Long-Term Follow-Up of Probands With Brugada Syndrome

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This study analyzes the natural history of a large cohort of probands with Brugada syndrome (BrS) to assess the predictive value of different clinical and electrocardiographic parameters for the development of ventricular fibrillation (VF) or sudden cardiac death (SCD) during a long-term follow-up. Baseline characteristics of 289 consecutive probands (203 men; mean age 45 ± 16 years) with a Brugada type 1 electrocardiogram were analyzed. After a mean follow-up of 10.1 ± 4.6 years, 29 malignant arrhythmias occurred. On multivariate analysis, a history of VF and syncopal episodes, fragmented QRS (f-QRS), spontaneous type 1 electrocardiogram, and early repolarization pattern were significantly associated with later occurrence of VF/SCD. In patients with drug-induced BrS, the accentuation or de novo appearance of f-QRS in other leads was always associated with VF/SCD. Cerebrovascular events occurred in 8 patients with atrial fibrillation (15.1%), most of them (75%) presenting as the first clinical manifestation. The time-to-diagnosis was found to be significantly shorter in those patients who directly came to our center than in those who referred to our center for a second opinion. In conclusion, systematic use of the pharmacologic challenge in patients with unexplained cardiovascular symptoms and/or atrial fibrillation might significantly improve the identification of BrS with a shortening of the time-to-diagnosis. The CHA_2DS_2VASc score might be inappropriate for predicting transient ischemic attack or stroke in BrS. This study confirms the independent predictive value of previous VF and syncopal episodes, f-QRS, type 1 electrocardiogram, and early repolarization pattern. In BrS a sufficiently long follow-up is necessary before conclusions on prognosis are apparent. **(Am J Cardiol 2017;119:1392−1400)**

Brugada syndrome (BrS) is characterized by a distinct electrocardiographic (ECG) pattern (type 1 coved pattern) in the right precordial leads in patients without structural heart abnormalities.[1,2] The disease carries a risk of sudden cardiac death (SCD) due to malignant ventricular arrhythmias.[2−7] Syncope and spontaneous type I ECG pattern have been consistently identified as markers of high risk in several studies.[8,9] It has also been reported that fragmented QRS (f-QRS) is an independent predictor of malignant ventricular arrhythmias in patients with BrS.[6,7,10] Data on long-term follow-up (>5 years) in patients with BrS are unavailable; no major BrS registry has a mean follow-up of >40 months.[10,11] The risk of sudden death in patients with BrS is a lifelong issue, not a matter of few years. This study analyzes our single-center up to 24 years' experience with the natural history of a large cohort of probands with BrS and assesses the predictive value of different parameters for the development of ventricular fibrillation (VF) or SCD during the follow-up.

Methods

Since 1992, all consecutive patients diagnosed with BrS have been included in a registry and followed up in a prospective fashion. The ethics committee of the Universiteit Ziekenhuis Brussel-Vrije Universiteit Brussel approved the registry. A total of 1,484 patients with BrS and/or family members coming from 589 families have been included in the registry from 1992 to 2015. Of them, we retrospectively analyzed data from 289 consecutive patients (203 men; mean age, 45 ± 16 years) with a Brugada type 1 electrocardiogram. All patients were probands and showed a typical Brugada ECG pattern with or without a sodium channel blocker challenge, which was defined previously (II report consensus conference[9]). A proband was defined as the member of a family first found to have the disease. Underlying structural cardiac abnormalities were excluded in all patients with noninvasive and/or invasive methods.

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See page 1399 for disclosure information.

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0002-9149/17/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2017.01.039

