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Etiological diagnosis, prognostic significance and role of electrophysiological study in patients with Brugada ECG and syncope☆

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ABSTRACT

Background: Syncope is considered a risk factor for life-threatening arrhythmias in Brugada patients. Distinguishing a benign syncope from one due to ventricular arrhythmias is often difficult, unless an ECG is recorded during the episode. Aim of the study was to analyze the characteristics of syncopal episodes in a large population of Brugada patients and evaluate the role of electrophysiological study (EPS) and the prognosis in the different subgroups.

Methods and results: One hundred ninety-five Brugada patients with history of syncope were considered. Syncope were classified as neurally mediated (group 1, 61%) or unexplained (group 2, 39%) on the basis of personal and family history, clinical features, triggers, situations, associated signs, concomitant therapy. Most patients underwent EPS; they received ICD or implantable loop-recorder on the basis of the result of investigations and physician's judgment. At 62 ± 45 months of mean follow-up, group 1 showed a significantly lower incidence of arrhythmic events (2%) as compared to group 2 (9%, $p < 0.001$). Group 2 patients with positive EPS showed the highest risk of arrhythmic events (27%). No ventricular events occurred in subjects with negative EPS.

Conclusion: Etiological definition of syncope in Brugada patients is important, as it allows identifying two groups with different outcome. Patients with unexplained syncope and ventricular fibrillation induced at EPS have the highest risk of arrhythmic events. Patients presenting with neurally mediated syncope showed a prognosis similar to that of the asymptomatic and the role of EPS in this group is unproven.

1. Introduction

Brugada syndrome is a genetic arrhythmogenic disease characterized by coved type ST-segment elevation in at least one right precordial lead, associated with an increased risk of ventricular arrhythmias, which can cause syncope and sudden death also as first manifestation [1–3]. All the studies on risk stratification in patients with Brugada ECG pattern agree in considering syncope as a risk factor for life-threatening arrhythmias [3–9].

Differentiation of syncope due to vagal response or orthostatic hypotension, which are the most frequent causes of syncope in the general population [10], from syncopal episodes due to ventricular arrhythmias is often difficult in Brugada patients, unless an ECG is recorded during the episode. Indeed, vagal nerve activation in these subjects can both cause neurally mediated syncope and act as trigger for ventricular fibrillation (VF) [11]. Determination of the etiology of syncope is important to identify the patients who require an implantable cardioverter-defibrillator (ICD). However, few studies have focused on the etiological differentiation of syncope in Brugada patients [12–14].

Aim of this study was to analyze the characteristics of syncopal episodes in the patients of the Brugada Registry of the Piedmont Region of Italy, by considering two groups with different probability of arrhythmic syncope, on the basis of history, clinical features, situations and results of the investigations performed. The role of electrophysiological

☆ All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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study (EPS) and the long-term prognosis in the two groups was also evaluated.

2. Methods

2.1. Study population

Consecutive patients with spontaneous or drug-induced Brugada ECG pattern were prospectively collected in the Brugada Registry of the Piedmont Region in Italy, from 2001 to 2014. >90% of the Cardiology Divisions in the Region with an electrophysiological laboratory participated in the study. The study was approved by the Medical Ethical Committee of our Institution. Diagnosis of Brugada ECG pattern was established according to the Consensus Conference criteria [1,2] and, since 2013, according to HRS/EHRA/APHRS expert Consensus statement [3].

The 825 patients in the Brugada Registry were classified according to the symptoms reported at the first clinical observation as: subjects with sudden death or aborted sudden death (22; 2%), subjects with syncope (195; 24%) and asymptomatic (608; 74%). Only patients with history of syncopal episodes, occurred at or before the inclusion in the Brugada Registry, were considered in this study. We splitted the 195 patients with syncope in two study cohorts on the basis of the nature of the experienced syncope: neurally mediated (group 1) or unexplained (group 2). Sixty-two of these patients were already included in the FINGER study [8], 67 in a study by Delise et al. [15] and 3 in the PRELUDE study [9].

2.2. Definition of syncope and data collection

Syncope was defined as transient loss of consciousness with spontaneous recovery, without neurological impairment [16].

Diagnosis of neurally mediated syncope was made in the presence of orthostatic hypotension (defined as described in the ESC guidelines on syncope [15]) or highly likely vaso-vagal syncope (≥1 typical prodromes, ≥1 typical triggers or situations - see Table 1B - and/or positive HUTT and absence of severe physical injuries). Syncope was considered of unexplained origin in the absence of the above-mentioned conditions (absent or brief prodromes, absence of specific triggering circumstances, loss of consciousness <1 min, and fast return to consciousness) [13], particularly when occurring during fever or after administration of contraindicated drugs (www.brugadadrugs.org) and in case of physical injuries due to syncope. In case of multiple syncopal episodes the diagnosis was based on the characteristics of the most severe one. Syncopal episodes were analyzed collegially by three physicians; in case of uncertainty, the classification was established by agreement. Patients were seen at the outpatient clinic or interviewed by telephone and questioned about personal and family history and about the syncopal event, as suggested by ESC guidelines on syncope [15]. In each subject we investigated the number of previous syncope, triggers, situations, prodromes, associated signs (incontinence, convulsions, agonal respiration) and duration of the loss of consciousness. We got information about other diseases, presence of autonomic neuropathy and medications. A family history of sudden unexplained death at age <45 years was recorded. Data on the occurrence of injury as a result of the syncope were collected. Patients underwent 12-lead 24-hour Holter monitoring, exercise test and head-up tilt test (HUTT), based on the physician's choice. HUTT was performed, according to the ESC guidelines [15].

