artery disease. PVS was performed in 50 patients without significant coronary artery stenosis and in 4 of the 5 patients with coronary artery disease, which induced VF/

Table 1
Clinical, genetic, electrocardiographic, and electrophysiological characteristics of all patients and patients with and without Coronary Artery Disease (CAD).

	Total patients $N=55$	Patients with CAD ($n=5$)	Patients without CAD ($n=50$)	P value
Number of males	53	5 (100%)	48 (96.0%)	0.86
Age (years)	50.4 ± 13.8 (24–79)	59.4 ± 7.2	49.0 ± 13.8	0.03
Symptomatic	10	1 (20.0%)	9 (18.0%)	0.83
Family history of SCD	7	0	7 (14.0%)	0.65
Spontaneous type 1 ECG pattern	31	1 (20.0%)	30 (60.0%)	0.11
Late potentials	27	2 (40.0%)	25 (50.0%)	0.64
SCN5A gene mutation	2	0	2 (4.0%)	0.86
PR interval (ms)	172.1 ± 24.9	170.8 ± 15.2	172.2 ± 25.8	0.99
QTc (ms)	413.3 ± 22.8	401.2 ± 14.1	414.5 ± 23.3	0.23
QRS duration (ms)	106.7 ± 17.6	102.4 ± 16.1	107.2 ± 17.8	0.84
EPS	54	4	50	0.87
AH (ms)	101.5 ± 20.0	126.3 ± 26.8	99.5 ± 18.3	0.03
HV (ms)	47.8 ± 10.4	37.0 ± 2.2	48.7 ± 10.3	0.19
Inducible VF/PVT upon EPS	49/55 (89.1%)	4/4 (100%)	45/50 (90.0%)	0.17
ICD implantation	19	1	18	0.17
Follow-up (months)	81.0 ± 47.5	67.1 ± 50.6	80.2 ± 49.4	0.22
Arrhythmic event during follow-up	1	0	1 (1.5%)	> 0.99

The number of patients is shown unless otherwise indicated. CAD, coronary artery disease; SCD, sudden cardiac death; EPS, electrophysiological study; VF, ventricular fibrillation; PVT, polymorphic ventricular tachycardia; ICD, implantable cardioverter defibrillator.