Informed consent was obtained from all patients, and clinical data, including data on age, gender, family history of SCD, history of syncopal episodes, history of VF episodes, and VF induction, during an electrophysiologic study were obtained from patient records. Many drugs have been reported to induce the type 1 BrS-ECG and/or (fatal) arrhythmias in patients with BrS. Therefore, patients with BrS were recommended not to use these drugs or to use them only under controlled conditions.[12] Ajmaline (1 mg/kg) was administered intravenously over a 5-minute period to unmask the diagnostic ECG pattern of BrS in case of a nondiagnostic baseline electrocardiogram. The test was considered positive for BrS only if a coved-type ECG pattern was documented in at least 1 right precordial lead (V_1 to V_3). The implantable defibrillator cardioverter (ICD) was indicated using the recommendations of the II Brugada consensus conference.[9] The decision to perform epicardial or endocardial lead implantation or to place the device in a thoracic or subcostal pocket was made according to the patient's age, anthropometric characteristics, and level of physical activity. The choice between single- and dual-chamber devices was driven by the presence of previous episodes of supraventricular arrhythmias or evidence of sinus node dysfunction. ICD programming at the time of implantation has changed over time. After our initial experience, the VF detection rate was increased from 180 to >200 beats/min for primary prevention implantations, and a monitor zone was added.[13] In accordance with more recently published data, long detection intervals (30 of 40 intervals) were adopted to avoid unnecessary therapies.[14–16] Conversely, in patients who underwent ICD implantation for secondary prevention, a monitor zone (>150 beats/min) and a fast VT zone (180 to 200 beats/min) with antitachycardia pacing and shocks were programmed in all cases, and supraventricular tachycardia discriminators were activated if available. All patients were also assigned to a time-to-diagnosis category characterized by those who directly came to our center and those who came for a second opinion with or without the diagnosis of BrS. Our diagnostic algorithm for syncope included the ajmaline challenge as a first-line investigation in all patients. Episodes of supraventricular arrhythmias, such as atrioventricular re-entry tachycardia, accessory pathway tachycardia, typical atrial flutter, atrial tachycardia, and atrial fibrillation (AF), were collected. In patients with AF we administrated anticoagulation based on the CHADS2 score guidelines from 2004[17] and the CHA_2DS_2VASc score from 2012.[18] All patients who had undergone catheter ablation for AF received anticoagulation therapy for a minimum of 3 months immediately after the procedure independently from the thromboembolic risk. Standard 12-lead electrocardiograms were recorded in the same way and were evaluated for the RR interval, PQ interval, QRS width, QT interval, ST-segment level at the J point, and number of positive spikes within the QRS complex in leads V_1 through V_3. Electrocardiograms were classified as Brugada coved type (type I), saddleback (type II), or normal. An electrocardiogram was considered diagnostic of BrS if there was a high take of QRS-ST in V_1-V_2 that usually occurs before the J point, followed by downsloping ST segment ST segment elevation generally concave with respect to the isoelectric line followed by a negative T wave (coved pattern),[1] in the presence or absence of the sodium channel blocker agent.[1] All baseline and drug-induced 12-lead electrocardiograms were recorded at a paper speed of 25 mm/s and an amplitude of 10 mm/mV with the right precordial leads positioned at the sternal margin of the third and fourth intercostal space. The presence of f-QRS was defined as an abnormal fragmentation within the QRS complex as ≥4 spikes in 1 or ≥8 spikes in leads V_1, V_2, and V_3, as described previously[6] (Figure 1). An early repolarization (ER) pattern was defined as an elevation of the J point in at least 2 consecutive leads. The amplitude of the J-wave or J-point elevation had to be at least 1 mm more than the baseline level, either as QRS slurring or notching in the inferior leads (II, III, and aVF), lateral leads (I, aVL, and V_4 to V_6), or both, as described previously.[19] The electrophysiologic study included basal measurements of conduction intervals and programmed ventricular stimulation, as previously reported by our group.[20] A patient was considered inducible if a sustained ventricular arrhythmia (VF, polymorphic VT, or monomorphic VT lasting >30 seconds or requiring emergency intervention) was induced. Clinical follow-up of patients consisted of physical examination and electrocardiography performed at least every 6 months in case of symptomatic and device therapy patients and every 1 to 2 years otherwise. Follow-up of ICDs was performed at 1 and 3 months after implantation and thereafter every 6 months in the outpatient clinic, combined with remote device monitoring provided by the cardiac device company. All available electrograms of appropriate and inappropriate shocks were analyzed by at least 2 independent investigators. An event during follow-up was defined as sudden death or appropriate implantable cardioverter-defibrillator therapy. Data are expressed as mean ± SD. A Student *t* test was performed to test for statistical differences between 2 unpaired mean values, and categorical data and percentage frequencies were analyzed by the chi-square test. On univariate analysis, 7 predictors were significantly associated with arrhythmic events. Multivariate analysis using Cox proportional hazards regression analysis estimated those 7 predictors and was performed in search of independent risk factors for arrhythmic events. This analysis was based on a stepwise algorithm, with the p value set at 0.05 for inclusion and 0.1 for exclusion. The effects of f-QRS alone and also in combination with the spontaneous type 1 pattern on arrhythmic events during the follow-up period were evaluated using the log-rank test and were described using a Kaplan-Meier curve. A p value <0.05 was considered statistically significant. Statistical analyses were conducted using the SPSS software (SPSS v20, Chicago, Illinois).

Results

In our cohort a noticeable amount of patients were men (70%; n = 203); a spontaneous type 1 ST elevation was observed in 27% of patients (n = 79), whereas the remaining patients (73%; n = 210) were diagnosed after a drug challenge using a sodium channel blocker. In the latter group, procainamide was used in 5 cases (2.4%), flecainide in 4 (1.9%), and Ajmaline in the remaining subjects