The presence of an underlying structural heart disease was ruled out through physical examination and echocardiography. PR interval was measured in lead II on the basal ECG. A genetic test, searching for mutations in SCN5A and SCN1B genes, was proposed to the patients with spontaneous type 1 ECG or familial Brugada ECG pattern.

2.3. Electrophysiological study

In the Piedmont Brugada Registry, until 2009, EPS was recommended to all the patients with spontaneous or drug-induced Brugada ECG pattern; thereafter, we no longer indicated EPS in asymptomatic patients without spontaneous type 1 ECG, but we continued to propose EPS to all the subjects with spontaneous type 1 ECG, even asymptomatic, and to the patients with unexplained syncope with or without spontaneous type 1 ECG [7]. After obtaining informed written consent, EPS was performed mainly according to a protocol with a maximum of 2 ventricular extrastimuli, from 2 ventricular sites (apex and right ventricular outflow tract), at 2 different pacing cycle lengths (600 and 400 ms); extrastimuli were anticipated in 10 ms decrements up to 160 ms or to the shortest coupling interval which resulted in ventricular capture. Alternatively, the PRELUDE protocol was applied [9]. EPS was considered positive if sustained ventricular arrhythmias (VF, polymorphic ventricular tachycardia (VT) or monomorphic VT lasting >30 s or requiring emergency intervention) were induced.

2.4. Device implantation and follow-up

Patients received ICD or implantable loop recorder (ILR) on the basis of results of the investigations and clinical judgment. ICD were programmed with a single VF zone above 210–220 bpm and a detection time of 18/24 cycles or 2 s. Patients with ICD were followed in the ICD clinic of the referring Center every 6 months. Data from ILR were transmitted and analyzed every month. Patients were considered to have an arrhythmic event at follow-up if VF or sustained VT were documented or sudden death (SD) or appropriate ICD shock (delivered for VF or VT) had occurred. Inappropriate shocks were defined as those delivered in the absence of ventricular arrhythmias. Patients without implantable devices were seen at the outpatient clinic of the referring Center at least once a year and the data sent to the Brugada Registry. Follow-up of patients receiving hydroquinidine was stopped at the beginning of the treatment.

2.5. Statistical analysis

Continuous variables satisfied the Shapiro-Wilks normality test and are presented as mean ± standard deviation, and compared with the non-parametric Mann–Whitney test.

Dichotomic variables are presented as number and percentages and compared with the chi-square test with Yates' correction or Fisher's test when more appropriate. Freedom from adverse events during the follow-up years is represented by the Kaplan-Meier curves and compared with the Mantel-Cox test. All tests were two-sided and statistical significance was defined as $p \leq 0.05$. All calculations were performed using SPSS 20 (IBM, Armonk, NY, USA).

3. Results

We focused on the 195 patients with history of syncope. Mean age at the inclusion in the Brugada Registry was 44 ± 14 years; 146 patients (75%) were males. Ninety-seven subjects (50%) had spontaneous type 1 ECG. Mean PR interval was 178 ± 30 ms. Genetic analysis was performed in 83 (43%) and mutations in SCN5A or SCN1B genes were found in 26 (31%). PR interval was 199 ± 40 ms in patients with SCN5A mutation and 179 ± 29 ms in those without mutation, ($p < 0.001$). Mean age at the first syncopal episode was 35 ± 16 years (range 2–68).

3.1. Baseline characteristics of the two groups

Tables 1A and 1B show the clinical characteristics of the 2 groups. Neurally mediated syncope (group 1) occurred in 118 out of 195 patients (61%). The remaining 77 patients (39%) had unexplained syncope (group 2). Mean age at the first syncope was 33 ± 16 and 36 ± 15 respectively; mean time from 1st syncope to the inclusion in the Registry was 12 ± 14 years in group 1 and 7 ± 11 years in group 2, $p = 0.02$. Mean number of syncopal episodes before diagnosis was 2.0 ± 1.5 in group 1 and 1.6 ± 1.3 in group 2 (p = NS).

As expected, in group 1 there was a higher prevalence of prodromes as compared to group 2. Cough, micturition, venipuncture, sight of blood or intense pain were situations predictive of neurally mediated syncope. At the opposite, loss of consciousness during driving and trauma occurred more often in group 2.

Table 1A
Characteristics of patients in the 2 groups (G1 = neurally mediated syncope; G2 = unexplained syncope).

	G1	G2
Number	118/195 (60%)	77/195 (40%)
Age at diagnosis (years)	45 ± 13	44 ± 14
Age at 1st syncope	33 ± 16	36 ± 15
Total number of syncope	2.1 ± 1.5	1.8 ± 1.2
Men	83/118 (70%)	63/77 (82%)
Spontaneous type 1 ECG	46/118 (39%)	51/77 (66%)
Family history of SD at age <45 years	12/118 (10%)	16/77 (21%)
Genetic test	42/118 (36%)	41/77 (54%)
SCN5A/SCN1B mutation	15/42 (36%)	11/41 (27%)
PR interval (ms)	185 ± 30	169 ± 29
Supraventricular arrhythmias	12/118 (10%)	7/77 (9%)
Tilt test	27/118 (23%)	10/77 (13%)
Positive tilt test	12/27 (44%)	1/10 (10%)
EPS	71/118 (60%)	57/77 (74%)
Positive EPS	24/71 (34%)	26/57 (46%)
Hydroquinidine	12/118 (10%)	10/77 (13%)
Loop recorder	13/118 (11%)	14/77 (18%)
ICD	23/118 (19%)	44/77 (57%)
Documented NSVT	8/38 (21%)	12/56 (21%)
Mean follow-up (months)	58 ± 46	67 ± 42
Events at follow-up	2/118 (2%)	7/77 (9%)

EPS = electrophysiological study; ICD = implantable cardioverter defibrillator; NSVT = non-sustained ventricular tachycardia; SD = sudden death.